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New CEO appointment reveals Merck's response to setbacks

Insider promotion suggests a period of incremental change, and a potential review of internal R&D.

Mark Ratner

Merck's announcement on 5 May that Richard Clark has been appointed CEO put an early end to speculation around the successor to current Chief Executive and Chairman, Ray Gilmartin, who had been set to retire next March.

The announcement also removes some of the uncertainty around how the company will make the transition from the Gilmartin era, now indelibly marked by the withdrawal of Vioxx and the failure of several of Merck's late-stage clinical programmes, including prominent treatments for diabetes and depression.

Promoting Clark — a 30-year company veteran — suggests a period of incremental change for the firm.

Overall, the news was greeted with a lukewarm response. Many analysts had hoped for an outsider to catalyse dynamic changes, and have criticized Merck for choosing a CEO without a background in medicine at a time when developing new drugs is a main priority for the company.

Merck has been keen to convey the message that Clark — president of the manufacturing division and former CEO of Merck's pharmacy benefits manager spin-off, Medco Health Solutions — is a strong leader and a "change agent", a phrase used endlessly on the conference call discussing the move by Merck board member Larry Bossidy.

Bossidy was also quick to add that Clark "has a real-world understanding" of the environment in which Merck operates, both a defence of his capabilities and a hint that the new CEO would be a calming influence on a stirred and shaken management.

Merck's CEO will have to prevent any brain drain as the company moves from internal innovation to more external programmes.

Yet despite the glowing character reference, Clark was not also appointed chairman. Instead, Bossidy will head a newly structured three-person executive committee that will act as chairman for the next 18–24 months. This, coupled with the fact that Clark is only 6 years from the mandatory retirement age of 65, suggests a caretaker role.

Merck has been keen to convey the message that Clark is a strong leader and a "change agent"

Bossidy, unusually vocal for a board member on such a conference call, rejected that notion, but also noted there are "some very promising people that will work with [Clark]. We certainly would like to think one of them will be available to replace him when the time comes, and continue the evolution."

For now, "it appears that the triumvirate will be pulling the strings," says Chris Shibutani, pharmaceuticals analyst for JP Morgan. Although perplexing from a leadership perspective, splitting the roles of CEO and chairman "probably makes sense under the circumstances," he believes. "People view the choice as safe. And there's nothing holding them back from naming Clark chairman in a year or two," Shibutani ▶

points out, giving Clark a more powerful mandate.

An outsider would have been particularly disruptive to a company of Merck's size and scale, adding weight to the logic behind an incremental move, suggests Shibutani. "I'd rather see moderate steps, without back-peddling," he says. "A mega-change agent from the outside would have been very disruptive," adds another Wall Street veteran, who did not wish to be named.

Having a 30-year veteran of the company as CEO creates stability above and below

Merck is already on unsteady waters internally. The company has been desperate to prevent any possible brain drain as the late-stage pipeline failures have forced the company to shift from its traditional emphasis on internal innovation to a more collaborative mix of internal and external programmes. And with its share price down, the stock-option incentives awarded to employees have been anything but a motivation to stay. "Having a 30-year veteran of the company as CEO creates stability above and below," says Shibutani.

The company also revealed that it has been engaged in a round of cost-cutting, led by Clark, who Gilmartin called "the driving force behind [Merck's] most far-reaching initiative to make the company more efficient and reduce its cost structure."

Although analysts expect the percentage spend on internal R&D to remain constant, the core role of Merck Central Research to the company's future is uncertain.

Clark has repeatedly said he is open to ideas that would enhance Merck's long-term value and grow the pipeline, including aggressively pursuing targeted acquisitions and licensing. "Merck is already as good as any pharma at assessing the quality of outside versus internal projects," suggests Roger Longman, editor of the health-care business information journal *In Vivo*.

Why big pharma needs to learn the three 'R's

Small companies continue to capitalize in finding alternative uses or improved versions of drugs originating from large companies.

David Bradley

Repositioning, reprofiling, repurposing. Whatever you call it, finding new careers for old drugs is fast becoming big business. Considerable revenues and savings are to there to be made in discovering alternative purposes for known compounds.

As Nobel laureate James Black famously said, "The most fruitful basis of the discovery of a new drug is to start with an old drug." With faith dwindling in new technologies to drive the drug discovery engine, the need for scientific approaches to cultivating new uses for existing drugs, or those that are about to enter the market, is rising in importance.

Small wonder then that companies have sprouted to fill the void. At least a dozen compounds are now in a strong new position and smaller companies are working on countless compounds.

Although big pharma is interested in obtaining additional indications for their existing compounds, companies seem reluctant to spin out separate business divisions to maximize uses for their products. Repositioning ideas are sped through the process from an internal champion, serendipitous observation, or from outside companies with proprietary insights.

