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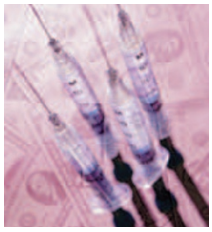

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Drug approval triggers debate on future direction for cancer treatments

Should new cancer treatments hit single or multiple targets?

Simon Frantz

Call it the Goldilocks approach to designing cancer drugs. Opinion has been growing that if traditional chemotherapies kill tumour cells indiscriminately but are highly toxic, and if newer drugs developed to pinpoint specific protein kinases in tumours provide a dramatic response, but in a smaller proportion of patients than hoped, then a balance might be achieved by designing drugs that hit not so many of these kinases as to be toxic but not so few as to be ineffective.

So what does the FDA approval of the first of these new multikinase inhibitors — Bayer and Onyx's Nexavar (sorafenib), approved for renal cell carcinoma at the end of 2005 — mean for the 'magic bullet' approach that brought us successes such as Gleevec (imatinib; Novartis)? Many researchers feel that because tumours are often complex mixtures of cells in various stages and states it is better to develop drugs that inhibit more than one kinase. "Many researchers would now think that no one target alone is probably going to be useful in all tumours of a class due to the great deal of heterogeneity that exists as well as the multiple ways a tumour cell can overcome any given insult," says Roy Herbst, Professor of Medicine and Chief of Thoracic Medical Oncology at the University of Texas MD Anderson Cancer Center.

Others say such statements are premature. "We can't say there should be a shift towards creating multikinase inhibitors at the expense of more specific inhibitors as we don't yet know whether the former drugs work by inhibiting more than one target in the tumour," says Carlos Arteaga, Professor of Medicine and Cancer Biology at Vanderbilt University, Nashville, Tennessee. Data on Nexavar suggest that its effects in renal tumours are likely to be due to inhibition of the vascular endothelial growth factor (VEGF) receptor, despite the fact that the drug was initially developed as a RAF kinase inhibitor, says Arteaga.

"It is compelling to think that you could get a better response if you hit two targets instead of one," says Charles Sawyers, Professor of Medicine at University California at Los Angeles. "I'm not against the idea; I just want to see the evidence that this is true." Gleevec, which Sawyers was instrumental in developing, turned out to be a multikinase inhibitor. The drug was designed to target ABL in chronic myeloid leukaemia, but inhibits another kinase, KIT, in gastrointestinal stromal tumours. "No one planned that in advance, I don't know how you really could," says Sawyers.

There are too many unknowns now to say how many targets future cancer drugs should block, says Charles Baum, Clinical Oncology Leader at Pfizer. "Evidence suggests that one candidate we are developing called sunitinib, which inhibits the VEGF and PDGF receptors, provides added therapeutic benefit in renal carcinoma than inhibiting VEGF alone," says Baum. "But for cases where we really know the specific molecular target well and there's one target that's driving the disease, then a single targeted agent is probably appropriate."

Understanding the molecular events that drive tumours and how any given drug is therefore working is crucial, but our knowledge in this area is far from complete, says Herbst. "We need to figure out what pathways lead to a drug response/improved survival, cause resistance or a lack of effect to a drug, and from this we can then hopefully understand what combination of treatments will have a better therapeutic effect," says Herbst. Identifying the driving mutations in the more common cancers is still a challenge. And despite improvements in techniques, getting workable biopsies of tumours is tricky.

But just as the approval of Gleevec allowed researchers to investigate how the drug works and how resistance occurs, so Nexavar's approval, and possibly more to come (see box), will help researchers pinpoint the important mechanisms in tumour response to multikinase inhibitors. How the future of cancer drug development will be determined is perhaps best summed up by the title of Herbst's targeted therapy programme at the university: 'From the lab to the clinic and back again'.

On target

Multikinase inhibitors in development:

- Sutent (sunitinib; Pfizer). VEGF receptor/PDGF receptor inhibitor at approval stage for kidney and gastrointestinal cancer.
- Zactima (ZD6474; AstraZeneca) VEGF receptor/EGF receptor/RET kinase inhibitor in Phase III for lung cancer.
- AG-013736 (Pfizer) VEGF receptor/PDGF receptor inhibitor in Phase II for kidney and thyroid cancer.

2005 approvals: Safety first

Analysts say that Vioxx has had a significant effect on drug approvals

Simon Frantz

If 2004 was a year to celebrate for drug approvals, then 2005 was a year in which to drown one's sorrows. After the increase in new molecular entities approved in 2004, the hope was that the pharmaceutical industry's R&D productivity was back on track after a few barren years (see graph). But with 20 novel medicines in total being approved in 2005, once again NME approval numbers dipped to all-time-low-levels. Worse still for big pharma, few multinational companies celebrated the thumbs up from regulators (for a list of the NMEs approved by FDA and EMEA, see online table 1 and online table 2.)

