FierceMedicalDevices
THE DEVICE AND DIAGNOSTICS INDUSTRY'S NEWS MONITOR

COMPANION DIAGNOSTICS: THE FUTURE OF MEDICINE.

▶ The story of Andy Hill is the kind of tale that champions of personalized medicine love to tell. A 46-year-old father of three, Hill was a healthy and fit nonsmoker when he developed a cough and mild chest pain. His doctor treated him for pneumonia, but the symptoms continued. It wasn't until he coughed up blood that the doctor sent him for a CT scan. A young nonsmoker with lung cancer? The chances were slim.

But Hill did have cancer—inoperable non-small cell lung cancer that had spread to his lymph nodes. He started chemo and radiation therapy. Eventually Hill developed a constant cough. Once a regular jogger and soccer player, he grew winded from climbing a flight of stairs.

That's when he ran across early reports about crizotinib, an experimental therapy designed to treat a small subset of patients with an aberrant ALK gene. The drug had aced an early trial. And that patient subset, estimated at 3% to 5% of NSCLC patients, sounded a lot like Hill. They tended to be young nonsmokers.

So, Hill and his oncologist decided to test for the ALK rearrangement that might qualify him for the crizotinib trial. He was positive. After a week in the trial, his cough and chest pain were gone. After three weeks of therapy, he could jog again. A few months later, his chest scans were cancer-free.

Hill still takes crizotinib every day, but everything else in his life has gone back to normal. Except, that is, for the fact that he's now the state senator for Washington's 45th District. After his crizotinib therapy—which he's nicknamed a "silver bullet" and his wife calls "a huge miracle"—he launched an election campaign, and won.

Much of the rest of the world now calls crizotinib by its brand name, Xalkori. Developed by Pfizer in record time, the cancer treatment won FDA approval on August 28, 2011 for the treatment of non-small cell lung cancer in patients with the ALK gene rearrangement. Abbott Molecular, a division of Abbott Laboratories, developed the diagnostic test to identify those patients, and it was approved the same day.

Hill's happy ending was covered by the *Redmond Reporter*, his hometown newspaper, and then picked up in a TEDx talk by oncologist and cancer activist Dr. Jack West. That video has since been passed around the cancer-treatment arena via YouTube. But what makes the Xalkori story so compelling for personalized medicine advocates isn't just the dramatic results it has produced in many patients like Hill. It's also the remarkable fact that the molecule that would become crizotinib was discovered only 6 years ago, and the specific ALK mutation implicated in lung-cancer growth wasn't identified until two years after that. By 2010, Pfizer and Abbott had dramatic Phase II data showing a 60% response rate. Crizotinib hit the FDA fast track, gaining approval several months ahead of the agency's schedule—and at least 6 months ahead of Pfizer and Abbott's goal date. The quick development process, the remarkable patient response, the FDA's quick action—these things have been heralded by personalized medicine for years. Finally, a real-world example confirmed

it all. The promise of the Human Genome Project, which delivered a draft sequence in 2001, might finally be coming to fruition.

"If you look back almost a decade ago, to the sequencing of the human genome, people thought things would happen almost immediately," Abbott spokesman Don Braakman told Thomson *BioWorld* at the time. "It's been a longer, more costly process than anticipated."

Even better, Xalkori and its companion diagnostic won regulatory clearance on the heels of another targeted drug and its test: Zelboraf, the breakthrough melanoma treatment for patients with a mutated BRAF gene. The drug, known in trials as vemurafenib, went from zero to approved in about 5 years. The Roche/Plexxikon drug got the FDA nod in tandem with a Roche Diagnostics test to identify BRAF-positive disease. Both approvals followed some long-awaited FDA proposals for regulating development of companion diagnostics.

"With these two new approvals and the FDA guidance, finally, these are multiple signs that personalized medicine has it right this time," says Joshua Cohen, assistant professor at the Tufts Center for the Study of Drug Development. "The drug and diagnostic developers are truly working together in concert to come up with combinations that impact outcomes in a positive way."

There are plenty of reasons why that's true. With the blockbuster business model dead, pharma companies are more interested in personalized medicine than ever. Budget-conscious governments and payers like the idea of paying to treat only the patients who will benefit. Regulators in the U.S. and Europe are moving forward with guidelines and processes designed to help, rather than hinder, development of personalized drugs and the diagnostic tests to go with them.

But many longtime challenges remain. Regulators and government payers never move quickly enough to keep up with progress, whether it's in science or in business. Intellectual property questions and regulatory

uncertainty have sidelined some investors. Drugmakers aren't universally convinced that targeted drugs are worth the time, trouble and money necessary to develop them, and diagnostics companies have their own reservations. In many ways, the drug business is still clinging to its mass-market blockbuster past, unconsciously or not.

"There's no obvious way to move personalized medicine forward," Edward Abrahams, president of the Personalized Medicine Coalition, said in an interview. "Regulation, reimbursement, coding, medical practice—all are set up as one-size-fits-all. It's all highly siloed. We have to break that down."

THE PROMISE OF HERCEPTIN

Just as no one talks about targeted drugs or companion diagnostics without referring to the Human Genome Project, no one goes for long without mentioning Herceptin. The breast cancer drug, and the diagnostic test for the HER2 protein indicating the need for its use, are a model for other drug-and-diagnostic combinations to follow. Reviewing the story of Herceptin and the HER2 protein test offers a chance to consider how future development might emulate it.

You could say that Herceptin's story begins with Gregor Mendel and his experiments with pea plants. Or that it starts when James D. Watson and Francis Crick first described the structure of DNA, drawing that now iconic double helix. Or when genetic changes were first linked to cancer-cell development, or when Genentech was founded, or when the HER2 gene was first sequenced. But the narrative really gains steam in the mid-1980s, with a series of breakthroughs that culminated in the discovery that a Genentech-developed mouse antibody known as 4D5 could suppress the growth of tumor cells that overexpressed HER2, which had been implicated in an aggressive type of breast cancer.

Genentech scientists humanized the 4D5 antibody. The company began

clinical trials. By 1995 patients were enrolling in Phase III studies that would test the anti-HER2 antibody in women with metastatic breast cancer, using a lab-developed test to select patients with HER2-positive tumors. Partly because only about 20% of breast cancers test positive for HER2 overexpression, researchers struggled to enroll patients at first. But after teaming up with some patient-advocacy and cancer research groups—and making a key change in one trial—the studies filled. That was in 1997.

In December 1996, Genentech had gone to Dako, a Danish diagnostics company, for help developing a commercial test to find those patients who overexpressed HER2. By May 1998, the two companies had submitted their applications for FDA approval—Herceptin's with the agency's biologics division, Dako's HercepTest at CDRH. FDA fast-tracked Herceptin's application. In September 1998, the drug and its companion diagnostic won FDA approval—as a treatment for women with metastatic breast cancer whose tumors overexpressed the HER2 protein, and as a means to identify those patients.

Later, Genentech was bought out by longtime partner and shareholder Roche. The company has won more indications for Herceptin, broadening its use to earlier stages of HER2-positive disease as well as in combination with various chemo drugs. And, significantly for Dako, it has added various HER2-expression assays to the drug's label; now, at least four diagnostic tests are approved for use with Herceptin, and Dako is no longer mentioned by name on the drug's label.

In its first 10 years on the market, Herceptin was used to treat more than 420,000 women with HER2-positive breast cancer worldwide. The drug has brought in tens of billions of dollars in sales. With global sales so far this year of almost $3 billion, it remains one of Roche's top three best-selling drugs.

The question during the years since Herceptin's debut has always been

this: Where is the next Herceptin? For more than a decade, no answer has been forthcoming. While the number of targeted drugs has grown, and so has the number of diagnostic tests designed to better select patients for drug therapies, there's been a dearth of drug-and-diagnostic pairings that moved through development, hit the market, and proved themselves together in clinical practice. Until Roche's Zelboraf won FDA approval for melanoma treatment along with its Roche Diagnostics BRAF assay, and Pfizer's Xalkori and its companion ALK assay from Abbott Laboratories got the agency's blessing soon after, a few drugs found their genetic predictors after they were approved. Some were approved for patients with particular genetic characteristics, but lab tests rather than FDA-approved assays were allowed; others went to market paired with a diagnostic identifying a biomarker that soon fell out of favor.

The reality of personalized medicine has made Herceptin look more like an exception, rather than the rule for others to follow. It's just one of the ways the field has failed to evolve as scientists or companies or patients initially had hoped. Given Herceptin's success—and the subsequent sequencing of the human genome—people came to expect personalized medicine, and soon.

But as the stop-and-start nature of the post-Herceptin environment for targeted drugs and companion diagnostics shows, everything about personalized medicine is in a state of flux. At conferences, drugmakers, diagnostics firms, regulators, consultants and lawyers talk about progress—and there has been plenty—but the conversation is still very much a prospective one. It's about "then" rather than "now." But at least it's about "when" and not "if."

