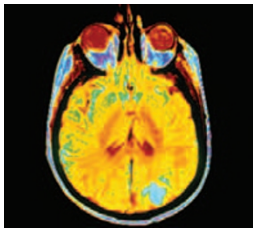
NEWS & ANALYSIS



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BiDil raises questions about race as a marker

Approval of 'race-based' drug is stimulating efforts to detect and predict true subgroups for drug response

Malorye Allison Branca

BiDil is the first drug approved for use in African-Americans only.

As expected, the launch of the first racially targeted drug, BiDil (isosorbide/hydralzaine; NitroMed), has spawned tremendous controversy. What's less easily anticipated is how drug developers will follow NitroMed's bold move in marketing their heart-failure drug for African-American patients only. Do more race-specific drugs lie ahead, or will better markers be uncovered? Hints are starting to trickle in.

Most researchers in the field agree that race is a "blunt tool", as Stella Davies of Cincinnati Children's Hospital Medical Center says. Race is just a surrogate for some as-yet-undetermined characteristic. "Skin colour doesn't cause the disparities," says Davies, who is investigating why black children with acute myelogenous leukaemia are more likely than white children to relapse and die after chemotherapy.

But those disparities can be quite striking. For example, middle-aged African-Americans are more than twice as likely as Caucasian patients to die early from heart failure. In a study of self-identified blacks, the drug reduced the death rate by 43% and the hospitalization rate by 39% compared with placebo. Those eye-catching numbers secured BilDil's approval by the FDA despite complaints that NitroMed was playing the 'race card' as a business tool.

NitroMed is already looking for better markers, says its Chief Medical Officer, Manuel Worcel. The company is currently analysing data from ten genetic markers linked to heart failure.

But Worcel is not convinced that genes hold the answer. "There is a different evolution of this condition in blacks compared to whites," he says. "We cannot rule out socio-economic factors yet." Access to care, treatment intensity, compliance and a host of other factors could just as easily be to blame.

When it comes to delving beneath the skin to identify differences at the molecular level, perhaps oncologists are closest to uncovering answers.

Howard McLeod from the Washington University School of Medicine, St. Louis, Missouri, points to a recent study of dihydropyrimidine dehydrogenase deficiency (DPD) as one of the first to show what he says is "a racial difference in frequency of an objective measure."

DPD leads to poor metabolism of fluorouracil — one of the mainstays of cancer treatment. Using a breath test that measures uracil catabolism, Lori Kay Mattison and colleagues at the University of Alabama in Birmingham presented data at the recent ASCO meeting in Orlando that showed that DPD deficiency occurred in 9.4% of blacks compared with 0.9% of whites.

Mattison's group also found previously unreported DPD-related genetic polymorphisms in African-Americans. "They've shown both a biochemical and genetic basis for the difference," says McLeod.

However, Iressa (gefitinib; AstraZeneca) offers a cautionary tale for those who think that the search for causative genes will be straightforward. Last year there finally seemed to be a good explanation for why only ▶

10% of lung cancer patients respond to this drug. The few patients who did well were mainly women, non-smokers or Asian. Specific mutations in Iressa's target, the epidermal growth factor receptor (EGFR), are more common in these groups, and apparently influence the drug's response.

Over the past year, though, the mutation data has been widely analysed, and other proposed markers have emerged. Now, new data from a large study of another EGFR inhibitor, Tarceva (erlotinib; OSI/Genentech), suggests that none of these offers a satisfying explanation (Tsao, M.-S. *et al. N. Engl. J. Med.* 353,133–144 (2005)).

"Skin colour doesn't cause the disparities"

Like Iressa, Asians are also more likely to respond to Tarceva. Although mutations did increase responsiveness to the drug, they were not linked to better survival. None of the other purported markers, including EGFR expression status or number of *EGFR* copies, was clearly predictive of response.

"This tells you how long it takes to define these issues," says James Doroshow, director of Cancer Treatment and Diagnosis at the US National Cancer Institute (NCI). "And it suggests we should be collecting tissue samples in all these trials." But as Doroshow states in an accompanying editorial to the Tarceva study, tumour samples were taken from less than half of the patients, and these were from either initial surgical specimens or initial or subsequent biopsies carried out before receiving Tarceva. Standardized approaches for sample collection are sorely needed.

Just banking the samples isn't the only barrier. Mutation analysis for *EGFR* costs several hundred dollars per patient, Doroshow points out. If a mutation occurs only 20% of the time, 1,000 patients will need to be tested to reach statistical significance. That quickly adds up.

Doroshow is hopeful that this will be addressed at the NCI. As part of a clinical trial restructuring initiative, NCI hopes to spend around $10 million per year on such testing, which is expected to come into effect in 5 years time. Clearly, other groups will have to face this problem too.