In recent years, the announcement of such woefully low approval numbers sparked vigorous debate on dwindling pipelines versus rising R&D costs, or raised questions about the wisdom of increasing M&A activity in larger companies. But the 2005 figures have been greeted with a more muted response, reflecting an industry waiting to see how more pressing concerns will play out. In particular, the fallout of Vioxx has created a culture of regulatory uncertainty, and as a result 2005 was perhaps unusual in that it was more notable for what was not approved rather than what was.

With many contributing issues to the regulatory landscape far from being resolved, Nature Reviews Drug Discovery asked analysts at leading firms what they thought the key approval trends were in 2005, and what trends they expect to see in 2006.

Drug companies are waiting to see what balance regulators strike between risk and benefit in 2006.

Mark Belsey and David Evans, Datamonitor

Key trend in 2005 approvals. Big pharma's high R&D investment was not rewarded with significant high-profile approvals. We forecast that none of the drugs launched in 2005 by the top 50 pharmaceutical companies will be blockbusters 4 years after launch, in contrast to six potential blockbusters approved in 2004. Drugs launched in 2005 target niche indications with limited revenue potential. In the US, the number of drugs approved in 2005 was down 44% on 2004, partly reflecting a shift in risk/benefit weighting at the FDA, which may be due to its increased wariness post-Vioxx. However, the agency is attempting to accelerate approval for drugs that demonstrate a significant improvement in efficacy, for example, by making greater use of surrogate endpoints.

Key trend in 2006 approvals. Drugs launched in 2006 are set to make a significantly greater impact after a low-key 2005. Combined sales of all products approved in 2006 4 years after launch are set to be 90% higher than the equivalent for 2005 launches. However, 2006 is still unlikely to recreate the blockbuster potential of 2004 launches: only three drugs set to be launched in 2006 — Pfizer's Indiplon for insomnia and Exubera (inhaled insulin) for diabetes, and Sanofi-Aventis's Acomplia (rimonabant) for smoking cessation and obesity — are forecast to reach blockbuster status within 4 years. Reversing the 2005 trend, 2006 could see the top 10 pharmaceutical companies recapturing the lion's share of approvals, especially in the United States.

Drug approval to watch in 2006. Although Indiplon may see the highest peak sales, Acomplia will be the most interesting launch, given the historical difficulties with obesity drugs and the huge potential market size.

Alex Grosvenor, Wood MacKenzie

Key trend in 2005 approvals. Product safety became the key focus as the fallout from the Vioxx withdrawal placed a lot of pressure on the FDA. The agency approved just 18 NMEs in 2005, versus 31 in 2004. The FDA attributes the slump to a decline in R&D productivity, but there is little doubt it has adopted a tougher stance on safety, especially towards products targeting chronic primary-care indications (for example, it rejected Bristol-Myers Squibb/Merck's Pargluva (muraglitazar) for type 2 diabetes and delayed Exubera). By contrast, the FDA has continued to support products targeting niche indications with an unmet medical need — 13 of the 18 approvals were granted under priority review.

> "2005 provided no sign of a recovery in productivity and was marred by regulatory uncertainty."

Key trend in 2006 approvals. Of the 23 NMEs with Prescription Drug User Fee Act (PDUFA) dates in 2006, there are five targeted oncology drugs (including BMS's dasatanib, and Pfizer's Sutent (sunitinib)), signalling that this product class is coming of age. However, 2006 is also likely to herald some ground-breaking medicines. Exubera promises to revolutionize the lives of diabetics by offering inhaled insulin — the first time a polypeptide has been delivered through the lungs. And Merck is seeking approval for Gardasil, a vaccine against the human papilloma virus, which is responsible for the vast majority of ovarian cancers and genital warts.

Drug approval to watch in 2006. In commercial terms, Acomplia is likely to be the key approval in 2006. As a cannabinoid CB_1 receptor antagonist, the product's unique mechanism blocks cravings, and is indicated for smoking cessation and obesity. We are forecasting sales of US$1.77 billion by 2009, but its sales potential is very much dependent on the labelling, for instance, whether it includes metabolic syndrome.

Andrew Jones, Ernst and Young

Key trend in 2005 approvals. 2005 provided no sign of a recovery in productivity and was marred by regulatory uncertainty. The year was punctuated by setbacks to development time lines brought on by the need for further clinical safety data; approvals conditional on the production of post-marketing safety data; approval failures; and restrictions placed on the marketing of certain products. The significant volume of black-box warnings issued was also a stark reminder that marketing approval does not guarantee success.

