First 'breakthrough' drugs designated, but dilution worries linger

The US Food and Drug Administration already has numerous ways it can speed up the market authorization of new medicines, ranging from 'accelerated approvals' to 'priority reviews' to its fast-track program. Even so, sometimes the existing mechanisms for speeding drugs to market—which typically require data from the traditional three phases of drug development—aren't fast enough for the millions of patients in desperate need of new medicines. With the first so-called 'breakthrough therapy' designation awarded last month, patient advocates see a signal that the FDA will green-light exceptional drugs more quickly with this new regulatory pathway, but some worry that if the designation is overused its value could be diminished.

On 6 January, Vertex Pharmaceuticals of Cambridge, Massachusetts, announced that two of its cystic fibrosis therapies—Kalydeco (ivacaftor) taken alone or in combination with an experimental agent called VX-809—had received the first breakthrough designations under the FDA's new program, which was codified into law in July 2012 as part of the reauthorization of the Prescription Drug User Fee Act.

Kalydeco, the first available drug that targets the defective protein responsible for cystic fibrosis, was approved last year after a lightning-quick three-month review for the 4% of people with cystic fibrosis who harbor a particular mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene known as G551D and are older than 6. Vertex is now seeking to gain broader approvals for the use of Kalydeco in younger children with the G551D mutation as well as those with other mutations that affect the CFTR protein in similar ways. Vertex is also advancing Kalydeco together with VX-809 for people with the most common type of cystic fibrosis mutation, known as F508del. "We see this new designation as a great opportunity to work with [the FDA] closely toward a mutual goal of bringing these potentially important medicines to the people who need them as soon as possible," says Megan Goulart, Vertex's senior manager of cystic fibrosis product communications and patient advocacy.

Despite granting the first breakthrough designations for Vertex's products, regulators are still fleshing out what exactly constitutes a breakthrough therapy—guidance documents are expected to be published by January 2014. However, last summer's law described it as something that can "treat a serious or life-threatening disease or condition and for which preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies."

Percy Ivy, associate chief of the Investigational Drug Branch at the US National Cancer Institute's Cancer Therapy Evaluation Program in Rockville, Maryland, likens the definition of a breakthrough drug to US Supreme Court Justice Potter Stewart's notorious 1964 definition of pornography. "You're just going to know it when you see it," Ivy says.

Of course, such nonstandard development programs existed before the breakthrough label. A study conducted by the Connecticut-based National Organization for Rare Disorders (NORD) looked at all therapies for diseases other than cancer that were approved as orphan drugs between 1983 and mid-2010. It concluded that two-thirds of approvals involved some degree of flexibility from the conventional data requirements, the majority on a case-by-case basis that fell outside the formal systems such as accelerated approvals that allow for scientific discretion in assessing effectiveness evidence. Nonetheless, the breakthrough designation adds some "predictability and transparency" to how and when flexibility will be applied, notes Mary Dunkle, vice president for communications at NORD. "We would rather have the system work with pathways that are documented and everyone is aware of," she says.

Break on through (to the other side)

What sets the breakthrough designation apart from other expedited drug development mechanisms—all of which have been in place at the FDA for at least 20 years—is the requirement of early clinical data demonstrating an unprecedented effect (see 'Drug development in the fast lane'). Fast-track designation, for example, can be granted off the back of promising preclinical data; accelerated approval status has more to do with surrogate trial endpoints. And although companies with fast-tracked drugs will receive earlier and more frequent

Drug development in the fast lane: FDA approaches to expedited approval.

	Fast track	Accelerated approval	Priority review	Breakthrough therapy
Eligibility	A drug that treats a serious condition and for which nonclinical or clinical data demonstrate the potential to address an unmet medical need.	A drug that treats a serious condition, provides meaningful therapeutic benefit over available therapies and demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit.	A drug that offers major advances in treatment over existing therapies or provides a treatment where no adequate therapy exists.	A drug that treats a serious condition and for which preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapies.
Designation	Can be requested at any time; FDA has 60 days to respond.	No formal process.	Requested at time of new drug or biologic application submission; FDA has 45 days to respond.	Can be requested at any time after investigational new drug application; FDA has 60 days to respond.
Clinical development	Earlier and more frequent communication.	Conditional approval granted using surrogate endpoint(s) from phase 2 trials or interim phase 3 data; confirmatory trials with hard clinical endpoints required.	Standard.	Abbreviated or condensed development, with earlier and more frequent communication and delegation of senior reviewers and a cross-disciplinary review team.
Review process	Option for rolling data submission; standard review after last data submitted.	Data submitted in one package; standard ten-month review.	Data submitted in one package; review time shortened to six months.	Data submitted as they are accumulated; review time shortened.
Established	1988	1992	1992	2012

Source: *Friends of Cancer Research's Conference on Clinical Cancer Research Issue Brief, Developing Standards for Breakthrough Therapy Designation, November 2012*

communication from the FDA, they won't get the 'all hands on deck' approach that is promised by the breakthrough designation. For breakthrough therapies, senior FDA managers and reviewers are expected to work closely with drug sponsors to design collaborative, multidisciplinary development plans that hasten timelines to approval and minimize the number of patients exposed to less efficacious treatments or placebos.