Neuroimaging heats up

New study hopes to validate imaging tools and markers for tracking Alzheimer's disease.

Mark Ratner

A big challenge facing developing drugs for Alzheimer's disease is that measurements of disease progression are mostly observational — such as the use of memory or cognitive tests — and require years of follow-up. Diagnostic imaging could reduce this time dramatically, but tools and methods are a long way from being validated. Now, initiatives are sprouting up to fill the gap.

In June, a public–private consortium known as the Alzheimer's Disease Neuroimaging Initiative (ADNI) launched an 800-patient longitudinal study across 50 clinical sites to validate structural imaging tools including MRI — measuring shape and size of the brain and hippocampus — and fluorodeoxyglucose positron emission tomography (FDG-PET) — measuring brain function or activity.

Four years in the planning, ADNI was established by the Foundation of the National Institutes of Health (FNIH), which supports the NIH through establishing both for-profit and not-for-profit relationships. ADNI aims to investigate technologies that have shown high potential in tracking disease progression, "but for which the literature is, frankly, confusing," says Pfizer's Peter Snyder, head of the ADNI study design group and chair of its Industry Scientific Advisory Board.

Confusion arises because different labs use different algorithms when imaging the brain, which can lead to varying results. "It became clear there was a need to collaborate across labs and platforms to develop a Gold Standard reference library to compare techniques," says Snyder.

As almost two-thirds of the US$60-million total budget for ADNI is being stumped up by federal funds, findings will be

Indian generics companies go on spending spree

The drive to expand globally is fuelling a spate of acquisitions in North America and Europe

K. S. Jayaraman

This year has been one big shopping season for generics companies hungry for acquisitions. But the past few weeks have shown that Indian companies are becoming the most aggressive buyers in the global market by snapping up several international firms. With several acquisitions made in the space of around 3 weeks between the end of June and beginning of July (see TABLE 1), why the rush?

Recent acquisitions by Sandoz, the generics arm of Novartis, and Teva have extended their lead as the top two generics companies, putting pressure on Indian companies to fight fire with fire.

Big players, such as Ranbaxy, Wockhardt and Dr. Reddy's Laboratories, have been testing the waters for some time. Now medium and even small companies are responding and raising the spending bar, as highlighted by Matrix Laboratories' acquisition of the Belgian drug maker Docpharma for US$263 million — the largest foreign acquisition by any Indian generics company.

This large-scale acquisition is unlikely to be the last, as Indian companies are increasingly looking beyond domestic frontiers to expand operations. Most top-tier Indian companies are seeking to manufacture in India and sell in the US and Western Europe.

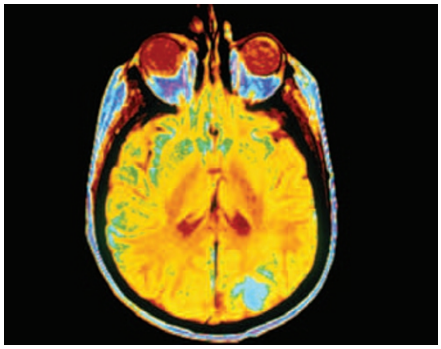
The moves are as much to expand operations globally as they are to protect against external suitors, with an M&A wave predicted in the Indian pharmaceutical industry in 2006. "It's a question of acquiring size in the target lucrative markets, or face becoming irrelevant as more and more US pharmaceutical companies now look at an India

Table 1 | **International firms recently bought by Indian generics companies**

Indian company (region)	Acquired company (country)	Cost (US$)
Matrix Laboratories (Hyderabad)	Docpharma (Belgium)	$268 million
Torrent Pharma (Ahmedabad)	Heumann Pharma (Germany)	$20 million
Jubilant Organosys (Mumbai)	Trinity Lab (USA)	$12.5 million
Nicholas Piramal (Mumbai)	BioSyntech (Canada)	$6 million

made publicly available, with baseline data expected by the end of the year.

The need for validated imaging tools and markers offset any industry concerns over sharing data and methods, or with conducting studies at a slower pace than companies are accustomed to. "The magnitude of getting agreement on clinical resources, diagnoses and the regulatory pathway to launch a new therapeutic made the need for developing a consensus



obvious," says William Potter from Merck, which joined ADNI last year.

All told, eleven companies have signed up as donors. Pfizer is the largest industry contributor, putting up $4.5 million over 5 years towards the project, along with access to antibodies and the processes for making them.

In the study, patients will be tracked for 2–3 years, and up to half of the subjects will contribute cerebrospinal fluid (CSF), a robust source of potential biomarkers such as tau, phospho-tau, amyloid and sulphatide.