Key trend in 2006 approvals. How regulators manage the tension between addressing product safety concerns and the need to support innovation and reduce the time drugs take to reach the market. The industry is waiting to see what balance regulators strike between risk and benefit, particularly for 'first in class' candidates. Stakeholders will also watch how the FDA will provide its critics with assurance of its ability to function without conflict of interest while working alongside the industry to progress projects such as the Critical Path Initiative. Ultimately 2006 must provide greater certainty over the future state of the regulatory environment, or confidence will be further undermined.

Leland Gershell, SG Cowen & Co

Key trend in 2005 approvals. The past year saw the approval of several drugs for so-called orphan diseases, including Tercica's Increlex (mecasermin), a recombinant form of insulin-like growth factor-1 (IGF1) for children with short stature who suffer severe primary IGF-1-deficiency (IGFD) and who are therefore resistant to treatment with growth hormone; and BioMarin's Naglazyme (galsulfase), an enzyme-replacement therapy for patients with mucopolysaccharidosis VI (MPS-VI). Although these products may be for niche indications suffered by only a few thousand patients, robust pricing and a receptive reimbursement environment can create substantial market opportunities.

> "2006 is still unlikely to recreate the blockbuster potential of 2004 launches."

Key trend in 2006 approvals. Under newer leadership at the FDA, we may see the balance of approvals shift toward drugs for major unmet needs such as cancer as compared with those for diseases for which several options already exist, such as hypertension, depression or high cholesterol. This may be foreshadowed by the recent approval of Onyx/Bayer's Nexavar (sorafenib) for advanced renal cancer in all treatment lines (its Phase III trials were conducted in the refractory setting only) versus the potential requirement for additional, extensive safety data on Pargluva before it may receive approval for type 2 diabetes.

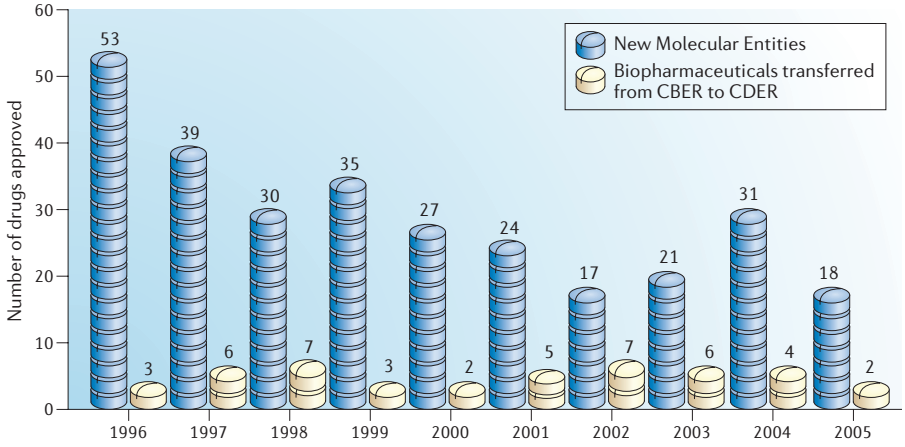
Drug approval to watch in 2006. A controversial example is Biogen Idec/Elan's Tysabri (natalizumab) for multiple sclerosis, which is under review following its withdrawal from the market early in its launch last year due to apparent toxicity.

Carole Jones and Tibor Papp, IMS Health

Key trend in 2005 approvals. Few innovative new medicines were approved in 2005, and approvals were mainly for 'me too' drugs that are not likely to have a significant impact on their therapy areas (for example, Aptivus for AIDS and HIV infection). The fallout from the withdrawal of Vioxx in 2004 continued throughout 2005, with further withdrawals and warnings for other cyclooxygenase-2 inhibitors. Oncology drugs saw important regulatory approvals in the European Union for Avastin (bevacizumab; Genentech) and Tarceva (erlotinib; OSI/Genentech), and new indications for established cancer therapies, such as Femara (letrozole; Novartis) and Xeloda (capecitabine; Roche).

Key trend in 2006 approvals. We could see faster drug approval times, with the 2002 amendment in the US to PDUFA; and new regulatory procedures in Europe to reduce regulatory workload and review times. 2006 could be a good year for generics. There should be more rapid pan-European approval for generic products using the new decentralized procedure available in 2006, and faster approvals in the mutual recognition procedure by the larger (consolidating) generic companies. And, of course, we might see the first of the biogenerics being approved in Europe.