Just witness the journal articles published about these drug-and-diagnostic pairings. Some use the broad term "personalized medicine," which really includes more than targeted drugs and their companion diagnostics. Others prefer "stratified medicine," because diagnostics don't individualize treatment, they identify groups of patients that will best

benefit from—or are least likely to be hurt by—particular drugs. Then there are the less concise suggestions: Dietmar Gross, SVP at Bayer Schering Pharma, last fall proposed one that, while precise, would hardly fit in a news headline: "I have a problem with personalized medicine because oncologists have always adapted therapies to individuals," Gross said at the 2010 BIO-Europe meeting. "In fact, the personalized healthcare we are discussing is not individual at all but is focused on patient subsets. We should call it 'tumor response markers for subsets' to be accurate."

And then there are the products themselves. Some use the term "targeted drugs" to describe the products aimed at patients with particular genetic characteristics. Others call them "personalized medicines." On the diagnostic side, there are several labels: companion diagnostic, pharmacodiagnostic, theranostic. And there are competing definitions for just what any one of these variously labeled diagnostics actually is.

No worries, says an article from *Drug Discovery World* that offers a snapshot of the business as of fall 2010: "The evolutionary process of a nascent and emerging discipline is embodied by chaos, confusion, and circumlocution." So, if navigating the drug-and-diagnostic field sometimes feels like walking through a funhouse, where the floors are constantly changing heights and the mirrors reflect distorted images, then that's just to be expected.

ONE CERTAINTY: A VARIETY OF OBSTACLES

Chaos, confusion and circumlocution aren't the sort of adjectives that inspire confidence. And if there's any one thing hampering the flow of targeted drugs and diagnostic tests, it's uncertainty.

Actually, only one thing about the field is certain at this point: The new world of genetically-minded medicine won't run along the old one-size-fits-all model that the pharma industry grew up with. A new one has to be assembled, with all the same basic pieces as the old one, but transfigured and rearranged. Drugmakers, diagnostics companies, regulators,

lawmakers, advocacy groups, lobbyists, researchers, investors, consultants, lawyers—they're all working on the transformation. The key pieces are as follows.

Slowly advancing science

It's no accident that much of the progress in personalized medicine has come in oncology. Scientists have been able to identify some single-gene mutations that drive some forms of cancer, though the entire picture is much more complicated than that. In other disease areas, including major, chronic illnesses such as diabetes, heart disease, and CNS disorders such as depression and Alzheimer's, fewer helpful biomarkers have been identified. A number of challenges exist, including such basic obstacles as a scarcity of tissue samples for use in pre-clinical development. Even when samples are available, such as DNA collected during clinical trials, sometimes "the science has not advanced sufficiently for companies to readily interpret pharmacogenic results," Tufts Center for the Study of Drug Development found in one study. So, in some diseases drugmakers would like to tackle with targeted therapies, such as depression, "there's this tremendous hunger for companion diagnostics," says Mark Trusheim, Executive-in-Residence and Visiting Scientist at the MIT Sloan School of Management, "but science hasn't advanced far enough yet."

Divergent business models

Drugs are expensive and time-consuming to develop. R&D projects are risky, too, with more than one-third of drugs failing in late-stage trials. But if and when a targeted drug gets to market, it can command premium pricing. It enjoys assured patent protection and, in some cases, is the only treatment available specifically for that population.

Diagnostic tests are far less expensive to develop, and moving them from research to market takes far less time, but they rarely have intellectual-property protection and aren't guaranteed market exclusivity for any time

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Reducing Risk When You Can't Co-Develop

BY MYA THOMAE

Ideally, drugs and their companion diagnostics should be developed in parallel. It's by far the cheapest and easiest way to proceed and spares the considerable effort of performing additional studies.

In the real world, however, co-development is frequently deemed impractical or simply doesn't happen. Deferring diagnostic partnership questions until after pivotal trials can put a project at risk, but it might also be the only path available. In such cases, it is well worth performing some sensible risk mitigation.

In one example scenario, a drug in development is intended for a condition that research papers have correlated with several biomarkers. The developer might decide to test for these biomarkers during Phase II and III trials. Phase III trials might reveal that one or more biomarkers have clinical relevance or they might reveal nothing at all. It may be impractical to bring multiple diagnostic products to the point of regulatory viability without even knowing what relevance those tests may have to the final product.

In such a situation, the diagnostic that is submitted for approval will likely differ from the diagnostic used during clinical trials. That means additional "bridging" studies will be required to show equivalency of results. Bridging studies can be painful and are well worth avoiding if you can. Where bridging studies are likely or unavoidable, it's still possible to reduce the pain by planning ahead.

When we advise our clients in this situation, we often suggest the following:

- Save all original samples (i.e., blood, not extracted DNA or RNA) so that there are materials available for a bridging study should one be necessary. This includes both positive and negative samples; both will be necessary to demonstrate diagnostic accuracy.
- Carefully consider how the assay cut-off is set for the trial. If the assay is quantitative, consider whether continuous measurements are necessary or whether brackets should be established. FDA will require many more samples to see clinical utility in continuous measurements.
- Use one standardized version of a single assay for the trial (even if it is a development version) so that comparison to multiple assays is not required.
- Ensure that the laboratory or sites running the assay do not make any changes during the trial. Even small changes in extraction methods or software can result in significant bridging studies later on.
- Even if the drug enters a pivotal trial without an approvable assay, consider beginning early discussions with potential diagnostic partners. Starting from scratch on a diagnostic partnership when drug approval is within sight is almost certain to result in a less robust and more expensive program.

Many drug developers hope to avoid discovering that a companion diagnostic will be required. Even when the goal is to avoid a companion at all costs, it may still worth considering the possibility and planning for this contingency. Having the flexibility to conduct bridging studies will help to ensure that a viable diagnostic can be made available should it be required.

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period. Labs can offer competitive tests that doctors can choose to use, at least until FDA shows that it plans to enforce targeted drug labeling that specifies FDA-approved diagnostics. What's more, because of the vagaries of Medicare coding and pegged-to-Medicare reimbursement levels, diagnostics companies have less pricing power. And when targeted drugs are intended for small patient populations, the return on investment for a one-time-use diagnostic that selects patients appropriate for a particular therapy can be nil.

The real problem, experts say, isn't the fact that drugs and diagnostics work along very different business models. The problem is that the two sides of the personalized-medicine coin don't understand how different they are. Even the enlightened few who have an inkling of those differences don't fully comprehend the challenges the other side faces.

Regulatory questions

FDA finally released proposed guidelines for development of companion diagnostics in July, to a tough audience of impatient drugmakers and diagnostics firms. About the same time, the European Medicines Agency released a white paper about using biomarkers in drug development. Though the update on FDA's thinking was welcomed—and some in the field see the guidance as detailed enough to go forward, at least for now—some want more details, and others want the agency to roll out one broad regulatory framework encompassing targeted drugs, in vitro diagnostics, lab-developed tests, and anything else that might affect personalized medicine. What's more, the new IVD guidelines are vague about the mechanisms FDA will use, internally, to facilitate drug-and-diagnostic development, given that each half of the potential couple has to proceed through a different pathway governed by a different FDA division. Then there is the outstanding question about whether FDA will move forward on regulating lab-developed tests (LDTs)—and if so, just what those regulations will look like.

Reimbursement hurdles

Even after a targeted drug or companion diagnostic has been approved, that doesn't mean a payer will automatically foot the bill. Private-sector payers, along with Medicare and Medicaid in the U.S., increasingly want to see proof that a diagnostic test will change patient outcomes. In Europe, reimbursement can be even more difficult to obtain, because authorities don't just want evidence of improved care, but evidence that the improved care will also be cost-effective. Plus, there are logistical problems: Medicare's payment schedule, which was developed in 1984, often slots companion diagnostic tests into categories that don't pay well. Coding for diagnostic tests is unworkably complicated. "[T]he reimbursement framework created decades ago is ill-equipped for an era of personalized medicine," said Abrahams, of the Personalized Medicine Coalition.

Uneven clinical practice

Clinical adoption has been slow for some companion diagnostics. Payers are partly to blame; only a few payers require documentation that a diagnostic test has been conducted before the targeted drug is prescribed, even when the diagnostic is recommended or required on the FDA-approved labeling. Nor do payers always pay for the proper screening. Doctor buy-in has been less than forthcoming for some tests, in some cases because diagnostic tests may measure a particular gene or risk, but clinical follow-up is unclear. FDA's labeling decisions can be influential: When the label recommends or requires a diagnostic test for drug use, doctors are more likely to order it than if the agency incorporates screening into the "information" section of a therapeutic label. What it comes down to for payers, doctors and the FDA is evidence of clinical utility—but without much clinical use, where's the data?

Cost as a deterrent

The high cost of some targeted drugs can prove to be a barrier to adop-

tion, because some patients simply cannot afford to pay their share. Some drugmakers have recognized this—Pfizer, for example, is offering co-pay assistance for its new, $100,000-plus lung cancer drug Xalkori—but this sort of back-end discounting isn't feasible for all drugs. Payers don't always like it either, because it thwarts their attempts to use tiered co-payments to keep a lid on costs.