Ownership and use of clinical samples collected in government-sponsored trials has been a dicey issue in the past. A US congressional committee is investigating whether samples collected in the NIH Intramural Research programme were either not kept track of accurately or used outside of their consented purposes.

In ADNI, however, which is part of NIH extramural funding, the grantee institution is officially responsible for the samples, and data will be shared even before publication. Guidelines on access and sharing of CSF collected in the trial should be in place by the end of the year, according to Susan Molchan, ADNI project officer at the NIH's National Institute on Aging (NIA).

Alternatively, focusing on measuring one or two endpoints linked to a single drug could be a faster way of moving a programme into clinical trials. Last month, Roche and GE Healthcare, neither of whom are funding ADNI, announced a Phase I collaboration around a Roche anti-amyloid drug candidate, due to begin next year.

Patients will be monitored for drug response using a hydroxylated benzothiole PET tracer biomarker from GE to track levels of amyloid plaque in the brain. The goal of this parallel drug–diagnostic development plan is to determine whether the Roche compound can decrease the amount of plaque, and whether this makes a clinical difference.

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entry to seek a level playing field in terms of cost structures," explains Vikas Dawra, who focuses on M&A in the Lifesciences sector at Yes Bank in Mumbai.

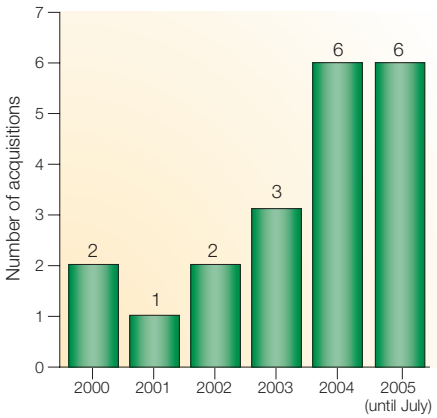
With Europe caught in a high-cost and low-growth squeeze, a number of small- to mid-sized firms are up for grabs. This has the added bonus of allowing Indian companies to kick start forays into these lucrative markets and instantly acquire local brands that would otherwise take years to build.

"We essentially bought a marketing company [Docpharma] that gives us access into generic markets of Belgium and southern Europe," says C. Satyanarayana, Chief Operating Officer of Matrix. In the case of Torrent's purchase of Heumann, the deal gives Torrent access to the German company's 90-year old brand name as well.

Another reason for the current activity is that cash is no problem. Private equity funds are flowing, and the government is not worried about outflow of money because its foreign currency reserves are brimming over.

Products for common diseases such as diabetes, cardiovascular disease and asthma are popular targets because they require lifelong medication, therefore providing a large, stable premium market. However, Indian companies are also targeting so-called 'grandpa' molecules, which have stable-priced mature markets. Companies can make a difference in these markets by using innovative delivery technologies — for instance, antibiotics in a flavoured crystalline form that you can carry in a pouch and eat without water.

Dr. Reddy's is one such company that prefers acquisitions "that have innovative product pipelines in niche and specialty pharmaceutical segments," according to their spokesman Ram Mohan. Their acquisition of Trigenesis Therapeutics, a US skincare company, is aimed at establishing Dr. Reddy's in the prescription dermatology segment, says Mohan. Ranbaxy's acquisition of the Spanish company Efarmes SA is aimed at developing products for pain management and treating diseases of the cardiovascular and central nervous systems.



This year's acquisitions have already matched last year's peak, and it looks like there is more to come. Source: Indian Pharmaceutical Alliance.

As most manufacturing standards are now harmonized, the M&A activities are unlikely to affect generics companies and the generics market in the way that innovative companies are affected, say analysts. "The major difference is that M&A creates pockets of dominance in certain territories or therapeutic categories. It is also many times a pre-emptive move to protect your own turf or to meet a competitor on his turf with a 'starting advantage'," says Dawra.

"On one hand the acquisition race for market expansion is a good thing," says Krishna Ella, CEO of Hyderabad-based Bharat Biotech. But Ella is unsure whether this should really be the goal of the Indian industry, or whether the engine of expansion should be fuelled by innovation. "If we go global with even one or two blockbuster drugs that will be great," he says.

Ella warns that the low-cost manufacture base that is emboldening overseas acquisitions will not last long if there is a rise in production expenses — such as salaries, cost of land and constructions — particularly in the high-tech clusters of Hyderabad and Bangalore. The high-intellect advantage will also be gone if multinational drug firms continue to set up bases in India and lure the manpower away from domestic firms. Ella says innovation and not expansion through acquisition is the key to going global.