Drug approval to watch in 2006. Exubera could be the first non-injectable insulin to receive approval. Also AstraZeneca's direct-thrombin inhibitor Exanta (ximelagatran) could also finally receive approval in the United States, being the first oral anticoagulant to be launched since warfarin more than 50 years ago.



2005 saw another dip in the numbers of new molecular entities approved for marketing by the US FDA. CBER, Center for Biologics Evaluation and Research; CDER, Center for Drug Evaluation and Research.

NEWS IN BRIEF

Good news for thalidomide

Trial and approval success for the notorious treatment originally developed for insomnia and morning sickness in the 1950s.

The lowdown: Celgene's gamble on exploiting the immunomodulatory characteristics of thalidomide is continuing to reap rewards. Under the brand name of Thalomid, thalidomide is already approved in the US for moderate-to-severe erythema nodosum leprosum, but a new study was halted early as the treatment also delays the onset of multiple myeloma. A Phase III trial on 270 patients showed that it took an average of 75.7 weeks for the disease to worsen in patients on Thalomid and dexamethasone, compared with 27.9 weeks for those on dexamethasone alone. Days earlier, a novel 4-amino-glutarimide analogue of thalidomide called Revlimid (lenalidomide) was approved by the Food and Drug Administration for severe anaemia associated with myelodysplastic syndromes with a deletion in the 5q chromosome. The company reported no sign of the birth deformities that plagued thalidomide, but the drug will still carry a black-box warning. Eyebrows were raised over the proposed cost of the treatment — between $4,500 and $4,700 a month, which is almost double the current cost of Thalomid — but Celgene maintains that this works out cheaper than the frequent blood transfusions that would be needed without the treatment.

Statins don't prevent cancer

Two metastudies fail to substantiate previous reports of cancer benefits for cholesterol-lowering treatments.

The lowdown: Studies focusing on cardiovascular outcomes hinted that statins might reduce the risk of developing cancer. But this exciting therapeutic prospect has been dealt a blow by an analysis of 26 studies involving more than 73,000 patients published in the *Journal of the American Medical Association* that showed no reduction in the incidence of cancer or cancer-related death (Dale, K. M. *et al. JAMA* 295, 74–80; 2006). The findings were not affected by separating hydrophilic statins, with their impaired ability to enter cells, from lipophilic statins, which by contrast readily enter cells. Likewise, naturally derived statins fared no differently from synthetic statins. Another study that focused on colorectal cancer incidence in over 132,000 patients enrolled in the Cancer Prevention Study II Nutrition Cohort also found no evidence for the anticancer effects of statins (Jacobs, E. J. *et al. J. Natl Cancer Inst.* 98, 69–72; 2006). Although a prospective chemoprevention trial designed primarily to assess association between statins and cancer would unequivocally provide the answer, according to a commentary by John McLaughlin that accompanied the colorectal meta-analysis, "it remains premature to conclude that a large chemoprevention trial with statins that is aimed at reducing colorectal cancer risk is warranted."

Success for rotavirus vaccines

GlaxoSmithKline and Merck both reported success for their candidate vaccines for the leading cause of diarrhoea-related deaths in children.

The lowdown: A vaccine for rotavirus infection has been sorely needed since the discovery of the pathogen in 1973. The first licensed vaccine, created by Wyeth, was withdrawn in 1999 after it was linked to a potentially fatal intestinal blockage called intussuseption in 1 in10,000 children. Despite the fact that proving that any new vaccine is safe would require trials on more than 60,000 infants, two pharmaceutical companies took on the challenge of creating a much-needed vaccine, and studies published in the *New England Journal of Medicine* seem to vindicate their efforts. Both vaccines appear to be free of side effects and protected children against several strains of rotavirus. GlaxoSmithKline's vaccine, Rotarix, which contains a weakened strain of live human rotavirus, showed 85% efficacy; Merck's RotaTeq, which is made up of five different disabled rotaviruses, showed 98% efficacy. The difference in efficacy profiles could reflect the populations studied: GSK tested its vaccine primarily among infants from low- and middle-income families in Latin America, whereas Merck tested its vaccine in the United States and Finland. One question that needs addressing is whether the vaccines will work as well in those populations in Asia and Africa, who are most affected by rotavirus infection.

India moves to protect traditional medicines

The Indian government is cataloguing its biodiversity to prevent theft from drug companies.