Global marketing challenges

Companion diagnostics can present a problem for marketing products in the developing world, which is increasingly important in Big Pharma's long-term growth plans. Lab services aren't as readily available or accessible as in developed countries, and too few targeted drugs have moved into emerging markets to gauge how willing governments might be to pay for the tests—and how much they'd pay for the drugs, which, in mature markets, are priced at a premium. Increasing development of in vitro kits can help address the lab-services problem.

Cautious investors

Venture capitalists and other investors aren't leaping into personalized medicine. Questions about regulatory pathways and reimbursement issues are partly to blame. There's also the question of intellectual property: Though a U.S. appeals court recently affirmed Myriad Genetics' patents on two breast cancer genes—which, in turn, validated the patentability of individual genes—plenty of questions remain about what's patentable in genetics. The Myriad case appears headed for the Supreme Court, which could lean the other way. Obviously, market exclusivity drives sales prospects, so uncertainty about IP means uncertainty about sales. Then there's the fact that the field is so new: Lacking a deep reservoir of performance data on targeted drugs and companion diagnostics, number-crunchers have developed few benchmarking models to guide investment decisions.

Compensation questions

How can the value of a market for targeted therapies be divided? How much should go to the drug, and how much to the diagnostic that serves to identify that drug's patient population? What's a fair way to compensate each partner? Are there any rules of thumb for the financial terms of co-development deals, or does each deal have to be a reinvention of the return-on-investment wheel?

The pioneers of this new business obviously have a lot of work to do. Fortunately, industry trends are conspiring to make that work worthwhile. It's partly necessity; drugmakers are quickly losing patent protection on their biggest drugs, which means billions of dollars in sales are evaporating from pharma's financial reports. Companies have spent billions on R&D to find replacements for blockbuster medications, but the batting average on in-development drugs, particularly in Big Pharma, has steadily declined. One of the few drug-development areas promising success has been personalized medicine, but until recently, using genetic tests to narrow a drug's market has seemed more like volunteering for a pay cut than capitalizing on a big opportunity.

Now, industry leaders are realizing they can no longer depend on drugs that are effective in only a fraction of patients. Payers, particularly government gatekeepers in Europe, increasingly look askance at new products that, on a population-wide basis, deliver questionable benefits. Drug companies have, in some cases, agreed to take on the risk themselves, by charging government payers only for patients who benefit from a drug. So, selling therapies to a subset of patients likely to benefit suddenly looks like a good business.

"Pharma has been incentivized by their repeated failures to find blockbusters to develop segmented therapeutics," Abrahams said. "By necessity, they're searching for companion diagnostics and drugs."

With a few major drugmakers leading the way—and racking up financial successes with targeted drugs—more pharma companies are realizing that even small groups of patients can turn products into blockbusters. If a targeted drug proves itself markedly superior to previous treatments, it can support higher prices and persuade doctors to adopt it quickly.

Other forces are at work as well. Laden with debt and suffering from declining tax revenues, governments around the world face increasing pressure to cut costs. Three years of anemic economic growth hasn't helped private-sector employers handle rapid increases in healthcare spending, either. So, as drug companies have looked to targeted therapies to refill pipelines and reverse sales declines, government and private-sector payers are hoping they can save money by treating a small group of patients likely to benefit from a drug, rather than underwriting the cost of treating everyone, including people who will find the treatment useless. "The reality is today, of the drugs a physician has in his armory, those will provide a benefit to only half of the patients," Roche Molecular Diagnostics CEO Paul Brown told the *San Francisco Business Journal*. "With that in mind, the logic behind personalized health care is pretty compelling, whether it's from a patient perspective, a payer perspective or a societal perspective."

Even for many doubters, the case for targeted drugs and companion diagnostics now outweighs the arguments against them. Or, in the language of drug development, the benefits outweigh the risks. Not every drugmaker is ready to act boldly on that knowledge. But some are, and a few have leapt in completely. "Some companies say they agree in principle, but they don't think they have to do it today. Some won't do it until they are forced to, until the payers say they won't pay unless they do," said Chris Wadsden of PricewaterhouseCoopers. "Some companies are leaders, and others are followers. It's interesting to me how many are comfortable being followers."

CO-DEVELOPMENT: LESSONS LEARNED?

There's a horror story people in the field often repeat, using the name of the drug like a warning flag. It's the cancer treatment Omapro (omacetaxine), originally developed by Australia's ChemGenex. One of the company's Phase III trials, testing omacetaxine for use in patients with chronic myeloid leukemia who didn't benefit from Novartis' Gleevec—and who also had the T315I mutation, which confers resistance to tyrosine kinase inhibitors. To screen patients for the mutation, researchers used different technologies, depending upon location.

When an FDA advisory panel reviewed ChemGenex's application for Omapro, agency reviewers pointed out several problems, two directly related to the diagnostic. First, more than a third of patients in a key trial did not have a confirmed T315I mutation when they enrolled. Second, and more importantly, FDA didn't like the trial's differing assay methods. No bridging study showed that the two assays worked similarly and consistently. Specifics on their performance—sensitivity, detection ability, reproducibility, and so on—weren't proven or even known. And ChemGenex hadn't offered information about the tests to FDA's Center for Devices and Radiological Health.

"The lack of having a uniform in vitro diagnostic test creates uncertainty about patient selection both in this trial and, more importantly, in a post-approval setting," FDA reviewers wrote. "If a patient does not harbor the T315I mutation but is falsely identified as [such], the patient may not receive more effective, less toxic therapy [than omacetaxine], such as dasatinib or nilotinib. Conversely, patients with a false negative ... would receive an ineffective therapy."

The uncertainty about the tests—and, by extension, about patient selection—led FDA to ask its expert panel for an unusual piece of advice. Rather than requesting a vote on approval, it asked the members to consider whether FDA should require a "well characterized in vitro diag-

nostic" to identify patients with the T315I mutation, whether that device should be reviewed by FDA before the drug was approved, and whether the diagnostic should be correlated to clinical trial results before approval as well.

The committee voted 7-1 in favor.

That the FDA had put such a question to its oncology committee was a surprise in itself. That the committee voted "yes" sent ChemGenex stock reeling. When FDA decided to follow its committee's advice, the stock suffered further. And the agency's meaning—not only for ChemGenex in particular, but developers of targeted drugs in general—was unmistakable.

"FDA has emphasized now in this new era of personalized medicine [that] it is important to make sure that the diagnostic tests that are out there in the market are validated and reproducible," ChemGenex CEO Greg Collier said after the advisory committee vote. "And that was a clear message ... the FDA has made generally to the public."

ChemGenex has since been working with FDA on a different application to get omacetaxine approved with an indication as a third-line treatment in patients who've failed to respond to two tyrosine kinase inhibitors, such as Gleevec and Sprycel. ChemGenex plans to file that application this year. In Europe, it withdrew its application for omacetaxine use in patients with the T315I mutation and told regulators it planned to submit a new application similar to its planned NDA in the U.S. Neither of those indications mentions the T315I mutation, so the prerequisites are clinical. No diagnostic test required.

The original FDA application remains open. ChemGenex said it was "continuing its discussions" with FDA's CDRH on approving a T315I diagnostic test. Since then, the company agreed to be acquired by Cephalon in a $163 million deal—and Cephalon, in turn, agreed to be bought by Teva Pharmaceutical Industries.

Whatever the final outcome on omacetaxine, ChemGenex has done the healthcare industry a service: Its experience with the FDA put drug and diagnostic developers on alert. "With a growing number of oncology drugs in development that target patients with defined genetic mutations," Datamonitor concluded, "the [advisory committee] vote highlights the importance of developing and validating an appropriate diagnostic to guide patient selection prior to regulatory submissions."

FDA GUIDELINES, INTERPRETED

Knowing that a targeted drug needs its companion diagnostic for approval is one thing; developing the two in concert is another. Yet, co-development is exactly what the FDA wants most, as its recently proposed guidelines for targeted drug development emphasize.

"In most circumstances, if use of an in vitro companion diagnostic device is essential for the safe and effective use of a therapeutic product, the IVD companion diagnostic device and therapeutic product should be approved or cleared contemporaneously by FDA for the use indicated in the therapeutic product labeling," the proposed guidelines state, adding, "FDA intends to issue approvals or approval and clearance for both products at the same time."

In this way, Herceptin was a textbook example, development-wise. The FDA's new guidelines—which ChemGenex executives no doubt wish they had been able to read several years ago—set out a regulatory process that, in its bare bones, mimics the Herceptin approach. So do the European Medicines Agency's nascent rules. The result both agencies are aiming for is the same: A targeted drug and its companion diagnostic, approved on the same day.

"These proposed guidelines support the development of innovative new targeted medicines and their corresponding diagnostic tests and are intended to provide manufacturers with greater predictability," Dr. Jeffrey

Shuren, director of the FDA's Center for Devices and Radiological Health, said in a statement when the guidelines were released. "It is the agency's goal to help stimulate early collaborations between drug and device makers so they can develop the best medical products for treating patients."