NEWS IN BRIEF

Stronger warnings needed for asthma treatments

An FDA Advisory Committee has recommended that black-box warnings should be added to the labels of the bronchodilator treatments Advair (fluticasone propionate/salmeterol; GlaxoSmithKline), Foradil (formoterol; Novartis) and Serevent (salmeterol; GlaxoSmithKline) to warn of asthma-related deaths.

The lowdown: The decision to add a warning and not to remove the drugs from the market will provide some relief for drug companies. These drugs have been under increased scrutiny since a Congressional hearing on Vioxx (rofecoxib; Merck) last year when FDA's David Graham expressed concerns about the safety of Serevent. Advair and Serevent already contain boxed warnings about the risk of asthma exacerbations, after preliminary results from the SMART study showed a small, but significant, risk of asthma-related deaths or life-threatening episodes in patients taking Serevent. Despite no conclusive evidence of risk associated with Foradil, lumping the drug together with Advair and Serevent suggests the effect could be shared by all treatments containing a long-acting β_2-agonist. It is still not clear how drugs designed to relieve asthma symptoms can, in some instances, make them worse. Also unexplained is whether there is a possible race effect, as the SMART study found that African-Americans had a higher risk of exacerbations. Efforts to uncover the underlying mechanisms by collecting DNA in all drug trials, for example, should be something that companies and regulatory bodies actively pursue.

Relationship problems for flu drug companies

Gilead is looking to end an almost 10-year-old licensing agreement with Roche Holding for the neuraminidase inhibitor Tamiflu (oseltamivir).

The lowdown: Gilead, which developed the drug, has accused Roche, which has exclusive marketing rights to the drug, of not fulfilling its side of the bargain. Roche allegedly has not done enough to manufacture Tamiflu (thereby creating supply shortages), has not began promotion of the drug in 43 of the 64 countries in which it is approved, and owes more than US$18 million in underpaid royalties from sales. Roche says it is surprised by the claims, but if a settlement isn't reached within 90 days, the dispute will go to arbitration, which could take a further 18 months to resolve. Fears that the dispute could affect the supply and stockpiling of Tamiflu to defend against a potential pandemic outbreak of avian flu have been rejected by Gilead and public-health experts.

Brazil and Abbott clash over AIDS drug

After a messy dispute over drug pricing, Brazil has decided not to infringe the patent on Abbott's protease inhibitor Kaletra (lopinavir).

The lowdown: This isn't the first time that Brazil has threatened to break patents and produce generics in an attempt to reduce the cost of a drug. In this case, Brazil issued Abbott with a 10-day ultimatum to reduce Kaletra's price from US$1.17 per pill to 68 cents to help cope with the country's rising incidence of HIV, and after days of negotiations an agreement was reached. The cost of Kaletra will drop to 99 cents per pill and continue to fall to 72 cents by 2010. Patients will also have access to a new version of Kaletra, called Meltrex, once it gains approval in the United States. Abbott has agreed to transfer its technology to a state-run laboratory in Rio de Janeiro to begin producing a generic version of Kaletra when the patent expires in 2015. But less than a week after this agreement was publicized, the new health minister of Brazil, Jose Saraiva Felipe, who took office the day after the agreement was reached, claimed that nothing had been signed and that negotiations would continue.

FDA restricts Iressa use

The agency has decided that no new patients will be given the lung cancer treatment Iressa (gefitinib; AstraZeneca).

The lowdown: This move is the first time the FDA has taken such action on a drug that has successfully gone through the accelerated approval process. It was taken after post-approval trials showed that survival did not correlate with the surrogate marker of reduced tumour proliferation, and in light of proof that an alternative epidermal growth factor receptor inhibitor, Tarceva (erlotinib; OSI/Genentech), can increase survival. From 15 September, only around 4,000 US patients receiving and benefiting from Iressa, as well as patients enrolled in non-Investigational New Drug trials before 17 June, will be able to receive the lung cancer drug. AstraZeneca can continue studies to see whether biomarkers are predictive of responders, and analysis of these new and old trials will determine the future of Iressa. The agency added that it will soon assess whether other drugs that have received accelerated approval have lived up to the promise of their surrogate data.

Impotence drugs receive blindness warning

The FDA has updated labelling for Cialis (tadalafil; Lilly ICOS), Levitra (vardenafil; GlaxoSmithKline) and Viagra (sildenafil; Pfizer) in light of post-marketing reports of sudden vision loss from non-arteritic ischaemic optic neuropathy (NAION).