The lowdown: The creation of a database that will contain more than 100,000 traditional herbal medicines, and thousands of plants and yoga positions, shows the fear India has over drug companies stealing traditional knowledge for financial gain, known as biopiracy. At a cost of around US$2 million, the 4-year effort will document traditional formulas found in ancient texts in Sanskrit, Urdu, Persian and

Arabic. Indian researchers say the database is needed because of recent attempts to patent traditional medicines. Fears were raised after a case in 1995, when two Indian-born scientists in Mississippi were granted a US patent on the use of turmeric to heal wounds. The Indian government protested, citing ancient Sanskrit texts describing the use of turmeric for the same purpose, and the patent was revoked. However, many non-Indian researchers say that there might have been a few intellectual-property cases involving traditional medicine, but there is no real evidence that biopiracy is taking place, so creating the database is a mission motivated more by national pride rather than the fear of biopiracy.

Stem-cell data faked

Pioneer made up embryo clone results, concludes misconduct investigation.
The lowdown: Suspicions and rumours surrounding Woo Suk Hwang were confirmed in January when the university committee charged with looking into scientific misconduct concluded that Hwang's data on cloning human embryos had been fabricated. Hwang's team stunned the scientific community with two *Science* papers, one in 2004 describing the first cloning of a human embryo, the other in 2005 announcing the creation of stem cells genetically matched to patients with medical conditions. But Hwang's peerless reputation in the field began to unravel towards the end of 2005, when ethical objections to the source of the eggs in the study quickly escalated to doubts about the science in the published paper. DNA-fingerprint data, and other evidence supporting the existence of a clone, turned out to be fake, said the Seoul National University committee. *Science* said it will retract the paper on tailored embryonic stem cells, and said it had received permission from everyone named in the 2005 article to make the unusual move. Why Hwang did this is still a mystery. The pursuit of fame, and the political and cultural pressures to publish the findings fast, have all been proposed. Prosecutors are investigating the possibility that someone could have maliciously contaminated the stem cell tissue.

Firms avoiding HIV vaccines

Pharmaceutical companies have no financial incentives to create HIV vaccines, says the US government's chief for AIDS research.
The lowdown: In a deposition for a colleague at the National Institutes of Health who was allegedly fired after raising safety concerns about federal AIDS research, Edmund Tramont said that the government is being forced to devote more resources towards creating a vaccine. Industry has no real incentive to do this, yet are likely to profit from any vaccine created, said Tramont. The industry's trade group PhRMA responded sharply to the claims saying that industry is currently developing 15 candidate vaccines. The tête-à-tête reflects the growing frustration over the failure to bring an HIV vaccine to market. The not-for-profit group, International AIDS Vaccines Initiative, says there are more than 30 candidate vaccines in total being tested mostly on a small scale in 19 countries. But given standard attrition rates and that most candidates are pursuing similar hypotheses and targets, the chances of one succeeding are slim. Recently, leading researchers stated that the US government is wasting its resources in funding a Phase III trial called RV144 on a combination HIV vaccine, as there is no evidence that either vaccine component works very well on its own (Frantz, S. *Nature Rev. Drug Discov.* 3, 195; 2004).

FDA announces two initiatives to accelerate drug development

Guidelines aim to get drugs into early-stage human trials quicker.
The lowdown: The initiatives are good news for small companies, government labs and, in particular, academic groups. The first, called the Exploratory Investigational New Drug Studies guidance will allow microdosing experiments to be used as a 'Phase 0', or a 'PrePhase I' study. The process of giving microdoses of less than 1/100th of a therapeutic dose to a few subjects to see whether the compound has any biological effect before conducting larger trials has been tried in Europe in the past few years. The second initiative aims to loosen the 'Current Good Manufacturing Practice' rules for small exploratory studies. The agency will provide direction and advice to researchers on how to safely prepare and produce small quantities of compounds in the laboratory that can then be used in people. Before, it was a one-size-fits-all approach, with small laboratories having to make tiny doses for initial human use under the same conditions as multinational companies making millions of doses. The two guidances are part of FDA's Critical Path Initiative aimed at streamlining and modernizing the drug-development process.

PATENTWATCH

To prevent, or treat?

A case concerning the validity of patents for a lotion used to treat sunburn highlights the importance of language in claim construction when patenting other therapeutic agents — specifically whether the invention is described as 'preventing' or 'treating' an ailment.

The lawsuit concerned was brought by Nicholas Perricone against Medicis Pharmaceuticals Corp., which was accused of infringing Perricone's two patents (US5,409,693 and US5,574,063) that claim methods for treating or preventing sunburn by the topical application of ascorbic acid in a fat-soluble form. A District Court in Connecticut, USA, ruled that some of the claims of Perricone's patents were invalid on grounds of double patenting as well as anticipation by an earlier patent (US,4,891,845) describing a cosmetic composition for topical application that contained several of the same ingredients that Perricone disclosed in the '693 and '063 patents. Perricone appealed and Medicis cross-appealed the ruling.