"This is really meant to signal from the agency that if you have a drug that shows a really unprecedented activity early on, they want to work with you to find the best course forward, rather than have you go it alone," says Jeff Allen, executive director of Friends of Cancer Research, a think tank and advocacy organization based in Washington, DC, that has actively championed the new breakthrough pathway.

Ultimately, Ivy expects patients to benefit as much as, if not more than, drug sponsors. Currently, individuals who are desperately seeking unapproved treatments but cannot enroll in a clinical trial must petition the FDA for a 'special exception use', yet drug companies are not always so keen to provide investigational medicines outside the confines of a controlled study. The breakthrough designation should increase drug access earlier on. "In the end," Ivy says, "I think the driver, goal and motivation for breakthrough therapies is to make treatments more widely accessible to patients who don't have other options."

However, onlookers say they hope the influence of a breakthrough designation won't be weakened by the FDA assigning it too frequently. "Like fast-track designations, I suspect they're going to give too many," says Greg Dombal, chief operating officer of Halloran Consulting Group, a Boston area firm that specializes in the life sciences industry. "And, in practice, its value could be slightly watered down because there are going to be a lot of things in there that shouldn't have that designation."

Elie Dolgin

Diagnostic lens turns to difficult-to-detect ovarian cancer

They say what you don't know can't hurt you, but that statement is particularly untrue when it comes to ovarian cancer. The most prevalent and aggressive type of ovarian cancer, known as high-grade serous carcinoma of the ovary (HGSC), is frequently diagnosed at stage 3 or 4, when treatment success plummets. Early phases of the illness have few symptoms, and even the signs seen in later-stage disease—such as bloating, pelvic pain and urinary urgency—are not unique to cancer and can be misinterpreted.

Whereas screening procedures for prostate and breast cancer have become routine elements of doctor visits, ovarian cancer screening tests remain bogged down in the development stage. But recent findings offer hope: a pilot study led by scientists at the Johns Hopkins Kimmel Cancer Center in Baltimore published on 9 January showed that it is possible to detect cancerous mutations in DNA shed from ovarian and endometrial tumors that has made their way to the cervix can be detected using a liquid Papanicolaou (Pap) smear sample (*Sci. Transl. Med.* **5**, 167ra4, 2013).

There is still a way to go, however. In the pilot study, only 10 of the 24 stage 1 cancers were detected. But the scientists behind the work are hopeful: "Our false positive rate was zero, which is exciting," says Luis Diaz, a Hopkins oncologist who led the study. "We hope to reproduce these results in a follow-up study with a larger number of cases with ovarian and endometrial cancer and in samples from healthy controls," Diaz says.

Others are working on molecular tests to glean more diagnostic information about ovarian health from liquid Pap smears, too. Alabama-based Swift Biotech has partnered with researchers at the University of South Alabama Mitchell Cancer Institute in Mobile who have been working on a proteomic-based test for the last five years. The analysis looks for a range of telltale proteins that originated in or near cancers in the ovary. "There is emerging molecular data that the majority of ovarian cancers originate in the fallopian tube," notes Rodney Rocconi, of the Mitchell Cancer Institute, one of the test's developers. A prospective validation trial, funded by a grant from the US National Institutes of Health, is currently ongoing in women with a detectable pelvic mass. Details about the test will be presented at the 2013 Society of Gynecologic Oncology annual meeting in Los Angeles this March.

Proponents of the liquid Pap test say that it provides superior detection of the local ovarian environment, but those developing blood tests for ovarian tumors say their assays have advantages such as convenience. And, in fact, a blood-based test already exists for women who have a detected pelvic mass that could be cancer. In September 2011, the US Food and Drug Administration granted market approval through the 501(k) pathway for a product from Pennsylvania-based Fujirebio Diagnostics that analyzes blood levels of the proteins HE4 and CA-125 with the so-called 'risk of ovarian malignancy algorithm'.

Measuring blood levels of CA-125 alone, without simultaneously measuring HE4, has shown limitations, however. A 2011 trial of over 78,000 women showed no benefit from a blood-based CA-125 biomarker and ultrasound combination test (*JAMA* **22**, 2295–2303, 2011). The test led to frequent false-positive results and too many unnecessary interventions and surgeries. And this past December, the US Preventive Services Task Force published a piece reaffirming its 2004 guidelines that recommended against screening for women who show no symptoms and who do not carry genetic mutations that increase ovarian cancer risk, such as the *BRCA* variants (*Ann. Intern. Med.* **157**, 900–904, 2012).

But other companies say they have better blood biomarkers. Canada's Soricimed Biopharma is working on a new blood-based test to detect mRNA transcripts of the TRPV6 protein specific to ovarian and other epithelial cancers. It is also developing a magnetic resonance imaging–based imaging test in conjunction with a fluorescent drug that specifically binds a protein found on the surface of ovarian tumors as a screening diagnostic.

Experts in the field are optimistic, particularly about the assays that look at DNA. "I would not be surprised if a genomic test such as [the one being developed at Hopkins] would ultimately become commonplace, particularly for women at high risk for ovarian cancer," says Robert Soslow, director of gynecologic pathology at the Memorial Sloan-Kettering Cancer Center in New York. And, according to Soslow, the focus of any screening test for ovarian cancer should be detection of HGSC: "That is the home run."

Anna Azvolinsky