"Repositioning requires a substantially multidisciplinary approach, which big pharma is inefficient in generating," says David Cavalla, who heads Cambridge-based Arachnova, a mid-stage development company based on therapeutic switches.

This is in spite of many success stories of expanded uses for drugs resulting from experimental observations — Pfizer's sildenafil (Viagra) in erectile dysfunction, Lilly's duloxetine (Cymbalta) in stress urinary incontinence and Celgene's thalidomide (Thalomid) in severe erythema nodosum leprosum are classic examples of drugs that ended up being used in entirely unexpected ways.

Potential new disease indications for, or improved versions of, existing drugs are cropping up in unlikely situations. A group led by David Gutmann of Washington University School of Medicine in St Louis, USA, has shown that the immunosuppressant rapamycin could help treat childhood brain tumours. Enzo Bonora of the University of Verona, Italy, has shown that imatinib (Gleevec; Novartis), for chronic myeloid leukaemia also has activity in type 2 diabetes. And, ironically, given its origins, Rakesh Kukreja of the Virginia Commonwealth University, USA, has demonstrated that Viagra can also reduce heart damage in patients on doxorubicin chemotherapy for breast cancer, leukaemia and sarcomas.

Pursuing such strategies would make commercial sense for big pharma. Starting with a known clinical history for a compound shortcuts much of the early testing and clinical trials, dramatically reducing development times and costs, says Christopher Lipinski, who consults for indications discovery company Melior Discovery. "Companies can leverage value out of their compounds without exposing themselves to new risks, as the upfront costs of preliminary testing clinical trials have already been done," he says.

One disincentive for big pharma is that an initial programme could be hampered by a problem in a repositioning programme. "Companies usually hold off on such efforts until the candidate gets approval for its initial indication or development for its initial indication has been discontinued," says Ted Ashburn, Senior Director of Business Development at Dynogen Pharmaceuticals, a biopharmaceutical company developing reprofiled drugs for genitourinary and gastrointestinal disorders.

Repositioning is not without its challenges, says Ashburn. "For instance, the original data package may not meet current regulatory standards, intellectual property issues can be complex, and gaining access to a positioning candidate's patent estate and data package can be difficult," he says.

So large pharmaceutical companies will begin to focus more on repositioning programmes only if ideas for repositioning are more attractive from an economic standpoint than their best ideas for original drug development programmes. The problem, however, lies in knowing which potential directions any one compound could go in and which to follow.

This inertia of big companies partly explains why smaller companies and outsiders can steal a march and come up with many of the repositioning ideas. Nevertheless, it is in big pharma's interest to devote more resources to its existing portfolios. Reprofiling will be become an increasing focus, rivaling drug discovery based on new chemical entities, for big and small companies over the next 10 years, predicts Cavalla.

Flu virus lapses shows quantum leap in technologies needed

Developing treatments that would calm pandemic fears need more funding and resources.

Cormac Sheridan

Recent extraordinary lapses in the monitoring of the influenza virus has revealed how vulnerable we are to the threat of a pandemic.

Regular disruptions in flu vaccine supply, the lapse that led to the recent worldwide distribution of a pandemic-like H2N2 strain, and fears that affected countries are failing to inform the World Health Organization of any changes in avian virus strains, have shown how current production methods for annual vaccines would be woefully inadequate in an emergency.

Classical approaches to flu virus prophylaxis and therapy have held sway for more than 50 years, and represent a key defence system against an outbreak.

But developing these vaccines — by growing the three most prevalent pathogenic strains recommended by the WHO in embryonated chicken eggs — is cumbersome and inflexible, requiring lead times of more than 6 months in advance of the flu season to enable manufacturers to produce sufficient volumes. Also, any pandemic strain of avian origin would be lethal for chicken eggs.

Initiatives are underway to improve the status quo. The UK's National Institute for Biological Standards and Control (NIBSC) is trying to build a 'seed reference library' of 10–15 strains corresponding to high-risk pandemic-like subtypes.

Should a pandemic emerge, says the NIBSC's John Wood, the library would allow rapid genetic comparison with the real pandemic strain. A close match could then be used to seed vaccine production during the early stages of a pandemic outbreak, buying around two-and-a-half months of time to ramp up production volumes.

One alternative is to remove the element of guesswork, by focusing on antigens that are conserved among influenza strains. Attempts to develop such universal vaccines have been underway for more than a decade, but supporters of the concept say progress has consistently been hampered.

"People are reluctant to accept the idea that perhaps there may be a way to use a more classical type of vaccine that is valid for many years against influenza," says Walter Fiers of the University of Ghent, Belgium, who is developing a prototype vaccine based on the extracellular domain of the M2 protein.