The lowdown: The week before the announcement Senator Chuck Grassley criticized FDA for acting too slowly on the label changes, because an FDA safety officer monitoring adverse event reports had highlighted the possible risk with Viagra more than 13 months earlier than an article in the March 2005 issue of *Journal of*

Neuro-Ophthalmology raised the problem. According to Grassley, the recommendation was well received, but no changes were made to the Viagra label. The agency said that it is not possible to say whether erectile dysfunction treatments are the cause of this eyesight loss, where blood flow is blocked to the optic nerve, or whether the problem is related to other factors such as high blood pressure or diabetes. The extent of the risk is also not clear. The agency recently said it has received 43 reports of NAION in men taking the three treatments, but Pfizer maintains that a review of all post-marketing ocular event reports has shown no evidence of increased risk of blindness with patients on Viagra. However, a report from CBS News claimed that more than 800 patients and doctors have reported eye problems to FDA after using Viagra during the past four years, with more than 140 cases of partial or total blindness.

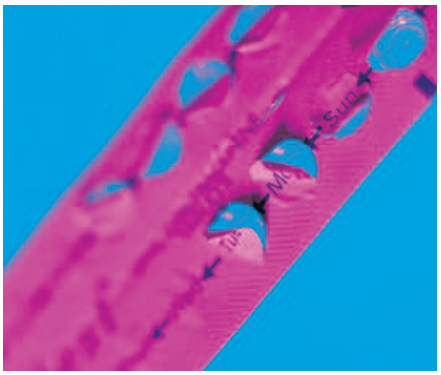
Study casts doubts on studies

A new study shows that around one-third of high-profile clinical studies produce results that don't hold up to further scrutiny.

The lowdown: That a single study can become refuted over time is not a revelation — after all, this is the nature of science. But the frequency with which this occurs should send a warning to scientists and editors to avoid giving selective attention only to the most promising or exciting results, and should also make the public more aware of the limitations of science. The study examined 49 original clinical research studies published in the *New England Journal of Medicine*, *Journal of the American Medical Association* and the *Lancet* during 1990–2003 that were cited more than 1,000 times in the scientific literature. Of these, 7 (16%) were contradicted by subsequent studies, and 7 (16%) had effects that were stronger than those of subsequent studies, meaning that almost one-third of the original results did not hold up

(Ioannidis, J.P.A. JAMA 294, 211–217, 2005). Non-randomized studies were more likely to be contradicted — 5 of the 6 highly cited non-randomized studies were either subsequently contradicted or reported stronger effects than later studies, compared with 9 of 39 randomized controlled trials. Of course there's no proof that subsequent studies are necessarily correct, but John Ioannidis from the University of Ioannina in Greece, author of the new meta-analysis, said that in all trials that were later contradicted or softened, the subsequent studies were either larger or better designed.

FDA to decide on morning-after contraceptive



The agency has set a deadline of 1 September to decide whether the morning-after contraceptive pill Plan B (levonorgestrel; Barr Laboratories) can be sold without a doctor's prescription.

The lowdown: Critics have accused the FDA of putting politics before public health in previous decisions over Plan B. In December 2003, an FDA Advisory Committee voted by 24–3 to approve Plan B for over-the-counter sales. But the agency, concerned that Plan B might not be used safely by young adolescent women without the professional supervision of a licensed practitioner, overruled the decision. Barr revised its application and submitted it again, but FDA failed to make a decision by the statutory deadline in January. Setting a new deadline has wider implications for the agency, as two Democratic senators, Hillary Rodham Clinton of New York and Patty Murray of Washington, had placed holds on Lester Crawford's nomination for the full-time Commissioner post until a decision was made on Plan B. With this barrier overcome, the Senate overwhelmingly voted 78 to 16 to accept the choice of Crawford to lead the FDA.

Parkinson's drugs can cause compulsive gambling

A class of drug for Parkinson's disease can cause unusual changes in personality in some cases.

The lowdown: The latest study evaluated 11 patients who developed pathological gambling tendencies after starting therapy with the dopamine agonists Mirapex (pramipexole; Boehringer Ingelheim) or Requip (ropinirole) for Parkinson's symptoms. One patient was a clergyman who became obsessed with gambling, and another was a woman who could not drive past a casino without going in and lost US$100,000, resulting in the break-up of her marriage. The habits stopped when the drugs were withdrawn. Six patients also developed other addictive traits, including compulsive eating, increased alcohol consumption and an insatiable appetite for sex (Leann Dodd, M. *et al. Arch. Neurol.* 62, 1–5 (2005)). Most cases were observed with Mirapex, although the side effect is relatively uncommon. A retrospective analysis reported cases of compulsive gamblers or sex addicts in 1.5% of patients taking Mirapex. The drug is thought to trigger this behaviour because it binds to the D_3 dopamine receptor, which is highly concentrated in the area of the brain devoted to mood, behaviour and rewards. Further studies could therefore reveal pathways and medications that curb addictive behaviour in general.