The key points were these:

- **FDA likes personalized medicine.** Drugs that require companion diagnostics are growing more common, and the agency wants to support that. "FDA encourages the development of therapeutic products that depend on the use of approved or cleared IVD companion diagnostic devices," the guidance states. Diagnostics may identify patients likely to benefit; they may identify those at increased risk for serious adverse reactions; they may monitor response so that treatment can be adjusted accordingly. The key phrase is "depend on." Diagnostics that are merely useful, rather than a determining factor in safe-and-effective use, don't qualify.

- **The "depended on" diagnostic has to work properly.** If the results from a diagnostic device determine the course of patient treatment, "[i]nadequate performance of an IVD companion diagnostic device could have severe therapeutic consequences." (Here, the FDA predictably uses Herceptin as an example. Not only is the drug ineffective in HER2 negative patients, but it also can trigger severe side effects. So, it's important to use an IVD device to identify only patients who could benefit.)

- **FDA oversight is necessary.** Because of the potential treatment consequences, FDA needs to review the diagnostic for safety and efficacy, provided the drug is safe and effective only when used with the test.

- **Risk determines the pathway.** The risk level, together with risk-mitigation controls, determines whether an IVD needs a premarket application or a simpler 510(k) clearance. The general feeling? Most

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Co-Development: The "Right" Way to Do It

BY MYA THOMAE

From a regulatory strategy standpoint, there's really no question: co-development is nearly always the ideal approach to a successful companion diagnostics (CoDx) application. What may be less obvious is why such an approach works best. Exploring that requires understanding how FDA approaches this type of application.

A CoDx approval requires two applications: one for the drug and one for the diagnostic that informs its use. The applications are reviewed in parallel at two different "centers" at FDA, typically CDER (drugs) and CDRH (devices). Because drugs and devices differ, these centers have subtly different policies. Understanding those differences is one key to achieving regulatory success.

One of the most confusing differences relates to CoDx labeling requirements. Drug labeling typically references a type of test, but diagnostic labeling must reference a specific drug. For example, the labeling for Zelboraf (vemurafenib) states that it is "indicated for the treatment of patients… as determined by an FDA-approved test." In contrast, its companion test is "intended to be used… for treatment with vemurafenib."

This difference can obscure a key challenge in diagnostic approvals: demonstrating clinical utility. CDRH does not typically consider measurement of a biomarker or analyte to be clinically useful by itself. Instead, CDRH considers a result to have clinical utility when clinical trials demonstrate that the result is useful (e.g., when used in conjunction with a therapy).

Thus, clinical trials should ideally demonstrate the clinical value of both the therapy and the diagnostic that will be approved in parallel. Failure to demonstrate the value of both may lead to a delay in the drug approval while additional studies are conducted on the diagnostic. Practically speaking, device development should be completed and the regulatory readiness of the device should be vetted prior to its use in pivotal trials.

Allowing (or expecting) the diagnostic to change significantly after trials will lead to time-consuming "bridging" studies to show that the results of the "new" test is equivalent to those provided by the test used in clinical studies. When multiple versions of a test are used during a trial or the studied diagnostic is unapprovable, a painful paradox can arise: there will be strong evidence that a companion diagnostic should be used, but insufficient evidence to support the approval of any specific product.

Both partners' applications must succeed for either one to succeed, thus it behooves both partners to work together as closely as is practical. Building partnerships earlier and embracing co-development provides the best opportunity to assess the development and regulatory readiness of a diagnostic partner in advance and greatly improves the chances of pivotal trials producing useful results for both products. CoDx projects are complex by nature, but taking the co-development approach can provide the best chance of success.

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IVDs will require a PMA, at least for now, because most of the companion-diagnostic action is happening in treatments for life-threatening conditions, such as cancer. "If used to make critical treatment decisions, such as patient selection, treatment assignment, or treatment arm, a diagnostic device will generally be considered a significant risk device," the guidelines state.

- **Existing diagnostic tests need FDA approval, too.** If an IVD is already on the market, but the diagnostic maker intends to sell it for a new use as a companion to a new drug, the agency must review it. That's because the new use would be "a major change ... raising new or additional questions of safety and effectiveness."

- **Co-development is the way to go.** "In most circumstances, if use of an IVD companion diagnostic device is essential for the safe and effective use of a therapeutic product, the IVD companion diagnostic device and therapeutic product should be approved or cleared contemporaneously by FDA," the guidelines state. That approval should ideally be based on evidence about the IVD's clinical performance and significance generated from the clinical trials of the therapy that depends upon it.

- **Drug- and device-makers should meet with both CDER and CDRH. Early.** "FDA encourages sponsors... to request a meeting with both relevant device and therapeutic product review divisions to ensure that product development plans will produce sufficient data," the guidelines state early on. Then, just to make sure readers get the point, the entire document ends this way: "FDA strongly encourages sponsors considering developing either of the products discussed in this guidance to request a meeting with both relevant device and therapeutic product review divisions as early in development as possible."

- **Non-exclusive labeling.** Information about the approved IVD will not

be included in the corresponding drug label. The therapy's label will identify "a type of FDA approved or cleared IVD companion diagnostic device (i.e., the intended use of the device), rather than a specific manufacturer's IVD companion diagnostic device." This, the FDA says, is to "facilitate" development of more than one FDA-approved companion diagnostic of that type. On the diagnostic's label, the companion therapy will be specified by name, or, sometimes, by drug class.

- **Ideal conditions don't always prevail.** "FDA recognizes there may be cases when contemporaneous development may not be possible," the guidance states, going on to set forth some potential scenarios. One, FDA might choose to approve a treatment even if its IVD isn't yet approved, if the drug treats a "serious or life-threatening condition" and no alternative treatments are available, and the benefits of using the diagnostic test are so impressive, they outweigh the risk of lacking FDA approval. Two, FDA may choose to approve new labeling on an existing drug, to stipulate use of an IVD, even if no approved or cleared IVD exists—but only if the benefits of doing so are quite "pronounced." The guidelines set out labeling examples for various permutations of these two scenarios.

NOT-SO-IDEAL DEVELOPMENTS

Apparently, the FDA has learned something from the grab bag of drug-and-diagnostic pairings that have evolved over the past decade. Since Herceptin, other targeted drugs have hit the market, with only a handful co-developed and co-approved with their companion diagnostics. It's instructive to consider these other examples, because while the Herceptin approach may be the ideal, the real world is often much messier than that. FDA's new IVD development guidelines acknowledge this, allowing that drugs and diagnostics might not always follow the simultaneous-approval model.

Consider Novartis' Gleevec, a highly successful drug that has revolutionized leukemia treatment. It's intended for use in patients who test positive for the Philadelphia chromosome. It was so successful in beating back chronic myeloid leukemia that FDA fast-tracked its approval, clearing it for sale just 10 weeks later. No diagnostic test was approved at the time. So, Gleevec's initial indication didn't refer to the patient's Philadelphia chromosome status. The diagnostic tests followed, not only for Philadelphia chromosome status, but also for tracking related BCR-ABL transcript levels, which are used to monitor Gleevec treatment. In October 2010, Novartis teamed up with Cepheid to develop a standardized BCR-ABL monitoring test, saying that variability in current lab-developed tests makes results difficult to compare test-to-test. If the FDA approves the Novartis/Cepheid approach, it would be the first agency-cleared BCR-ABL diagnostic test, the companies said.

Or look at Selzentry, the Pfizer HIV fighter targeted at the strain of the virus known as CCR5-tropic HIV-1. During clinical trials, the company used the Trofile assay to identify patients with that form of HIV. When the FDA approved Selzentry in 2007, its first label included the somewhat cryptic instruction that "Tropism and treatment history should guide the use of Selzentry." That was later changed to read, "Tropism testing is required for the appropriate use of Selzentry." The agency didn't require Pfizer or its lab partner, Monogram BioSciences, to put the Trofile test through FDA review. The assay remains the accepted screen for potential Selzentry patients.

Then there's KRAS, a gene that's proven useful at predicting colorectal cancer's response to Amgen's Vectibix and Bristol-Myers Squibb/ImClone/Merck KGaA's Erbitux. Its utility as a biomarker only surfaced after both drugs were approved—along with companion diagnostics that tested for another genetic quirk.

The two drugs are EGFR inhibitors, so early efforts to select colorectal cancer patients focused on tests identifying people with the EGFR muta-

tion. Each of the two drugs was approved concurrently with its own diagnostic test aimed at flagging patients with EGFR mutations. But after some time on the market, the KRAS biomarker surfaced. Research data started to accumulate suggesting that KRAS might affect response to the EGFR drugs. One study found that 45% of patients with KRAS mutations did not respond to Vectibix at all. "There was no ambiguity," Amgen development executive David Chang said at the time. "People with mutant KRAS shouldn't be treated [with Vectibix]."

Oncologists began to turn to other drugs. Amgen saw Vectibix sales start to erode, with first-quarter 2008 sales amounting to $34 million, down from more than $50 million the previous year. European regulators actually acted on the research, approving Vectibix for a new indication in advanced colon cancer, but only in patients with the unmutated form of KRAS. The EMA gave Erbitux a new approval for front-line colon cancer treatment—also only in patients without a mutated form of KRAS.