The Meriden, Connecticut-based biotechnology company Protein Sciences aims to launch its FluBl0k vaccine — based on purified recombinant hemagglutinin antigen produced in insect cell culture — in 2007, but the company's COO, Manon Cox, says it could have been on the market ten years ago.

"What has been in our way is [lack of] money," says Cox. The big players have been unwilling to embrace innovation. "These guys have no incentive whatsoever to do anything other than what they are doing," says Cox.

Klaus Stohr, head of the WHO's influenza programme, believes that the best way out of the current impasse is to launch a major, long-term global initiative to develop a cross-subtype-specific universal vaccine. Current spending on influenza vaccines, he estimates, is running at US$3 billion annually. If health authorities channelled 5% of this into a ten-year cooperative research programme, this would produce substantial improvements.

The WHO is encouraging the European Commission to consider this issue in its Priority Medicines sub-programme within its forthcoming Seventh Framework Program of research spending, although industry's response to the idea remains to be seen, says Stohr.

Meanwhile, other companies are pursuing alternatives to existing antiviral drugs. Treatments that can be stockpiled in advance offer an immediate means of fighting a pandemic infection and, potentially, limiting its spread. But the current best-sellers — neuraminidase inhibitors, including oseltamivir (Tamiflu; Roche) and zanamivir (Relenza; GlaxoSmithKline) — block viral entry and spread, yet offer limited efficacy and serve only to shorten the duration of illness.

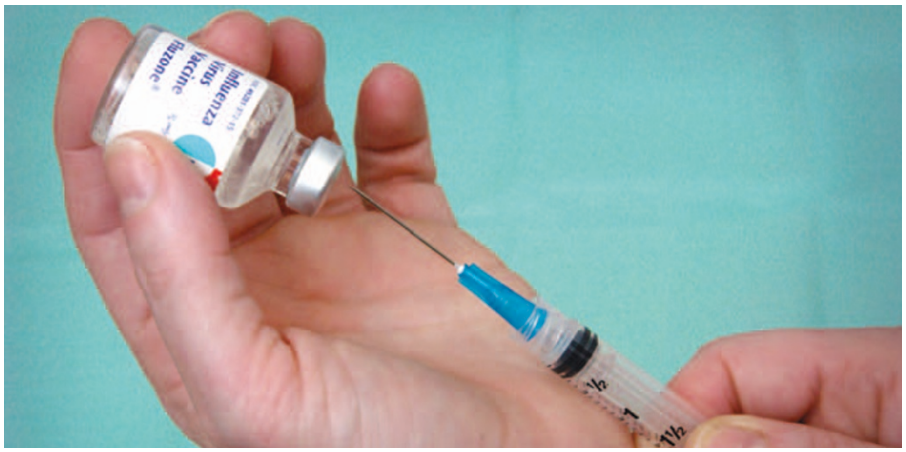
"Regular disruptions ... have shown how current production methods for annual vaccines would be woefully inadequate in an emergency."

Alternatives, however, are at the early stage. NexBio, a San Diego-based biotechnology company, is developing a recombinant protein called Fludase containing the enzyme sialidase, which blocks viral entry to the epithelial cells lining the respiratory tract. "Our plan is to file an Investigational New Drug application by the end of this year and start a clinical trial during the first quarter of next year," says NexBio's Chief Scientific and Medical Officer, Fang Fang.

RNA interference (RNAi) is also being examined as a potential prophylactic and therapeutic option. Jianzhu Chen, Professor of Immunology at Massachusetts Institute of Technology showed that short interfering (si)RNAs specific for conserved regions of the influenza virus genome could both prevent and treat virus infection in mice. A team led by Suzanne Epstein at the FDA showed a similar effect with the same siRNAs in mice exposed to pandemic-like H5 and H7 subtypes.

Alnylam Pharmaceuticals is also interested in developing RNAi-based treatments to combat a pandemic threat. "The early work we are doing is examining how many different siRNAs we would need," says COO, Barry Greene. "It is likely you would need more than one."

A big step would be to target siRNA delivery to the lungs. Last month, Chen reported improved delivery of DNA and siRNA to mice lung tissue by full deacylation of a commercially available polyethylenimine vector. (Thomas, M. *et al.* PNAS 102, 5679–5684; 2005). "If an inhalable formulation can be developed that would be very, very significant," he says.

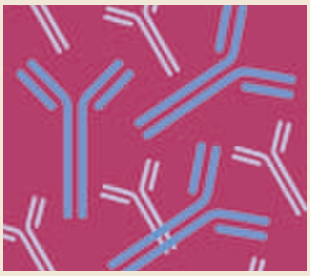


Centers for Disease Control and Prevention

Current flu vaccine production methods would be inadequate if a pandemic strikes.