On appeal, the Federal Circuit upheld the ruling of double patenting as well as sustaining that several of the claims in the Perricone patents were anticipated by the '845 patent. However, the Appeals Court reversed the District Court's ruling of anticipation and infringement on certain claims. The District Court had reasoned that "[the '845 invention] would inherently function in the claimed beneficial manner when topically applied to the skin" — that is, by virtue of its ingredients and formulation, it is obvious that the '845 invention could treat sunburn in the same way described by Perricone. But the Appeals Court ruled that the District Court erred when basing its anticipation analysis on inherency, because the issue is not whether, if applied to skin sunburn, the lotion would treat said sunburn, but whether the '845 patent discloses the application of the lotion specifically to treat sunburnt skin. As the '845 patent only suggests that the lotion might prevent sunburn and does not disclose the application of the lotion to treat sunburn, the Appeals Court overturned the District Court's ruling of anticipation, and the case was remanded back to the lower courts. This case provides an interesting example of the how language in claim construction can be crucial when disclosing drugs that can prevent and/or treat an ailment.

***Perricone versus Medicis Pharmaceutical Corp.* No. 05-1022, -1023 (20 Dec 2005):**
http://www.fedcir.gov/opinions/05-1022.pdf

Heart drug double trouble for AZ

The US District Court for the East District of Missouri has ruled that two of AstraZeneca's key patents for its blockbuster angina drug extended-release metoprolol succinate (Toprol-XL) are invalid. The ruling comes after AZ sued generic drugmakers KV Pharmaceutical Co., Andrx Pharmaceuticals and Eon Labs Manufacturing after they filed Abbreviated New Drug Applications (ANDAs) for generic versions of the drug. The judge ruled that AZ's compound patent USP5,081,154 and its composition patent USP5,001,161 were invalid because of double patenting, and unenforceable because of inequitable conduct. Although none of the generic versions of Toprol has yet been approved, the ruling will hit AZ hard — Toprol-XL is its fourth-best-selling drug and brought in US$1.29 billion in revenue in 2005 and had at least 18 months of patent protection left. AZ will appeal the decision.

Look-alike not too alike

The first in a series of cases brought by the Japanese pharmaceutical company Eisai Co. against 12 generic drug companies accused of selling look-alike generic drugs has been dismissed by a Tokyo District Court. Eisai filed legal action under Japan's Unfair Competition Act claiming that the companies' generic versions of Eisai's gastritis and gastric ulcer medication, teprenone (Selbex) look too similar to their own branded drug. Japanese Unfair Competition Law prohibits several types of unfair competition, including "using an indication of goods which is identical with or similar to another person's identification of goods which is widely recognised among users and thereby causes one person's goods to be confused with another's". Eisai claim that similarities between the press-through pack sheet and the capsule design of generic versions of teprenone and Selbex could pose a risk to medical institutions and patients who might confuse the two products. The claim against Taiyo Yakuhin Co. was rejected by the Tokyo Court but no judgment has yet been made on the 11 other cases.

More court rulings safeguard Lipitor

Following Pfizer's success against Ranbaxy's challenges against its atorvastatin (Lipitor) patent in the UK and the US, the Court of First Instance in Madrid, Spain, brought more good news for the company when it ruled that the patents for Lipitor are valid and enforceable. The case was brought by Ratiopharm Espana and will be an important indicator for forthcoming challenges by other Spanish generics firms. In another ruling, a challenge brought under Andean Pact Law against Pfizer's Venezuelan patents for the crystalline form of atorvastatin and the process for its manufacture was dismissed by an Andean court, giving Pfizer protection against further challenges in Peru, Ecuador and Venezuela.

Joanna Owens

PATENT PRIMER

Patenting antibodies

Philip Webber

Abstract | Antibody technology has advanced a long way since the early days of Kohler and Milstein's antibody-secreting murine hybridomas[1]; and although Kohler and Milstein's invention was not patented, patent protection for the new generation of murine, chimeric, humanized and human antibody-based drugs is essential to safeguard their future development.

The claims of a patent application must concisely define the matter for which patent protection is sought[2]. In patent applications that relate to antibodies, the claims generally define the antibodies by reference to one or more of the following: the antigen to which the antibody binds; a hybridoma; or the sequence of the antibody polypeptide. The BOX gives some examples of the different ways that antibodies can be claimed.