Then, at the American Society of Clinical Oncology meeting in 2008, more data went public, and KRAS became the talk of the session. In one study, researchers found that 36% of patients have a mutated form of the KRAS gene that rendered them unresponsive to Erbitux. So, the drug should be restricted to those with the "wild-type" or unmutated form of the gene, the study authors said.

Merck KGaA had sponsored the study, so the drugmakers were already on board with that idea. "It will reduce the size of the market," John Johnson, CEO of Erbitux maker ImClone, now part of Eli Lilly, told the *Wall Street Journal*. "But we want the physician and patient to know who is likely to" benefit from the drug.

ImClone and Amgen went to FDA asking for new restrictions on their drugs. They cited the recent KRAS studies and requested label changes that would require genetic screening before patients could use Erbitux or Vectibix. In advance of the meeting, Amgen CMO Sean Harper said, "We

believe the data ... that will be presented today indicate that the benefit-risk profile of Vectibix is improved by restricting use to those patients ... whose tumors have wild-type KRAS genes." ImClone's Hagop Youssoufian went further: "The data are … nothing less than transformational," he said.

The FDA's advisory panel didn't agree. It deemed the data—some of it based on retrospective analysis of earlier trials—inadequate to determine whether KRAS was really to blame for the non-response. It recommended the agency require new studies and new data before changing the drugs' labeling.

The companies would eventually get their way, but not before most everyone else in the cancer field started acting on the KRAS news, without direction from the FDA. Labs quickly began offering KRAS testing, and soon, clinical recommendations from two key organizations helped persuade payers to jump on the bandwagon. The National Comprehensive Cancer Network, which publishes influential treatment guidelines, revised its protocol for metastatic colorectal cancer in November 2008, to recommend that all patients' tumors be analyzed for KRAS status—and that EGFR inhibitors be used only in patients with wild-type KRAS tumors. The American Society for Clinical Oncology issued a "provisional clinical opinion" in April 2009, recommending that patients eligible for treatment with EGFR drugs have their tumors tested for KRAS mutations. Patients with mutations "should not receive anti-EGFR antibody therapy as part of their treatment," ASCO said. Of course, payers liked the fact that KRAS testing could save money and time otherwise spent on expensive cancer drugs that didn't work.

Then, in July, the FDA followed through. Vectibix and Erbitux got new labels saying that their use "is not recommended for the treatment of colorectal cancer with" KRAS mutations. The labels also included the retrospective analysis of trial data, showing that anti-EGFR monoclonal antibodies "are not effective" for patients with the KRAS mutations.

"KRAS wasn't the drug target, it was downstream," points out Trusheim of MIT. "They needed a couple of years of real experience in humans. The FDA-idealized approach in that case doesn't seem to be quite feasible."

The EGFR-to-KRAS scenario illustrates several issues facing companion diagnostic development, and not only the fact that FDA's "contemporaneously developed" ideal is just that. It also reminds us that cancers—and other diseases drugmakers want to target—are complicated, and the science around them is constantly evolving. Regulators sometimes have to act on incomplete information. Timelines for biomarker discovery, drug research, and diagnostic development don't always mesh neatly. Clinical practice can differ radically from FDA instructions. And FDA faces the unenviable task of regulating a field that's changing too quickly for even the experts to keep up. This, at a time when the agency is perennially understaffed, underfunded, and pressed by lawmakers, industry and the public to police manufacturing at home and abroad, but not too much; speed up approval of new drugs, but without blessing any drug that might turn out to be unsafe; and forge new regulatory trails for biosimilar drugs, social-media marketing, and, of course, personalized medicine, quickly yet comprehensively, in ways that are industry-friendly and cost-conscious, but not so much so that public health and safety are compromised.

"The FDA is trying—they want to move," Roche's Brown told the *San Francisco Business Journal*. "But I don't think they're able to move at the pace of science and clinical practice. They're aware of the issues, but they can't keep pace."

So, one can understand the frustration among the drugmakers and diagnostics companies that knew the FDA had been working for years on regulatory guidelines for their targeted development projects. Everyone from academics to consultants to think tanks to doctors to trade associations to the Personalized Medicine Coalition agitated for action, but none was forthcoming until the proposed guidelines made their debut in July of this year.

That release kicked off a 60-day comment period—and there was plenty of comment. Some saw the guidance as a positive sign in itself. "It's a milestone," Joshua Cohen of Tufts said. "When FDA comes out with these guidances, it serves as a milestone, a benchmark, and the industry now can say, for instance, Xalkori is consistent with FDA guidance." The PMC's Abrahams called the guidelines "a good first step." His colleague at the PMC, Public Policy Director Amy Miller, said, "People in the industry are gratified to see FDA say, 'Here's how we're going to do this. Talk to us, early and often, all the time.'"

Others cast a more skeptical eye on the FDA document. They wanted more specifics about the FDA's plans to work across CDER and CDRH boundaries. They were unsatisfied by the labeling guidelines, because they lacked any suggestion of exclusivity for the IVD that jumped through all those regulatory hoops during the co-development process. Sponsors questioned the FDA's power to enforce the stipulation of "an FDA-approved test" for use with the targeted therapy—and if the FDA had the power, just how did it plan to follow through? Who could monitor which diagnostics were being used for which drugs?

And then there's the fact that the guidance did not address lab-developed tests at all. In July 2010, FDA officials promised that LDTs would soon be regulated. Since then, the agency has issued some broad statements about just what those regulations might entail. Obviously, companies need to be able to rely on consistency and clarity in what they are being told.

"If it's the plan to do so, then they need to do it in, ideally, one very clear guidance," Rina Wolf of XIFIN said. "There's the specter of regulation being held over our heads, but we're not seeing it being applied consistently yet, and we can't get an answer on when it will happen."

Meanwhile, however, development projects are moving forward. Despite the FDA shortcomings that Roche's Brown has pointed out, the company wrapped up its co-development project in record time, winning approval

ahead of the agency's deadline. "It's been very much about getting the two R&D programs (RMD and Plexxikon) in sync very early on and getting the technology in sync with the two arms of the FDA for the test," Brown told the *Business Journal*. "This close collaboration has been very important. It becomes very symbiotic."

Abbott and Pfizer had a similar experience at the agency: The two companies would submit their approval applications to different FDA divisions, but they approached the FDA together, said Kathryn Becker, president of Abbott Molecular's oncology business. The companies met jointly with representatives of CDER and CDRH. "The FDA was supportive in pulling meetings together to review processes," Becker said. "Overall, we had fantastic support from FDA."

The general view of FDA guidelines is that they tend to follow practice rather than blaze new trails. The IVD companion diagnostic guidelines are no exception. What rules FDA put forth were based on requirements it had already been imposing in experience. But putting them down in black-and-white, and releasing them to the public, might have inspired the agency on its own contributions to co-development. It looks as if Roche's diagnostics and pharma divisions, along with Abbott and Pfizer, not only served as guinea pigs for FDA's incipient rules, but may also have helped accelerate the agency's evolution toward better support of personalized medicine.

THE DEVELOPMENT DISCONNECT

The goal of any co-development project can be boiled down to this from a 2007 *Nature* paper co-authored by Mark Trusheim and two of his MIT colleagues: "A viable stratified medicine" that possesses "a sustainable, meaningful therapeutic benefit that exceeds the costs of identifying the appropriate patients."

Well, that's a simple statement describing a straightforward end prod-

uct. Unfortunately for drugmakers and diagnostics companies, getting there is a lot more complicated. When companies collaborate on a co-development project, the overall goal—coming up with a "viable stratified medicine" along with a means of identifying patients for it—can find itself muddied by the very different economic underpinnings of the drug business versus the diagnostics business.

"There's a business model challenge in terms of bringing drugs and diagnostics together," said the PMC's Abrahams. "Diagnostic development projects tend to be on a short time line and are low-cost, but to align them with high-cost drug development can be problematic.

"These are different kinds of people with different expectations, different technologies and different backgrounds," Abrahams said. "It's not easy to bring these camps together."

One problem, observers say, is that some drug companies don't understand the diagnostic development process. They think a test may require 6 months, rather than a couple of years, to develop. They figure a test may require only a few performance studies. That may be enough to use a test in research mode, but to get to market, a diagnostic company has to gauge test sensitivity, run interference testing, develop instrumentation in parallel with manufacturing, show reproducibility of results, and so on. "Some drugmakers think, 'What's the big deal? You draw blood and test it and you're done,'" Myraqa's David Kern said. "They don't understand the other things that go into developing a diagnostic."

The time and cost involved in developing a test are substantially less than in developing a drug. But the mismatched timeline can be a disadvantage for both sides. A drugmaker may not be sure that a diagnostic test is crucial to a project until the latter stages of development. So, the company may be understandably reluctant to spend money on diagnostics development, either with a partner or in-house. That means bringing in a diagnostics partner late in the game, potentially delaying

approvals—and definitely raising the risk of friction between partners as the drug company pushes for a companion diagnostic, on the double. If a drugmaker realizes too late that it needs to commercialize the lab test used to select patients, the company has to find a diagnostics partner that wants to take an application to the FDA, and then hope that researchers saved all their samples, and further hope the results are the same as in the clinical trial.