PATENTWATCH

No winners in Rasmusson versus SKB case

The US Court of Appeals for the Federal Circuit has ruled against both parties in a case concerning a drug for prostate cancer, resulting in both sides effectively losing the intellectual property they were fighting over.

The case concerns finasteride, a selective 5α-reductase inhibitor that works by preventing the conversion of testosterone to dihydrotestosterone, high levels of which are associated with prostate cancer. Rasmusson and SmithKline Beecham (SKB; now GlaxoSmithKline) both hold patents relating to the use of selective 5α-reductase inhibitors, and in 2001 the US Patent and Trademark Office (PTO) declared an interference between a patent application filed by Rasmusson and one filed by SKB. Rasmusson and colleagues attempted to have SKB's claims rejected by proposing that the filing date of their earlier applications enabled the later drafted claims. In retaliation, SKB moved to deny Rasmusson the benefit of these earlier applications and added further claims to the interference declared by the PTO.

The case was originally heard before the Board of Patent Appeals and Interferences (BPAI), which sided with SKB, deciding that Rasmusson was not entitled to benefit from a priority filing date because the claims lacked sufficient written description — specifically, a lack of data demonstrating the effects of finasteride in treating prostate cancer — to enable the latter patents. Although Rasmusson argued that efficacy is not relevant to enablement, the Court of Appeals disagreed and upheld the BPAI's original decision to deny Rasmusson a priority filing date.

At the same time, Rasmusson and colleagues had also claimed that the European counterpart of their first patent application anticipated SKB's patent that had been filed a year later, but the BPAI disagreed. However, on this matter the Appeals Court sided with Rasmusson and reversed the BPAI's ruling.

The Appeals Court decision was made on the basis of what constitutes enablement of a prior art reference and it would seem that the law for 'anticipation' and 'interference' is different. Although Rasmusson's original patent lacked enough written description of the therapeutic use of finasteride to be enabling under interference law, the law for anticipation states that "a disclosure lacking a teaching of how to use a fully disclosed compound for a specific, substantial utility … is … entirely adequate to anticipate a claim". So in conclusion, although Rasmusson has lost the interference case to SKB, the reversal of the second decision in Rasmusson's favour means that SKB's patent is anticipated and remanded to the BPAI, with both parties expected to lose their patents.

http://www.fedcir.gov/opinions/04-1191.pdf

Joanna Owens

Purdue pharma loses OxyContin patent appeal

A US Federal Court of Appeals has said that patents held by Purdue Pharma LP on oxycodone (OxyContin) cannot be enforced because of misrepresentations to the US Patent and Trademark Office (USPTO) relating to the discovery of the painkiller.

Purdue sued Endo Pharmaceuticals for patent infringement in 2000 after Endo filed an Abbreviated New Drug Application with the US FDA to sell generic, controlled-release versions of oxycodone medications for the treatment of moderate to severe pain. Endo's oxycodone treatments were approved in 2004 but their launch was delayed because of the patent dispute.

The Federal Appeals court judged, however, that Endo's generic painkillers do not infringe patents held by Purdue because of inequitable conduct. This is an unexpected ruling; in most cases in which district courts have made findings of inequitable conduct, the Court of Appeals has either reversed or vacated those rulings.

In this case, Purdue had informed the USPTO that it had discovered an oxycodone formulation for controlling pain over a fourfold range of dosages, compared with an eightfold range for other opioids. But OxyContin's inventor, Robert F. Kaiko, admitted that he had carried out no clinical studies on the fourfold dosage range for oxycodone and had no evidence to support this claim. Purdue admitted that Kaiko's 'discovery' was made solely in his head, but claimed that it was valid even though the company was unable to prove it to be true. In his ruling, Judge Stein of the Southern District of New York wrote that "Purdue made a deliberate decision to misrepresent to the US Patent Office a 'theoretical argument' and an 'expectation' as a precisely quantified 'result' or 'discovery'."

Endo plans to launch four strengths of generic oxycodone immediately. But Purdue intends to exercise its right to seek review of this decision by all 12 judges of the federal circuit.