NEWS IN BRIEF

Anti-angiogenics steal the show



Positive results for anti-vascular endothelial growth factor (VEGF) drugs were presented at the annual meeting of the American Society for Clinical Oncology.

The lowdown: All eyes were on the latest Phase III trial data for bevacizumab (Avastin; Genentech) in non-squamous, non-small-cell lung cancer, which showed an increase in median survival of 12.5 months on chemotherapy/Avastin compared with 10.5 months on chemotherapy alone. After 2 years, overall survival was 22% in patients given Avastin/chemotherapy compared with 17% on chemotherapy. Side effects still cast a shadow over Avastin: 5% of patients on Avastin had life-threatening bleeds, although only 1% died. Whether this is a consequence of, or independent from, Avastin's known effect of elevating blood pressure by inducing nitric oxide is still unknown. Positive results on Avastin were also presented for second-line metastatic colorectal cancer and breast cancer. Less positive were data from Novartis/Schering-Plough's multi-VEGF inhibitor PTK/ZK. Interim trial results on 1,168 patients failed to show a significant improvement in progression-free survival of colorectal cancer patients on PTK/ZK/FOLFOX chemotherapy versus FOLFOX alone. But 40% of PTK/ZK/FOLFOX patients with a high level of the enzyme lactate dehydrogenase — which indicates the presence of tissue damage — did show significantly improved progression-free survival. Final results are expected in the second half of 2006.

New FDA safety initiatives proposed

A new bill aims to move the FDA's drug safety office to a new centre for post-market review.

The lowdown: The bill, sponsored by Senators Charles Grassley (R-IA) and Christopher Dodd (D-CT), would allow the new FDA office to impose fines on drug companies that fail to conduct certain studies, to order label warnings without discussion with companies and to review direct-to-consumer advertising. Companies that fail to conduct studies or meet deadlines for them would be fined US$250,000 for every 30 days of delay. FDA officials also announced measures for a Drug Safety Oversight Board, which would include members from various FDA offices, and would probably result in more Advisory Committee meetings. Critics maintain that this is not enough, but others ask whether plans to make drug safety evaluation independent from FDA's regular review procedures would lessen the priority of drug safety assessment within the normal agency's working practices.

Monster diabetes drug approved

The FDA has approved exenatide (Byetta; Amylin) for type 2 diabetes.

The lowdown: Byetta is the first-in-class mimetic of an incretin hormone. The treatment, derived from the saliva of a poisonous lizard called a Gila monster and found in the Arizona desert, mimics the action of the hormone glucagon-like peptide 1, which stimulates insulin production only when blood sugar levels are high. Byetta's journey to approval has been a rocky one. John Eng at the Veterans Affairs Medical Center discovered the hormone, but his institution declined to patent the substance, saying it was not directly relevant to veterans. Eng patented it by himself and licensed it, after much effort, to Amylin, which in turn licensed rights to Lilly. As documented in an article in the *Wall Street Journal* entitled 'How Eli Lilly's monster deal faced extinction — but survived', the partnership between Amylin and Lilly saw its fair share of conflict, but eventually resulted in product approval. Byetta's commercial success is likely to depend on how many users are willing to undergo the twice-daily injections and whether it can be approved as a stand-alone treatment.

Good news for stroke drug?

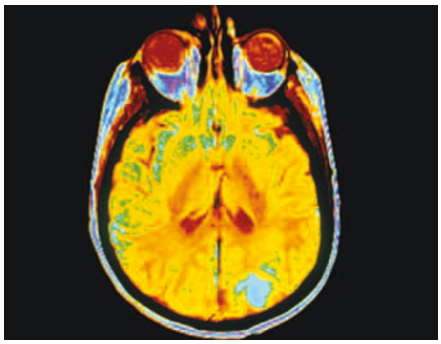
AstraZeneca has reported mixed results for a Phase III trial of its stroke treatment NXY-059 (Cerovive).

The lowdown: The Cerovive trial is arousing interest because it is thought to be essential for AstraZeneca's short-term future success. Cerovive (which AZ is licensing from Renovis), together with tesaglitazar (Galida) for diabetes, are the only drugs that the company has in Phase III trials. Initial analysis of the Phase III results provides both good and bad news. Patients taking Cerovive showed statistically significant improvements compared with patients taking placebo, according to the Modified Rankin Scale, which measures brain damage and disability. But no significant difference was found using the National Institute of Health Stroke Scale for stroke severity. AZ is pursuing a relatively risky strategy by testing Cerovive in Phase III trials without proof of human efficacy, but the company said it will view these results with two ongoing clinical trials.