If the pharma company teams up with a diagnostics company early on, the latter may find itself with a viable test that it can't sell immediately, and may not ever. "You might have to wait to commercialize your diagnostic for two or three years or more before you find out whether the drug is going to work," Myraqa CEO Mya Thomae points out. "From the diagnostics point of view, you strike a deal with pharma to be paid for the development work, and then hang on while the drug company is going through its process. That's where it doesn't match up with diagnostics and pharma."

"It's almost serendipitous to get the two to come together at one time," Chris Wasden of PricewaterhouseCoopers says.

The low cost-high cost dichotomy on the development side comes along with a low price-high price dichotomy on the commercial end. Diagnostic development can be in the tens of millions rather than the hundreds of millions or even billions for drugs. Still, with a relatively low-priced diagnostic to sell, there's not enough potential revenue to make projects worthwhile for some smaller diagnostics companies. Large developers, such as Abbott Molecular, have established platforms that support hundreds of tests, so they often don't have to begin with a ground-up approach. Adding another low-priced diagnostic to the catalog isn't an enormous revenue-raiser in itself, Trusheim notes, "but over time, it's a very good business for them. Where it's more of a problem is with a small diagnostic with one or two novel tests."

And then there's the problem of market size. Some targeted drugs are directed at small subsets of patients. That can work for a drugmaker that can charge $50,000 or even $100,000 for a course of treatment. But the potential revenue stream is a lot smaller for a diagnostic test that, in the best-case scenario, might sell for a few thousand, but might be priced at only a few hundred dollars. "Drugmakers have to understand that they shouldn't expect a diagnostic company to get excited about 4,000 tests a year when some are running hundreds of thousands of tests a year," Kern said. "Drug companies can look at a small market and say, 'Wow, if we hit this we can be really successful.' And when you turn around and look at it from the diagnostics side, at 4,000 tests a year you're practically operating under the Humanitarian Device Exemption. They're thinking, 'How am I going to make any money off this?'"

Beyond the number of patients, there's the question of frequency. Will each patient submit to the diagnostic once? If so, then the test-maker can earn revenue only off that one-time test, whereas the drugmaker treating the selected patient will be selling its product to the patient for months, years, or even longer. Even when a test has to be given to 20 patients to find one eligible for drug therapy, the balance of potential sales is heavily weighted toward the pharma side. "Depending on what kind of drug you're looking at, the drug company may be looking at selling the drug for a lifetime," Thomae said. "But if a diagnostic is doing genotyping, that's a one-time result, and that's all the company gets. It's a one-time reimbursement, where the drug company can sell the drug for many years to the same patient."

"The challenge for some of these diagnostics companies, if you're talking about a drug going toward a small market, the drugmaker can make a lot of money off of it, but from the diagnostics perspective, it's, 'What's in it for me?'" Kern said. "The diagnostic people will test the patient once. It's a big challenge for a lot of these relationships."

Finally, there's the question of exclusivity. Drugs in development are protected by patents, and sometimes are eligible for additional exclusivity from the FDA. No other company can enter the market with a competing drug until the patent expires (or a court fight is resolved in its favor). Diagnostic tests don't benefit from the same exclusivity. On drug labels, the brand name of a companion diagnostic isn't specified. The label only mentions the type of test required. In fact, in its recently released development guidelines, FDA says the labeling is kept open to encourage development of additional tests, to broaden access to the right diagnostics as much as possible. The more tests available, the better for the drugmaker; easily available diagnostics means easier access to the targeted drug. And as MIT's Trusheim points out, "Without exclusivity, it's very difficult for a diagnostic company to price to value."

Without legal exclusivity, one threat always looms: the possibility of a lab-developed test. Labs can knock off screening tests for targeted drugs, essentially becoming almost-instant generic competitors. "If we have put a test through the FDA, then everyone who uses it should be 100% comfortable. We go through the hoops," Roche's Paul Brown told the *San Francisco Business Journal*. "But the problem is any lab out there can make its own homebrew test. It's nowhere near as stringent as what we have to go through with the FDA."

Thomae agrees. "There's the risk that you go through a full validation under FDA rules, via a PMA, and you get out onto the market and find a lab-developed test can do the same thing without FDA approval," she said. "We need to consider whether that uneven regulatory ground is a problem for this diagnostic area."

It's true that FDA intends to link targeted drugs only with agency-approved diagnostic tests. Abbott Molecular's Becker points out that the labeling for a targeted drug and its companion diagnostic are designed to reinforce each other. "FDA is certainly helping to support the fact that

the FDA-approved test is the only validated way to identify the patient population most appropriate for these therapies."

But it's as yet unclear how the agency plans to enforce that specification, especially given the fact that promised regulations covering lab-developed tests haven't yet appeared. In the case of Zelboraf, the targeted melanoma drug from Roche, patients are targeted using a screening for the BRAF genetic mutation. The diagnostic test from Roche Diagnostics was approved on the same day as the drug. But as Myraqa's Thomae points out, "Other labs are offering BRAF testing. So far the FDA has not shut down those folks."

"It's not clear that FDA has any enforcement power even if they put the name brand on the label," MIT's Trusheim said. Rina Wolf of XIFIN, who often works with lab-developed tests, says the agency believes it does have the power, but she questions how officials would exercise it. "The FDA does have the right, they feel, to exercise individual judgment and could send a 'come and talk to us' letter," Wolf said. "Right now that pathway is very unclear."

What's more, the agency's resources are already strained. FDA is under political pressure to better police the safety of drugs and drug ingredients, to inspect factories around the world, to speed up approvals for branded and generic drugs, and to improve its diagnostics-approval pathway, not to mention develop guidelines for biosimilar development, social-media marketing, and additional rules for personalized medicine. Electronic tracking via payer databases isn't possible; most payers don't require proof that a diagnostic has been administered before a targeted drug is prescribed, Tufts' Joshua Cohen notes. Billing systems don't code for specific tests, but for broad testing categories. "It will go in under the type of test, so FDA wouldn't know whether it's, say, a FISH test for ALK or for HER2," MIT's Trusheim points out. "It couldn't be designed more effectively to thwart any kind of enforcement."

Plus, who at FDA would handle the job? "The industry can fairly question the FDA's ability, from a human resources perspective, to really do this in a fair and timely manner," Wolf said, "because they are seemingly short of appropriate staff already."

For all these reasons, drugmakers have been offering financial incentives for companion diagnostics companies to put time into a project. If the market is small, and the potential ROI is correspondingly small, then kicking in development costs is the least a pharma company can do, experts say. Assisting with marketing and commercialization costs might have to come on top of that, depending on the project. For Xalkori and its ALK assay, Pfizer shared development costs, but the two companies are each charged with marketing their own product. Abbott Molecular will focus on promoting its test to pathologists, Becker said, while Pfizer will handle promotions to oncologists. Abbott might target some promotions toward medical centers specializing in non-small cell lung cancer, too. "Where appropriate we will work together on key programs," she said.

Whether it's simply development cost-sharing or more than that, some drugmakers would rather do without the added cost, especially companies that aren't 100% convinced that targeting drugs to smaller populations is a smart business model. In spite of all the talk about a new era of targeted blockbusters—and the math that shows premium-priced drugs restricted to subsets of patients can easily surpass the $1 billion threshold—some companies are putting only halfhearted effort into pairing their prospective drugs with diagnostic tests. A few privately say they'll have to be dragged into personalized medicine, and they'll kick and scream all the way, Wasden of PwC says.

"We've seen some pushback from drug companies to the idea that a diagnostic has to be part of their solution," Wasden said. "They don't want to be bothered by it."

SHARED CHALLENGES

Some obstacles have nothing to do with differences between drugmakers and diagnostics companies. Intellectual property is one big hurdle. As Wasden says, the patent question is almost wide open. Are individual genes patentable? Complex genetic relationships? Algorithms? Pathways? "What is actually patentable in genetics today?" he asks. "There are a lot of different points of view on this."

Because patent protection means pricing power and long-term revenue, it's difficult to determine whether some development projects are worthwhile. When you add in the questions about regulatory clearance and reimbursements, it's enough to spook investors. "These are issues that in investors' minds, in executives' minds, make a difference when they're making a decision to pursue a project," Abrahams points out.

To put it simply: "There's a lot of frustration," Wasden says.

Companies themselves are devoting more resources to investigating biomarkers and looking for ways to stratify patient populations. According to a study by the Tufts Center for the Study of Drug Development, the average increase in investment in personalized medicine was almost 80% between 2006 and 2010. The expected increase, companies said, between 2011 and 2015 is somewhat less than 60%—still a high figure, and dollarwise, perhaps about the same, given the larger baseline. That average includes some high-investing outliers, however: The median increase in investment was around 30% from 2006 to 2010, and is expected to be a bit less than that over 2011-2015.

"We've never had more insight into genetic pathways and the genetics of tumors than we do now," Gary Gilliland, Merck's chief of oncology R&D, told the *Wall Street Journal*. That knowledge has touched off "an end-to-end change in the way we develop new drugs for cancer patients and the way we do business."