Antibodies defined by antigens

Traditionally, the European Patent Office (EPO) has readily granted claims of the following format, particularly if the protein antigen itself satisfies the criterion for patentability: "An antibody which binds specifically to protein X" (BOX, example 1). In such claims, the antibody is being defined indirectly — that is, by reference to the antigen to which it binds. Care needs to be taken, however, to ensure that such claims do not inherently cover known antibodies, particularly if the protein is a member of a family of well-known proteins and antibodies against such proteins are already known. In such circumstances, a claim of the following format should be considered: "An antibody which binds to protein X, but not to protein Y", where protein X is the novel protein and protein Y is a known one having epitopes in common with the novel protein.

In the US, claims of the above formats are allowable, but the US courts have recently imposed a requirement that the antigen to which the antibodies bind must be a "fully characterized antigen"[3].

Antibodies defined by hybridoma

In cases in which the antigen that the antibody binds to is already known and some antibodies to that antigen have already been publicly disclosed, a general claim to antibodies against that antigen will lack novelty. However, claims to antibodies that are directed to specific epitopes on that antigen might still be possible (assuming that the known antibodies are not directed to those epitopes).

If the invention relates to a specific monoclonal antibody which is produced by a hybridoma, the invention can be claimed by reference to that hybridoma (see BOX, example 2). The question then arises as to how it is possible to describe the hybridoma in the patent application in a manner which will allow the skilled person to put the invention into practice. The answer is to make a deposit of the hybridoma under the Budapest Treaty with an International Depository Authority[4].

The scope of a claim to a monoclonal antibody defined by a hybridoma will in general be relatively narrow — that is, it will generally only provide protection for the specifically deposited antibody and not other antibodies that are directed to the same epitope. However, deposited hybridomas can also be used to define an epitope on a particular protein and a claim can then be tailored to any antibodies which bind to that epitope[5].

Antibodies defined by sequence

With the advent of phage-display libraries and readily available DNA-sequencing apparatus, antibodies are now often defined by reference to specific amino-acid or nucleic-acid sequences (see BOX, example 3).

It should be noted, however, that if an antibody is known (for example, an antibody that is produced by a known hybridoma), merely determining the sequence of that antibody will not render that antibody novel — it is still the same (known) chemical entity. However, specific fragments of that known antibody might still be patentable, particularly if they have surprising or unexpected properties.

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3. Noelle v. Lederman 355 F.3d 1343, 1349 (US Fed. Cir. 2004)
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5. DakoCytomation Denmark A/S. Dako as monoclonal antibodies against human protein Mcm3, process for their production, and their use. Patent EP 1165615 (2000).

EXAMPLES OF CLAIMS TO ANTIBODIES

The following are examples of different ways of claiming antibodies.

- Example 1: WO2004/041863
  "An anti-IFNγ polypeptide comprising at least one anti-IFNγ single-domain antibody".
- Example 2: WO03/086456
  "An isolated monoclonal antibody or antigen-binding fragments thereof encoded by the clone deposited with the ATCC as PTA-2700"; "The isolated clone deposited with the ATCC as PTA-2700".
- Example 3: WO02/092017
  "An antibody or an antigen-binding fragment thereof that specifically binds the capsular polysaccharide of *Streptococcus pneumoniae* serotype 3 (*S. pneumoniae* PPS-3), wherein said antibody or fragment comprises a heavy chain amino acid sequence comprising an amino acid sequence selected from the group consisting of:
  (a) the amino acid sequence encoded by the DNA sequence set forth in SEQ ID NO: 1;
  (b) the amino acid sequence of residues 31 to 104, inclusive, of the amino acid sequence encoded by the DNA sequence set forth in SEQ ID NO: 1; and
  (c) the CDR1, CDR2 and CDR3 amino acid sequences encoded by the DNA sequence set forth in SEQ ID NO:1".

(In patent applications that refer to nucleotide and/or amino-acid sequences, such sequences are usually listed in a separate section of the patent application called a 'Sequence Listing' in which each sequence is given a unique Sequence Identifier Number — for example, SEQ ID NO: 1, SEQ ID NO: 2 and so on).

AN AUDIENCE WITH…

Steven Nissen

Steven Nissen, Medical Director, Cleveland Clinic Cardiovascular Coordinating Center

Steven Nissen is Medical Director of the Cleveland Clinic Cardiovascular Coordinating Center, an organization that directs multicentre clinical trials. He is a pioneer of cardiovascular imaging and his research focuses on using imaging techniques to assess the progression and regression of coronary atherosclerosis. Nissen has served as Chairman of the FDA CardioRenal Advisory Panel for 5 years and in March 2006 will begin a 1-year term as President of the American College of Cardiology. He recently took on the role of Lead Investigator of the high-profile PRECISION trial investigating the relative safety of cyclooxygenase-2 (COX2) inhibitors compared with conventional non-steroidal inflammatory drugs (NSAIDs).