European regulators review antidepressants in children

The European Medicines Agency has said that all members of two classes of antidepressants should not be used in children and adolescents except in their approved indications.

The lowdown: The recommendation that all selective serotonin-reuptake inhibitors (SSRIs) and serotonin–noradrenaline-reuptake inhibitors (SNRIs) raise the risk of suicide-related behaviour and hostility has raised eyebrows with UK regulators. After a safety review in 2003, the UK Medicines and Healthcare Products Regulatory Authority (MHRA) deemed Prozac



to be the only safe and effective antidepressant that could be prescribed to children. Prozac, the MHRA says, is the only antidepressant that has shown effectiveness in clinical trials, and although it isn't approved for children, doctors are allowed to prescribe the drug if they assume responsibility for doing so. EMEA's recommendations for antidepressants will take 3 months to ratify, during which time the MHRA will seek to change the proposal.

End of a genomics era

Celera Genomics has filed an Investigational New Drug application for a histone deacetylase inhibitor in cancer.

The lowdown: In doing this, Celera has officially moved from human genome sequencing and selling data to developing therapeutics and diagnostics. The sequencing model is no longer strategically relevant and has been a source of cash consumption, estimated to be approximately US$7 million for fiscal year 2005, as many of the subscriptions were prepaid. Its proteomics platform continues to yield novel cancer targets that have been the focus of several partnerships for drug discovery and development, which contributes to cost-effective clinical progression. Also, Celera Diagnostics, a 50–50 joint venture with Applied Biosystems, is generating product sales and making discoveries for incorporation into future new products.

Debate over heart failure drug

A committee at the Cleveland Clinic recommended that it should continue using the heart-failure drug nesiritide (Natrecor; Johnson & Johnson) despite safety fears.

The lowdown: The decision overrules around 50 members of the clinic's cardiovascular medicine department, who had voted unanimously to restrict the use of the recombinant B-type natriuretic peptide treatment. Two recent meta-analyses suggested that Natrecor increased the risk of kidney impairment and death, and in April the FDA recommended that mortality data should be added to the label. Despite going against the recommendation of its cardiologists, the Clinic's committee made eight recommendations for review by hospital directors before becoming official policy. Johnson & Johnson have asked the cardiologist Eugene Braunwald from Harvard Medical School to convene an independent panel to evaluate Natrecor.

US army says no to Nexium

The US Defense Department plans to stop reimbursing its staff for isomeprazole (Nexium; AstraZeneca) from this summer.

The lowdown: This could be bad news not just for AZ, but the industry as a whole. Nexium, AZ's top-seller, has been plagued by controversy as to whether its efficacy compared with generics justifies its higher costs. But this is the first time that the Pentagon has decided to remove a licensed drug from the department's formulary for financial reasons. And as the decision should save several tens of millions of dollars, this could be the first of many such decisions from Pentagon officials, who are desperate to control a $5-billion-a-year pharmaceutical budget. Some analysts fear that the rejection of Nexium could also have a knock-on effect in the government's planned Medicare insurance programme that will reimburse elderly patients for prescription drugs.

Rebranding PhRMA

PhRMA's new president has outlined new directions for the US industry's trade group.

The lowdown: The moves, proposed by Billy Tauzin, aim to help rebuild public trust over drug pricing, safety and advertising. PhRMA members are developing a voluntary code of conduct for direct-to-consumer advertisements to ensure that advertisements are targeted to the appropriate patient groups, and to help educate the public further about the risk and benefits of drugs. But while trying to earn back the public's trust, the group will still dispute policies such as a proposed ban on DTC ads for the first 5 years after approval and importation of medicines from abroad. Consumer groups reacted to the proposal unfavourably, worrying that voluntary principles will do little to persuade companies from changing current marketing tactics. PhRMA will also become more media-friendly, said Tauzin, to dispel its reputation for 'no-comments.' The new PhRMA won't be seen overnight: the ad standards hope to be issued by June or July, and it will take at least 2–3 years before the moves yield results, according to Tauzin.

GSK boost for vaccines

GlaxoSmithKline has announced a US$300-million acquisition of Corixa.

The lowdown: The deal shows GSK's confidence that its vaccine portfolio will be a key revenue driver, reaching an estimated value of US$19 billion by 2010. Key to the deal is the acquisition of Corixa's US manufacturing facility, which produces the novel adjuvant monophosphoryl lipid A (MPL). This adjuvant boosts patients' immune response and is used in several GSK vaccines in development, including the potential blockbuster Cervarix for preventing cervical cancer, and vaccines against herpes simplex, varicella-zoster and influenza viruses. GSK also acquires assets to its tuberculosis and immunotherapeutic cancer vaccines, which contain antigens discovered by Corixa.