As the Tufts study points out, personalized medicine requires "a significant investment in ancillary technologies," including equipment and know-how to perform micro-sequencing and to investigate and validate biomarkers. The sheer magnitude of resources required has some drug developers teaming up with multiple partners, including academic medical centers. Some necessary resources remain scarce, however. Consider tissue samples for biomarker development. They're hard to come by in some cases, and even when tissue samples have been properly stored and labeled, developers don't always have legal access. And basic scientific hurdles stand in the way, too. Animal models, for instance, are notoriously poor, so biomarkers can't truly be validated until patients are treated, Trusheim says.

So far, biomarkers are used most often in the early phases of drug discovery and development, with all the companies participating in the Tufts study reporting that their discovery strategies include biomarkers and targeted therapies. The companies are using biomarkers to evaluate compounds they're working on. Some are requiring personalized medicine endpoints for all trials, and they use the endpoints to determine whether to go forward with development, Tufts found. But only a few companies—a little more than 20%—require all in-development compounds to have an associated biomarker. And many noted that their primary goal in developing biomarkers is to generate more information about their potential products. Taking a biomarker all the way through to clinical use isn't as important.

Even companies that have been aggressively moving forward into personalized medicine have their fears about biomarkers. Ruediger Weseloh, senior director at Merck Serono, acknowledges that companion diagnostics are a driving force in drug development. He's seen growing pressure within the company to deliver biomarkers that can measure a drug's effectiveness. "Diagnostics is going everywhere and there is no way around it now," he said at BIO-Europe last fall.

Along with that commitment, however, is the lingering worry that developing targeted drugs will not only cost money, but threaten the viability of prospective drugs. "[T]he scary part is thinking there is a biomarker out there right now that will suddenly appear," Weseloh said, "and slash our lead drug candidate revenue potential by 90%."

The risk on the diagnostics side isn't insignificant, either. Companies can find themselves at the end of a failed Phase III drug trial, holding a diagnostic test that suddenly has no clinical utility. "One of the challenges in doing deals for companion diagnostics is how to share the risk of developing a companion diagnostic for a drug that may fail," John Freshley of Compendia Bioscience has suggested. "Companies need to be prepared to deal with this situation."

But, at bottom, the biggest shared obstacle is the sheer challenge of developing biomarkers, diagnostics and targeted drugs. "The biomarker is not enough," Novartis' molecular diagnostics chief Michael Nohaile told *Life Science Leader*. "It's the first, and in many ways, the most critical step, but you also have to have a very high-quality, reproducible testing system that allows it to work, and that is actually quite hard." Indeed, one of the most often repeated quotes about these development projects comes from an executive at Novartis' cross-town rival, Roche. "The reality of personalized medicine for a pharmaceutical company is that they must hit the jackpot twice," Christian Meisel, who heads up Roche's oncology and translational medicine business. "First, with an effective drug therapy, and then with the companion diagnostic to prove that effectiveness."

SETTING UP A PARTNERSHIP FOR SUCCESS

Still, there are ways that pharma and diagnostics makers can improve their chances with a co-development project—or at least minimize the fallout if the project fails. The first: Setting up the partnership. Careful selection of a partner is paramount. Drugmakers need to choose diagnostics makers that understand the market and understand what it takes to

get a product through the FDA, Kern says. "Not just any diagnostic partner will do," he says. "Brilliant scientists and researchers who've formed a diagnostics company may not be business-savvy."

Even if it's between two units within the same company, the initial agreements and communication are crucial. Abbott's Becker says her company draws upon its experience with biotech partnerships when setting up collaborations with other drugmakers. "One of the first things we do is to get our teams together, set up a steering committee, and work to understand everyone's roles and responsibilities. We need to be able to communicate at all levels with our partners to be successful."

Partners also have to agree on the finances—and on the assumption of risk. There are a variety of business models for that, most of them confidential. As *Nature Reviews Drug Discovery* reported in May, Genomic Health offers two examples. In its fee-for-service model, drugmakers pay to use its clinical platforms; in return, the pharma company owns and controls everything. "Then there's the collaborative zone, where maybe a riskier or unproven drug is involved and so we are hesitant to spend a lot of money developing a diagnostic in case the drug fails," Executive Chairman Randy Scott told the journal. "There's going to have to be some shared risk-taking there."

JOIN FORCES EARLY

The next bit of advice has been codified by the FDA: Pair up early. Up to now, it's been common for drugmakers to decide to partner with a diagnostics maker toward the end of Phase II or even during Phase III trials. But that's far from optimal. A study in *Personalized Medicine* found that companies created the most long-term value when they partnered for co-development early on. "The greatest gains were realized the earlier the planning for companion diagnostics was incorporated into the development cycle," the study authors wrote.

Phase I isn't too early; in fact, some experts who've worked on successful diagnostics projects say drugmakers should begin thinking about potential diagnostic partners during Phase I. By Phase IIA, proof-of-principle data should be on the way for the diagnostic, and by the time Phase II trials begin, a diagnostic test should be in development so that a final version of the assay can move with the drug into Phase III.

"You need to have clinical trials with a companion diagnostic so you're not doing a Phase III without a companion diagnostic," Wasden said.

Using a lab test in Phase III can complicate things for co-approval at the FDA, as the Omapro experience illustrates. FDA raises questions about any change in a lab test during a trial. That's not to say it can't be done: Pfizer worked with Monogram Biosciences on the Trofile assay to identify HIV patients appropriate for Selzentry, and has supported the company with follow-up research as competitors surfaced. Lab tests can also become in vitro diagnostics; some labs have worked with drugmakers during trials, then volunteered to develop the necessary data to take it into the FDA for approval. Either way, if the goal is to standardize a lab-developed test, as Pfizer's Selzentry partner did, care is needed, especially in light of the FDA's pledge to regulate more lab-based diagnostics. "If you're developing a new test, be very aware of what the FDA requirements are so that you're following [Quality System Regulations] to the best of your ability," Wolff says. "That way, should the FDA take action, you don't have to totally reinvent your processes. You're ready to deal with FDA."

REMEMBER THE PAYERS

The other do-it-early advice concerns reimbursement. It's not enough to show that a test works to identify a particular subgroup of patients. Payers want to see that clinical practice changes as a result—and in a way that improves care, saves money or, preferably, both. Collecting evidence of clinical utility is crucial to making a case for payers. The issue, Tufts

Center for the Study of Drug Development found, is that payers see a disconnect between the efficacy of a diagnostic test—does it measure what it purports to measure?—and its influence on health outcomes. Almost across the board, a majority of surveyed payers agreed that a companion diagnostic accurately identified patients who would respond to a drug. But in almost every case, fewer of them recognized conclusive evidence that a diagnostic improved health outcomes.

"It doesn't mean you won't get reimbursed by anyone," says Cohen, who wrote the survey report. "But it does tell you they're waiting for FDA to give them the go-ahead."

One exception, according to the survey, which was taken this year: The HIV drug Ziagen (abacavir), associated with a diagnostic test to identify patients with the HLA-B*5701 allele, which shows they are most likely to experience a potentially fatal sensitivity reaction. A majority of payers considered the diagnostic test effective, and the same number agreed that it affected patient outcomes.

The KRAS test was approved very quickly as well, Trusheim says. It had no trouble obtaining reimbursement because it was clearly saving costs by identifying patients who would not benefit from a drug. "Payers thought this was great," he says. "Now they were saving money."

What does this mean for development partners? Payers are most likely to foot the bill if, first, they have evidence that the test's use will change the way the drug is actually used. Second, they're more likely to pay for a diagnostic if the targeted drug's labeling says a diagnostic test is "required" for use, not "recommended" and certainly not thrown in under the "for information purposes" section. Negotiating the language on a therapy's label can be a fraught process, especially in this field, where the science is advancing so rapidly. In the middle of all that, companies need to remember that the FDA's word choice and placement here can seriously help or hurt their case for reimbursement. In both cases,

it's all about proof that a diagnostic doesn't just work, but adds value to treatment.

"With this whole focus on comparative effectiveness, payers are going to have it be all about economics," Wasden said. "Really understanding that and applying that to these drugs is going to be what drives the payers. Drug companies and diagnostic companies have to have their value proposition in place."

The good news is that, once clinical utility is proven, prescribers are much more likely to use drugs that are targeted to particular patients via companion diagnostics, IMS Health has found. That's because the test offers evidence of a positive outcome for their patients. But that doesn't guarantee a strong uptake for a new targeted drug and its companion test. When targeted drugs are priced at $50,000, $60,000, even $100,000-plus, patient co-pays can be an issue. Twenty percent of that sort of price puts these drugs beyond the reach of many. Patient assistance programs can help, but they're not a panacea. High cost-sharing is such an issue, Tufts' Joshua Cohen says, that it even payers see it as an obstacle to clinical uptake. Doctors sometimes resist diagnostic tests, limiting their prescribing of a drug as a result. That makes educating physicians paramount to personalized medicine. It's a new way of practicing medicine. Expect a learning curve. As Cohen points out, "They haven't been brought up that way."

CAN CO-DEVELOPMENT BE LESS COSTLY?

