US: the year in review

The key moments in US pharmaceutical law this year, summarised by **R Joseph Trojan**, registered patent attorney and trial lawyer with Trojan Law Offices

It has been an active year for the courts in issuing decisions that will have an impact on the pharmaceutical and medical devices industry. Here are just a few of the highlights from 2008.

Reverse payment agreements do not violate antitrust laws

In October 2008, the Court of Appeals for the Federal Circuit issued a critical decision holding that reverse payments are not per se antitrust violations. See *In re Ciprofloxacin Hydrochloride Antitrust Litigation*, 544 F 3d 1323 (Fed Cir 2008). Reverse payments are payments made by a patent owner to a generic drug maker to end litigation where the generic drug maker challenges the validity of the patent for the drug. These payments have been in the hundreds of millions of dollars.

Reverse payments have been criticised for a variety of reasons, including the fact that they limit competition by allowing potentially invalid patents to remain in force. Essentially, a drug company is paying off a generic competitor to maintain monopoly power for the drug. Some companies believed reverse payments were a per se violation of the antitrust laws and sought to have the practice banned. The Federal Circuit disagreed, holding that it was a proper exercise of monopoly power granted by a patent.

However, not all reverse payment agreements may be legal. The Federal Circuit held that such agreements will be analysed under a rule of reason analysis. But with the guidance provided in the court's decision, it should be possible now to craft reverse payment agreements that can avoid, or at least survive, an anti-trust challenge.

The facts underlying this case are as follows. Barr challenged Bayer's patent for its drug Cipro. Bayer settled with Barr and made US$398m in payments to Barr in exchange for Barr's agreement not to challenge the validity or enforceability of the Cipro patent nor sell a generic version of Cipro until at least six months before the patent expired. Bayer then filed for re-examination and its patent was found valid against other companies' challenges to the patent. Multiple plaintiffs filed suit against Bayer and the companies with which it had reverse payment settlements for federal and state anti-trust law violations and under consumer protection laws.

According to the Federal Circuit, the settlement agreements were not so pernicious to be considered per se violations of anti-trust law. The court applied the rule of reason, in which the plaintiff bears the initial burden of showing that the payment has had an actual adverse effect on competition. Observing that the very essence of a patent is the right to exclude others from making, selling, using or importing the patented invention, the court found the payments were in the scope of an inventor's patent rights and no anti-competitive effect of the payment agreement was established.

Patent Office has unlawfully shortened the life of patents

Normally, a trial court opinion would not be included in a December round-up of important decisions. But the case of *Wyeth v Dudas* is an exception. The District Court in Washington DC issued a decision in September that radically altered the way the Patent Office determines the expiration date of patents. This decision can potentially add years to the life of drug patents and medical devices.

Generally, a patent expires 20 years after the filing date of the patent application. In the event of a delay in the application process, time is added on to the patent if the delay is caused by the Patent Office (often referred to as 'A delay'). Another part of the patent law provides additional time for every day greater than three years after the filing date that it takes for the patent to issue (often referred to as 'B delay').

At issue in *Wyeth* was the interplay of these provisions. The patent law does not permit double counting. The Patent Office had always interpreted double counting to mean that A and B delays should be calculated separately and only the greater adjustment should be used. Thus, a patent would be extended by the length of the A delay or B delay, whichever is longer, but never A *and* B.

The court in *Wyeth* disagreed with the Patent Office, holding that the only way that the A and B periods of time can be classified as double counting is if they occur on the same day. Thus, A and B delays should be added together to the extent they do not occur on the same days. Under *Wyeth*, many patents that have been pending for more than three years before issuance will now be entitled to additional time. For some patents, the increase in time will be significant.

However, the time to act is limited. Any challenge to the calculation must be filed between the time that the Notice of Allowance issues and the payment of the issue fee is made. At the very most, there is a three-month window of time in which to act to request additional time. Proper attention to this critical issue can be worth tens of millions by adding time to the end of the patent when successful drugs and medical devices typically experience their best sales. Unfortunately, for patents that have already issued, there is no easy remedy.