PATENTWATCH

Lilly holds onto Zyprexa patent

In a long-awaited decision, Eli Lilly's patent (US 5,229,382) covering the schizophrenia drug olanzapine (zyprexa) is valid, enforceable and infringed, according to Judge Richard Young's ruling of the Southern District of Indiana.

Three generics manufacturers challenged the validity of the 1993 patent protecting the basic molecule until 2011. Miami-based Zenith Goldline Pharmaceuticals, Indiana-based Dr. Reddy's Laboratories and Israeli-based Teva Pharmaceutical Industries argued that the patent was not valid because discovery of the drug's molecular structure was obvious and that a previous Lilly patent that expired in 1995 had covered it. The companies also claimed that Lilly misled the patent office and omitted certain test results when applying for the patent.

In the 1970s and 1980s, Lilly produced a novel class of compounds called thienobenzodiazepines — tricyclic compounds with thieno, benzo and diazepine rings fused together. Two patents were issued for this compound class (US 4,115,568 and US 4,115,574,), which have identical technical disclosures, but different claims. The compounds contain halogen atoms; flumezapine was noted as a particularly active compound, but after further preclinical testing this compound was dropped due to toxicology concerns. Olanzepine differs from flumezapine by removal of the halogen atom.

The case hinged on a comparative dog toxicology study that Lilly conducted in 1990, which compared olanzapine to a related and previously patented compound, prior to filing a patent application with the US Patent and Trademark Office (PTO). According to Lilly, the outcome of the study showed that olanzapine had an expectedly superior therapeutic profile, and did not raise cholesterol levels or increase the production of the milk-producing hormone prolactin in the same way as other compounds of the class. The generics companies tried to prove that the dog study was flawed and that olanzepine was not novel and therefore not deserving of unique patent protection.

During the prosecution of the '382 patent, Lilly disclosed that the most closely related prior art was the matter claimed in the '548 patent, but the company did not disclose the '574 patent. However, the patent examiner found this prior art in a search and it was taken into account in the examiner's final decision, and so Lilly cannot be penalized for their omission. Judge Young ruled that the generics companies have not proven by clear and convincing evidence that Lilly concealed prior art nor data from the dog study with the intent to deceive the PTO.

Melanie Brazil

Eli Lilly & Co. versus Zenith Goldline *et al.*: http://www.lilly.com/news/pdf/zyp_opinion_041405.pdf

Merck and Integra battle on

German company Merck KGaA and Integra Lifesciences continue to argue over Merck's alleged infringement of Integra's peptide patents in a case that has significant ramifications for the pharmaceutical industry. The case, now awaiting a decision from the US Supreme Court, hinges on the scope of an 'FDA exemption' statute that allows scientists to ignore patents while they conduct research on drugs that they hope will be approved by the FDA. Merck argues that their preclinical experiments were all aimed at getting FDA approval and that the exemption therefore protects them, but Integra maintain that Merck's experiments were general biological research not protected by the statute.

Integra holds patents protecting its RGD peptides, a group of integrin-binding compounds discovered and patented originally by scientists at the Burnham Institute. Merck became interested in integrins as anticancer targets and in the mid-1980s collaborated with scientists at the Scripps Institute to show that blocking integrins can inhibit angiogenesis. Their work, using the Burnham Institute's RGD peptides, led to several potential cancer therapies including one drug currently in clinical trials. However, in 1996, after Merck declined to license the relevant patents, the Burnham Institute (and subsequently Integra) sued for infringement, claiming that the use of three specific RGD peptides in Merck's research was in violation of their patents.

The case has since lingered in US District and Federal courts. The Federal Circuit upheld the District Court's decision to award damages to Integra, stating that the FDA exemption statute exists primarily to ensure that generic drugs can enter the market as soon as possible after patent expiration on a branded drug. Because Merck's research was not 'solely for uses reasonably related to the development and submission of information to the FDA' , the Federal Circuit ruled that the exemption does not apply. The case has now moved to the Supreme Court, where Merck is expected to have argued that the FDA exemption should include *in vitro* and *in vivo* preclinical research in addition to clinical trials as a requisite to information submitted to the FDA.

The lawsuit has divided the research community, with large pharmaceutical companies warning that any ruling that narrows the scope of the FDA exemption will stifle drug discovery research and increase development time and costs. However, companies that produce research tools used in drug research are alarmed by the leeway given to the pharmaceutical industry and are demanding stronger patent protection for their products.

Oral arguments in the case were heard at the Supreme Court on 20th April. The drug discovery industry awaits the outcome.