Endo also intends to continue to pursue an antitrust claim and seek damages against Purdue arguing that the company has been selling OxyContin based on patents that were fraudulently obtained. Connecticut Attorney General Richard Blumenthal has launched an antitrust probe to determine whether Purdue prevented the development of less-costly generic alternatives. In a similar case, Bristol-Myers Squibb agreed to pay US$93 million to settle antitrust claims that it improperly prevented the sale of generic versions of the anticancer drug paclitaxel.

http://www.fedcir.gov/opinions/04-1189.pdf

Melanie Brazil

PATENT PRIMER

The Orange Book

Laurie L. Hill

Escalating drug prices are at the centre of the raging debates on the seemingly uncontrollable costs of providing healthcare. Making available generic substitutes for the more expensive, patented drugs is a core element of many healthcare cost-reduction plans. In the United States, the Orange Book serves to promote expedited entry of generic drugs into the marketplace while simultaneously protecting the interest of drug patent owners.

The Orange Book provides a public and detailed listing of drugs and drug products approved for use and sale in the United States by the US Food and Drug Administration (US FDA). Formally known as *Approved Drug Products with Therapeutic Equivalence Evaluations*, its original embodiment was as an orange-covered printed publication. Although it is now available exclusively online, the moniker 'the Orange Book' remains.

What you can find in the Orange Book

The Orange Book lists several categories of drugs: approved prescription drug products with therapeutic equivalence evaluations; approved over-the-counter (OTC) drug products for those drugs that may not be marketed without a New Drug Application (NDA) or an Abbreviated New Drug Application (ANDA) because they are not covered under existing OTC monographs; drug products approved under the Orphan Drug Act; and a cumulative list of approved products that have never been marketed or have other limited uses. The listing is updated monthly. Drugs approved only on the basis of safety tests or pre-1938 drugs are not included in the listing.

The Orange Book makes available a considerable amount of information on the listed drugs, including the active ingredient, proprietary name, drug applicant name and drug applicant number. Also provided is a series of uniform terms and codes defined within the Orange Book that indicate the various parameters evaluated for the listed drugs. Such parameters include pharmaceutical equivalents, pharmaceutical alternatives, bioavailability, bio-equivalent drug products and therapeutic equivalents.

Patent information for the listed drug products is also included in the Orange Book. The NDA review process requires the identification of any patents held by the applicant that claim the drug or a method of using the drug that could reasonably serve as a basis for patent infringement if a person engaged in the manufacture, use or sale of the drug without the appropriate patent license. Once the NDA is approved, the patent(s) identified by the NDA applicant is listed in the Orange Book, as well as its expiration date and current exclusivity data. The FDA publishes this information provided without review and will also add patents issued subsequent to the NDA approval.

Role in the generic drug industry

The patent information listed in the Orange Book serves the holder of approved drug patents as well as the generic drug maker. In the United States, a new drug can be legally sold only after the FDA determines that the drug is both safe and effective. The manufacturer of a new drug seeks approval from the FDA through the submission of a NDA. The NDA presents clinical data on safety and efficacy from studies carried out by the applicant. If the drug is patented, a generic drug company cannot perform those tests or enter the market without infringing the patents, and therefore either has to challenge the patent by making or using the drug or wait until the patent has expired. Waiting until the patent expires provides a *de facto* extension to the patent term because of the time required to conduct the necessary clinical trials. In an effort to streamline this process and expedite generic drug entry to the market, the Hatch–Waxman Act of 1984 revised the requirements for generic drug makers. Under this act, the generic drug maker can rely on the safety and efficacy clinical data submitted by the NDA applicant. The generic drug maker submits an ANDA that seeks to establish that the active ingredient in the previously approved drug product is the same as the active ingredient in the product made by the generic drug maker and that the generic product is bio-equivalent to the previously approved product. By eliminating the costs of expensive clinical trials, the federal government hopes to allow generic drug products to be ready for the marketplace at the time of patent expiration or to have sufficient economic incentive to challenge patents that might be invalid or which do not necessarily cover the generic drug product.

However, in exchange for avoiding the same expensive clinical testing required for an NDA, the ANDA applicant also must make certain certifications regarding the patents listed in the Orange Book as protecting the previously approved drug (BOX). If the ANDA application included a 'paragraph IV' certification of invalidity or non-infringement, the certification itself constitutes an act of patent infringement under the Hatch–Waxman Act. The patentee then has 45 days to file a patent-infringement suit. If the patentee files such a suit, the FDA cannot approve the ANDA until 30 months have passed, unless the case is decided before then or the court otherwise modifies the 30-month period. These certifications and the resulting 30-month stay on generic drug-product approval is an attempt to balance the desire for timely entry of the generic drug product into the market against the patent holder's rights and its investment for the approved drug product by allowing the patent holder to fully defend the relevant patent rights while allowing the generic drug maker to work towards preparing a drug product for market.

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REQUIRED ANDA CERTIFICATIONS

The ANDA applicant must certify for a proposed generic drug as to each patent that claims the approved drug either: no patent information has been filed with the FDA (that is, no patents are listed in the Orange Book); the patent has expired; the patent will expire on a particular date; or the patent is invalid or will not be infringed by the manufacture, use or sale of the generic drug.