How did you arrive at the proposed PRECISION study design?

We know from the VIGOR, APPROVe and APC trials that the COX inhibitors appear to increase the risk of atherothrombotic cardiovascular events including myocardial infarction (MI) and stroke compared with placebo. We've not, however, tested the conventional NSAIDS and we always assumed that they were neutral — that they didn't have the antiplatelet effects of aspirin, but that they wouldn't produce harm either. Epidemiological studies were suggesting that all of the NSAIDs posed a risk, and so we faced a fundamental conundrum in medicine: arthritis and cardiovascular risk are both extraordinarily prevalent as age increases, so the population taking anti-inflammatories overlaps substantially with people at cardiovascular risk. If a patient walks into my office with arthritis and heart disease, what do I give them? Ibuprofen, naproxen or the remaining COX inhibitor, celecoxib? The only way to answer that question is to do a massive head-to-head trial in people of sufficient risk to actually get enough cardiovascular events for precise results. That's what's driving the sample size, which currently is looking like 21,000 patients. That will give us about 768 cardiovascular events during a mean exposure of 2 years. When we're done we hope to be able to advise both prescribing physicians and patients about the pain reliever you can take that carries the lowest risk. Now, there are also differential risks for gastrointestinal (GI) toxicity, so the primary endpoints are cardiovascular toxicity, but we're also going to find out about GI bleeding and GI tolerance by collecting ulcer events, and we're going to find out about arthritis efficacy. The COX2 inhibitors were very good pain relievers so if there is a relative risk for cardiovascular events we need to establish the relative benefit on symptomatic pain. We can then inform patients about what benefits they might expect and at what risk.

How do you respond to criticism that the trial is unethical?

If you don't know which of the three drugs is safest then there's not an ethical question, there is equipoise, which is what is required for a clinical trial. I feel very strongly that any of the three drugs we're studying could prove to be superior for safety, and if that's the case then the trial is entirely ethical.

What about suggestions that the trial will give Pfizer more time to protect Celebrex?

This trial has a unique governance model — the design is not Pfizer's, it's ours. It's an academically directed trial designed to answer a scientific question, not a marketing-driven study by Pfizer. It also doesn't buy anybody any time, because all three of these drugs are already being prescribed in the dark by people who don't know their relative safety. What would be inappropriate is to do the kind of trials that have been done in the past that study smaller numbers of patients for shorter lengths of time and exclude patients at high cardiovascular risk. Every other trial has been designed to minimize the potential hazards of the drugs — we haven't done that.

How did you end up getting involved with Pfizer in this study?

I think Pfizer recognized that this trial had to provide a definitive answer and that it had to be done by people who would be trusted. I have been a very outspoken critic on issues of drug safety, and I believe that Pfizer asked me to direct this programme because it knew that the trial goes beyond answering conventional scientific questions; it's in the realm of the public and the media, and that means it has to be done right. One thing I insisted we do, and this is unprecedented in a pharma trial to my knowledge, is to put the entire trial database in the public domain housed at the US National Heart, Lung and Blood Institute one year after the trial is finished. The results have to pass the scrutiny of the most critical individuals and so we will do it in a way that's never been done before.

Have there been any specific challenges to setting up this trial?

We have a problem with the European Agency for the Evaluation of Medicinal Products (EMEA), which has declared celecoxib to be contraindicated in patients with cardiovascular disease, so we are not allowed to do the trial in EU countries. What's fascinating about this, and it's almost inexplicable, is that the EMEA has had input into the trial design. So they want to see the results, and they want input into the design, but they won't let us do the trial in their countries. For example, the EMEA requested that we allow rheumatoid arthritis patients in the trial, and we agreed to that in large part to give the EMEA the data that they seek — and yet they won't let us collect the data in the countries that they regulate. So we're going to do it in Eastern European countries, the US, Canada, Australia, South America and possibly in India, but we would have been a lot happier if the EMEA had granted us the necessary waivers to do the trial in EU countries.

Was it difficult to avoid conflicts of interest?

Avoiding conflicts of interest is so pivotal in this trial that I asked each member of the executive committee, the governing group and the data safety and monitoring board to sign a statement that they will not accept any honoraria, consulting fees or any other monies, not only from Pfizer but from any maker of a drug in development or existing in this class. I think it was the right thing to do. We're really excited about this trial — and we're going to do this one right.