Joanna Owens

PATENT PRIMER

Inherent anticipation

Daniel M. Becker

The doctrine of inherent anticipation, in which anticipation is found despite the absence of express disclosure in a prior art reference, has recently enjoyed a remarkable revival. In the past few years, various three-judge panels of the Court of Appeals for the Federal Circuit have significantly expanded the reach of this doctrine, increasingly affirming the inherent anticipation of claims that had been crafted specifically to extend the scope or the duration of pharmaceutical patent protection.

The traditional doctrine

A US patent claim is anticipated if, and only if, each and every element set forth in the claim is described in a single prior-art reference. A claim is barred by statute if an embodiment having each and every element is placed on sale by any party more than 1 year prior to the patentee's earliest effective filing date.

Two types of anticipation exist: express anticipation of a claim refers to the express disclosure of one element of the claim in a prior-art reference, whereas under the traditional common-law doctrine of inherent anticipation, anticipation can be found even if one of the required claim elements is not expressly described, as long as the missing element inheres in the prior art.

Traditionally, two provisos have circumscribed the reach of this doctrine. First, inherency cannot "be established by probabilities or possibilities". For, example, the mere fact that a certain outcome could result is not sufficient. An element will be found inherent only if it is the "natural result flowing from" the express disclosure, and only if it invariably results in that outcome. Second, century-old Supreme Court precedent has established that accidental or unintentional results, not appreciated as inherent to the claim by a person of ordinary skill in the art, do not constitute anticipation. However, several recent cases discussed below illustrate that the scope for inherent anticipation has been extended and that the converse is now true.

Appreciation no longer required

In the case of *Abbott Laboratories vs Geneva Pharmaceuticals* (Fed. Cir. 1999) Abbott sued various parties that had proposed to market the Form IV anhydrate of Abbott's α-adrenoceptor antagonist drug, terazosin hydrochloride. Abbott owned patent claims that protected both its marketed dihydrate salt as well as various polymorphs of the compound.

On the record before the Federal Circuit, it was undisputed that a company not party to the lawsuit had made at least three sales in the United States of Form IV anhydrate more than 1 year before Abbott's earliest effective filing date, and also that none of the parties to the sales then appreciated the identity of the particular crystalline form involved in the transaction. Despite the lack of such contemporaneous appreciation, the court invalidated Abbott's claim on the Form IV anhydrate, holding that the prior sales had inherently included this polymorph. The court also denied Abbott's contention that the earlier acts had been 'accidental' or 'unwitting', distinguishing the Supreme Court cases as applying only to prior art that produced "no useful ... result."

More recently, a different Federal Circuit panel found that Schering's claims to the orally administrable loratadine metabolite, descarboethoxyloratadine (DCL, marketed as Clarinex), were inherently anticipated by the company's earlier-filed patent disclosing the parent compound (marketed as Claritin). The court expressly held that "inherent anticipation does not require that a person of ordinary skill in the art at the time would have recognized the inherent disclosure." (Fed. Cir. 2003)

Entire invention can now be inherent

The *Schering* case is further remarkable for the proposition that the entire invention, rather than a single missing element, can be found to inhere in the prior art, even in a prophetic prior disclosure. Although the prior art supplied no express description 'of any part' of the DCL metabolite, because the formation of the metabolite in readily detectable amounts is the 'natural result flowing' from loratadine administration the court held the prior patent to inherently anticipate claims to DCL as a chemical compound (see BOX).

Methods can inherently anticipate

Prior art methods can inherently anticipate both compounds, as in *Schering*, and later-claimed methods. Yet another panel of the Federal Circuit affirmed the invalidation of an Eli Lilly claim to a "method of blocking the uptake of monoamines by brain neurons" through the administration of fluoxetine hydrochloride (Fed. Cir. 2001). The appeals court affirmed the lower court decision that the claim was inherently anticipated by the disclosure, in another Lilly patent, of a method of treating anxiety with fluoxetine hydrochloride. The Federal Circuit ruled that there was no patentable distinction between administering fluoxetine hydrochloride for treatment of anxiety and the resulting inhibition of serotonin uptake caused by administration of the drug.

CLAIMING METABOLITES IN THE NEW INHERENCY ERA

In the court's conclusion of the Schering case, inherent anticipation did not preclude patent protection for metabolites of known drugs. However, patent protection is available for metabolites of known drugs if claim construction is done effectively. In claims in which compounds are defined by structure only, metabolites might not receive protection because the scope of such claims include chemical species derived from the parent compound in any surroundings, including within the human body as metabolites. Therefore, as the Schering case illustrates, such claims are inherently anticipated by the prior-art disclosure of a parent drug that is metabolized into the claimed compound. It is, however, possible for a skilled patent drafter to construct a compound claim for a metabolite to avoid anticipation by claiming it in its pure, isolated form, as part of a pharmaceutical formulation, or by claiming a novel method of administering the pure, isolated metabolite or its pharmaceutical form.