The ANDA applicant is required to provide notice to the patentee and the holder of the approved NDA that it has submitted such certifications. If the certification is that the patent is invalid or not infringed, the ANDA applicant must include a detailed statement of the legal and factual basis for its opinion of invalidity or noninfringement.

CAREER PATH

David T. Wong

David Wong's journey to becoming one of a team of scientists to revolutionize the treatment of depression by developing the drug fluoxetine (Prozac; Lilly) began at school in Hong Kong where the principal, Herbert Noble, "a wonderful teacher", first piqued his interest in chemistry, a fascination that he carried with him into college at National Taiwan University. With the encouragement of his parents, he left Hong Kong for the United States, where he majored in chemistry at Seattle Pacific University. "Being a small college, the classes were small, but we had wonderful professors who maintained my interest in chemistry, especially organic chemistry." Wong then had the opportunity to take a summer internship in synthetic chemistry and received his BS in 1961. A year later, he commenced graduate studies at Oregon State University where he received his MS in biochemistry in 1964 and obtained his doctorate in biochemistry at Oregon Health and Science University in 1966, followed by postdoctoral training at the University of Pennsylvania.

Wong found that writing grants in academia could be frustrating, so he decided to look for a job in industry, and he had only one company in mind. Having seen the Lilly logo on his grandmother's diabetes medicine and later at a conference, Wong knew that was the company he wanted to work for.

According to Wong, it was not popular for a newly trained postdoctoral fellow of a reputable mentor to join a pharmaceutical research laboratory in the late 1960s and early 1970s. But, despite objections from graduate and postdoctoral mentors, he went ahead and joined Lilly Research Laboratories in 1968. "I was surprised when Irwin Slater offered me the position of a senior biochemist at Lilly Research Laboratories, but I was even more taken aback by his response when I asked if there were particular areas of research he would like me to work on. He said, 'You are a well-trained biochemist. You should be able to decide on your own'".

After Wong's initial proposal to conduct research on the biochemistry of calcium as a potential target was rejected as unsuitable for drug discovery, he became bold. "I initiated studies of uptake processes of monoamines without asking for permission, and from then on much of my 32 years at Lilly was spent doing pretty much what I was interested in and excited by."

Those who suffer from depression might now be thankful that Wong decided that this was his interest. In 1993 he was a joint Recipient of the Pharmaceutical Manufacturers Association Discoverer's Award for his part in the discovery of Prozac, a drug that is now used to treat millions of patients with depression. "Prozac was definitely a team effort. The collaborations between Ray Fuller and I led to many successful projects besides the discovery of Prozac. Throughout my career I have been fortunate to have very effective partnerships with scientists. My colleagues in medicinal chemistry served as mentors to me in many respects. In the late 1970s, William Lacefield showed me how to create an Invention Disclosure Memorandum, which led to co-inventorship of a US patent; and then in the mid-1980s working with David W. Robertson we designed and synthesized new molecules that resulted in the discoveries of duloxetine (Cymbalta), an inhibitor of serotonin and norepinephrine uptake, and dapoxetine, another selective inhibitor of serotonin uptake. Finally, in the mid-1990s I worked with Yao Chang Xu, Vincent Rocco and Kumiko Takeuchi in shaping molecules from multiple chemical scaffolds to have bimodal activities as antagonists at serotonin-1A receptors and serotonin transporters.

"There are times when I get frustrated that I no longer have a laboratory in which to test my ideas!"

"I hope that the work I have been part of has improved the quality of life for many people"

Because of the wonderful mentorship that Wong received, he plans to give something back and has arranged a summer undergraduate internship for synthetic chemistry endowment fund and a scholarship endowment for majors in chemistry or biochemistry at two of the universities at which he studied. Wong particularly enjoys the opportunity to interact with students and work with them on ideas, and says he wants to give more time mentoring as an Adjunct Professor and engage in a neuropharmacology project of his interest. "There are times," he says, "when I get frustrated that I no longer have a laboratory in which to test my ideas!"

Wong advises that to move from academia into industry and carve a career requires a willingness to engage early in existing drug discovery projects and be an uplifting person with a 'can-do' attitude. "You need the ability to focus and persevere, and to have devoted associates and to nurture those associates and colleagues to understand your research so that they become partners in the projects." He cites his greatest achievement as the successful collaborations that have resulted in the discoveries of therapeutics for treatment of mental illnesses. "Although it would be presumptive to say that I could have foreseen the outcome of our effort, I hope that the work I have been part of has improved the quality of life for many people and perhaps has even saved lives."