The hope is that developing drugs and diagnostics in tandem will end up shrinking the size of clinical trials necessary for approval, and shortening the development timeline. "Clinical biomarkers assist by enriching patient populations in clinical trials with better responders, thereby reducing the size of the trial sample required to detect significant efficacy," the *Nature* paper stated, "and possibly shortening endpoint observation times when the clinical biomarker is an accepted surrogate for a longer-term endpoint

such as survival." Plus, using biomarkers to weed out patients likely to experience toxicity problems "could further reduce development risks," the authors concluded.

If all that is possible, then so is reducing the cost of developing targeted drugs—at least theoretically. When trials are restricted to likely responders, and those patients respond, that could reduce the size of trials, decrease the number of necessary trials, and spur faster FDA review. "This whole thing is that 45% of all Phase III trials fail. That's a pretty high percentage considering you've already gone through two phases," says Chris Wasden of PwC. "If you can screen out the non-responders, then all you have left in the trial are people that you have a 99% chance that it's going to work. You should get much more efficacy than in a broad, population-based study, because in so large a population, it's difficult to see a measurable effect."

But, as the *Nature* study authors acknowledge, costs might actually increase. After all, there's the added expense of validating a clinical biomarker so that a diagnostic can then be approved. If the targeted drug works in a small minority of patients, many prospective trial participants would have to be screened to find enrollees. Getting enough participants might require adding trial sites.

"At present, implementing a PM strategy is likely to increase the cost of R&D," said a report from the consulting firm Diaceutics, published in the journal *Personalized Medicine*. Just witness the increased investment in targeted therapies found in the Tufts study. Investing in biomarkers, pharmacogenetics and diagnostics might be offset by smaller Phase III trials, but as the Diaceutics report states, "failure to consider potential targeting strategies sufficiently early in the planning process can undercut these potential cost savings." And moving into co-development tentatively—or incompletely—can be costly.

What about shortening the development timeline? If Roche's experience

with Zelboraf, or Pfizer and Abbott's with Xalkori, could be taken as an indication, the answer is yes. Both drugs went on the agency's fast-track timeline. Both were approved months before the FDA had projected. Earlier launches means more on-patent time on the market, increasing the overall return on investment.

There are plenty of reasons not to take Zelboraf or Xalkori as a representative example, however. "There are biomarkers that worked very well in the case of Xalkori and Zelboraf, because the drug target was the biomarker," Trusheim points out. "The hypothesis for why the drug worked was a mutation in that particular protein that the drug directly treated. There, they could make the timelines fit very well, because they had such a strong, nearly certain, hypothesis going into clinical trials."

Then, in the case of Xalkori, the diagnostic was already in Abbott's product stable. It had to be validated along with Xalkori in trials, but because it was already commercialized, there was no need for a bridging study that would account for a change to an IVD from a lab-developed test, or from one platform to another.

Even Zelboraf's developer isn't sure that targeted drugs would be any less costly to develop. Personalized medicine can result in many potential benefits to patients and the drug development process. A personalized healthcare approach can result in more efficient, targeted and faster development programs, and can be potentially better for patients in both efficacy and safety by identifying who should receive a medicine and who should not," the company said in an emailed statement. "However, it's also a complex process and involves other elements of development that may have substantial costs, such as biomarker discovery programs and the development and validation of the diagnostic in addition to the medicine."

Too few drug-diagnostic pairs have emerged into the market to show whether costs will generally rise or fall, or whether the timeline will

shrink. Companies may find that they get better at co-development projects with experience. Productivity could increase. Perhaps with growth in targeted drugs and companion diagnostics, regulatory wrinkles and reimbursement pathways will be evened out. The U.S. government might step in with incentives that change the calculus completely. The next several years will tell.

BLAZING A BETTER TRAIL

As so often happens when promising new technologies emerge, the expectations for personalized medicine ballooned into hyperbole almost instantly. Genome sequencing seemed like a door into Tomorrowland, where cures for stubborn, life-threatening diseases would materialize alongside monorails, rocket shuttles to Mars, James Bond-style gadgetry, and Space Mountain. Now, years later, genomics haven't become the simple secret passageway into disease that so many had hoped. In fact, sometimes it seems that personalized medicine has fallen into the same trap as the Robinson family on "Lost in Space": Doomed to search a baffling universe for the way home.

That's not to say that Tomorrowland is completely out of reach. Getting there, however, appears to require more time and effort. "The concern about this whole area has been, is this ever going to be the technology of tomorrow?" Wasden of PwC says. "People have been talking about the role of genetic and molecular diagnostics for years and years now, and it seems like the more we learn, the more complex it gets, and we find all these reasons why it will take longer."

Some systemic changes could help, and experts say support is growing, particularly as budget restrictions have lawmakers looking for ways to put healthcare costs under control. "Personalized medicine addresses the issue of increasing healthcare costs; its further adoption should be part of any deficit-reduction strategy Congress employs," Brian Munroe of the PMC, has said.

PMC is working on ways to blaze the way for personalized-medicine projects. Proposed changes include clarifying regulatory pathways, untangling reimbursement, rationalizing coding systems used by Medicare and other payers, and developing incentives to make the cost and effort worthwhile. It's not just the atmosphere in the U.S. that needs help, but also in Europe, where regulatory and reimbursement hurdles are slightly different, but no less burdensome. "[R]egulatory systems on both continents are not well-positioned to evaluate personalized medicine products nor are reimbursement systems configured to provide companies with a predictable, value-based return on their investments," said the PMC's Abrahams.

For instance, PMC has suggested that an organizational committee at Health and Human Services be established to work on personalized medicine issues, partly to help smooth out differences between the FDA and the Centers for Medicare & Medicaid Services. If a decision at the FDA conflicts with a decision at CMS, the committee could help. The committee would be charged with supporting the development of personalized medicine by reviewing policies, procedures and regulations—covering everything from regulatory approval to Medicare coverage to proper training for healthcare workers—and suggesting changes.

"I think our FDA provision has a chance because there has been a lot of discussion in the community about improving the regulatory environment for personalized medicine, and there's a will at FDA to do that," says Miller, PMC's public policy director.

The FDA recently set out some new initiatives to spur innovation, and one of its stated goals is "building the infrastructure to drive and support personalized medicine." In outlining those new initiatives, the agency says it's in the process of developing guidelines for the design of clinical trials for co-developed diagnostics and drugs. It's also working on an internal plan for reviewing co-developed tests and therapies to help speed the process along.

The fact that FDA Commissioner Margaret Hamburg tapped Dr. Stephen Spielberg as a second-in-command is a promising sign, observers feel, because he's an expert in personalized medicine. His is a new position, Deputy Commissioner for Medical Products and Tobacco, and it oversees the CDER, the CBER, and the CDRH. The agency says that the new deputy commissioner's role will be "[t]o spearhead efforts for a seamless integration between the Centers as they must increasingly work together to promote highly innovative personalized therapies using the latest science and streamlined processes and procedures."

PMC also has suggested a tax credit for R&D in personalized medicine, whether on the drug side or the diagnostic side. The idea would be to also incentivize partnerships between a diagnostic company and a drug company.

Meanwhile, Rep. Anna Eshoo of California is working on a new version of the Genomics and Personalized Medicine Act. Eshoo asked PMC for its input, and the group put forth its ideas for an HHS advisory committee, R&D tax credits and more. The most recent attempt at a genomics bill, introduced last year, also would have commissioned the Institute of Medicine to evaluate billing, coverage and reimbursement for personalized medicine; set up a grant program to support genomic data collection and analysis; and require the National Institutes of Health to set up a biobank for research purposes, among other things. Miller says Eshoo is planning to introduce the new bill by year's end. "Now is the time for a national effort to move personalized medicine forward," Eshoo said at a recent briefing on Capitol Hill.

Looking beyond these suggestions, MIT's Mark Trusheim sees the possibility not only of new co-development projects. Existing drugs could use diagnostic assistance as well, so he envisions incentives for diagnostics makers to identify biomarkers and develop tests for already approved mass-market drugs. Epilepsy, depression, and high cholesterol are only a few of the disorders whose treatment could be revolutionized by the right

biomarkers and the right diagnostic tests. “That’s a huge opportunity lying fallow because of reimbursement and regulatory issues,” Trusheim says.

It can’t hurt that new drugs and tests have recently hit the market. At recent conferences, promising data from late-stage studies have made their debut. New partnerships between drugmakers and diagnostics companies are announced several times a week. Once more of these projects pay off, Abrahams says, and the treatments make their way into the clinic, the will for progress will be even stronger. “What really moves this is when patients and doctors see solutions,” he says. “When they actually see this stuff working.

Here’s an analogy, offered by Tufts Institute for the Study of Drug Development. HIV was identified as the cause of AIDS in 1984, but it took at least 12 years of work to develop the drug cocktails that effectively made HIV a chronic disease rather than an immediate death sentence. “Even with fast-track approvals and patient advocacy and everyone pushing for cocktail therapies, the truly efficacious therapies came in the ‘90s,” Cohen says. “What that means is that we shouldn’t be too surprised that it’s taken so long for the Human Genome Project to really pay off.” ●