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AN AUDIENCE WITH...

Jan M. Lundberg

Jan M. Lundberg, Executive Vice-President, Head of Global Discovery Research, AstraZeneca

Jan Lundberg had medical training at the University of Gothenburg before obtaining his PhD and subsequently becoming professor in the Department of Pharmacology at the Karolinska Institute in Sweden, where he worked on cell signalling. He joined Astra AB in 1995 as Head of Preclinical Affairs, and was then promoted to Senior Vice President, Head of Global Discovery, after the Astra–Zeneca merger in 1999, before taking on his current role as Head of Global Discovery Research in 2002. He has published more than 500 scientific articles in the cell signalling field, has been a member of the Swedish Medical Research Council and the Advisory Board for Drug Approvals at the Swedish Medical Product Agency, and in January 2003 was appointed Honorary Doctor of Pharmacy at Uppsala University.

AstraZeneca has had several setbacks with Crestor, Iressa, Exanta and now Galida. Is there a problem with drug development at AZ?
There are risks associated with introducing new therapeutic paradigms like Iressa and Exanta. Since Discovery is contributing with, for example, translational science and safety assessment, we need to provide solutions together with our Development colleagues to satisfy regulators. However, I do feel that the regulators and the media need to appreciate that the issue is benefit versus risk and not only risk. As an industry we have a responsibility to patients to bring forward innovative treatments. The alternative is to forever stick with suboptimal and in some cases dangerous therapies, such as warfarin.

But with Iressa, isn't the issue with efficacy, not safety?
I'm certain that efficacy will be shown for Iressa in the correct patient population. A subpopulation of non-small-cell lung cancer patients are really benefiting from Iressa, possibly due to gain-of-function mutations in the EGFR pathway. In clinical practice, patients have been given Iressa and symptom improvements have been observed with treatment. Another way, although more invasive and time-consuming, would be to take tumour biopsies and analyse for mutations and make treatment decisions on that basis.

Are all of AZ's recent setbacks a reflection of ineffective trial design?
The paradigm for when critical decisions are made in drug development is changing and for novel drugs we're still learning how and when to choose the right sub-population. Ideally, you would have biomarkers or diagnostic tests when you start early clinical trials, but these tests are often only available once the drug has been conditionally approved and is on the market. I think our recent experiences will help us to design the optimal clinical trials from the beginning in future programmes.

That's quite an expensive experiment, isn't it?
It is a key part of pharmaceutical R&D to apply new advances in science and technology to overcome these challenges, which has been a characteristic of the pharmaceutical industry for many years.

How will recent setbacks affect your R&D investment?
It has not affected R&D investment. In times of difficulty it is pleasing that we had a record output from discovery and early development this year. Our expansion of drug discovery and efforts to increase productivity since the merger are really paying off.

If all four drugs above don't make it, what's in the pipeline and what changes to development will you make?
We are committed to innovative pharmaceutical research and the development of new medicines that benefit patients and improve health. We have several upcoming Phase III opportunities and encouraging recent data for Cerovive in stroke, but will certainly continue to work hard on the projects we have had difficulties with to turn them into successes. For example, Prilosec was considered problematic by regulatory authorities and then became the world's largest selling pharmaceutical, so we have not seen the end of our novel agents. Discovery of new therapies is a long-term activity and experience tells us that the most successful discovery organizations in big pharma are those that have a combination of pressure of delivery but also a long-term vision and persistence.

Is AZ going to focus more on targeted therapies now?
Discovery will continue to be opportunity-driven and depend on our scientists' ideas and how well these comply with the target–product profiles created by medical need and market demand. I agree that more targeted approaches can get us faster to market and then, after approval, the indications can be expanded.

What is your response to suggestions that AZ marketed Crestor too quickly because of financial difficulties?
We are an ethical company that introduces our products after regulatory agency approval based on their safety and efficacy for patients, and Crestor is now approved in 73 countries worldwide.

How much responsibility do you think the regulators should take for drug safety?
They clearly have a key role and I think the pharmaceutical industry and regulators should have a partnership, together with society, to produce better and safer medicines.

And when those within the partnership give conflicting views?
Judgement should be made on the overall risk/benefit related to the current available therapy and severity of the disease.

Within the FDA alone there have been conflicting views about Crestor. How do you feel about that?
We have been very public about the properties of Crestor and the data are available on a dedicated website. We have very good clinical evidence showing that Crestor is more efficacious with a similar safety profule compared with other marketed statins.