Brand name drug maker held liable for harm caused by generic drug manufactured by another company

In a rather remarkable case issued in November from the California Court of Appeal, brand name drug manufacturers can now be held liable for harm caused by consumption of generic versions of their drugs manufactured by other companies if the brand name manufacturer provided inadequate warnings for the brand name drug. This expansive decision effectively holds brand name drug manufacturers

responsible for the misuse of another company's generic product even when there is no relationship between the two companies.

In *Conte v Wyeth, Inc*, a consumer developed a serious and irreversible neurological condition and alleged that the condition was due to long-term consumption of a generic prescription drug. In addition to suing the generic manufacturers, the consumer sued the name-brand manufacturer, Wyeth, alleging that the manufacturer failed to adequately warn of the dangers of long-term use of the drug in its product labelling and the Physician's Desk Reference monograph.

Under a negligence theory, the Court of Appeal of California reversed summary judgment in favour of Wyeth, holding that 'a common law duty to use due care owed by a name-brand prescription drug manufacturer when providing product warnings extends not only to consumers of its own product, but also to those whose doctors foreseeably rely on the name-brand manufacture's product information when prescribing a medication, even if the prescription is filled with the generic version of the prescribed drug'.

Whether or not the doctor foreseeably relied on Wyeth's warnings is an issue that will be determined at trial. Interestingly, a finding that the generic manufacturer was not liable was affirmed. The court determined that there was no evidence that the doctor relied on warnings provided by the generic manufacturer for the generic drug, even though the labeling and warnings for the generic drug must be identical to those for the name-brand drug under federal regulations. Hence, the maker of the generic drug that caused the harm to the patient was let off the hook by the Court of Appeal while the name-brand drug manufacturer was left to defend the lawsuit. It will be interesting to see if this case is taken up by the California Supreme Court.

The double standard in patent law enjoyed by state universities may come to an end in 2009

It is well known that state universities have made significant contributions to biomedical research and have received a large number of patents for their efforts. Universities regularly sue to enforce their patent rights and receive significant revenue from licensing of patented technologies. There is no question that States take full advantage of the patent system. Yet because the universities are instruments of the states, they are immune from being sued themselves for patent infringement under the 11th Amendment to the US Constitution. To many, it seems patently unfair for a university to use the patent system and the federal courts to create and enforce patent rights, but claim they have a right to infringe other patents with impunity. In 2008, the Supreme Court asked for briefing on this issue in a case that may open the door to patent suits against states.

In *Biomedical Patent Management Corp v State of California*, the Federal Circuit reaffirmed the state's 11th Amendment sovereign immunity, holding that although the state had previously waived its immunity from suit by intervening in an earlier case involving the same parties and subject matter, such prior waiver would not preclude the state from invoking sovereign immunity in a separate or re-filed lawsuit.

Plaintiff Biomedical Patent Management Corp (BPMC), owner of a patent directed to a method for screening birth defects in pregnant women, alleged that the State of California, Department of Health Services (DHS), performed laboratory services, and induced others to perform services, that infringed its patent. There had been three other lawsuits involving the same patent and the same parties.

Generally, a waiver of 11th Amendment sovereign immunity occurs if the state voluntarily invokes the jurisdiction of a federal court or if the state makes a clear declaration that it intends to submit itself to the jurisdiction of a federal court. BMPC argued that California basically litigated away its sovereign immunity through its aggressive patent enforcement in the courts.

Although the Federal Circuit found that DHS had waived its sovereign immunity by intervening and asserting claims against BPMC in an earlier lawsuit, the earlier waiver would not bar the state from invoking sovereign immunity in a later or re-filed lawsuit involving the same parties and subject matter. The court thus affirmed the dismissal of an infringement case against the DHS.

BPMC has petitioned for *certiorari* to the Supreme Court and the Supreme Court has indicated its interest by asking for briefing from all parties. The petition raises the question of whether a state's ability to invoke and reject federal jurisdiction at will undermines the patent system. It is argued that waiver of immunity if a state regularly sues on its patent would remedy the existing inequity and at least partially restore the balance intended by Congress in the Patent Act. It remains to be seen how the Supreme Court will strike the balance.

Safe harbour provision for research uses no longer as safe

For many years, biomedical researchers have benefited from a safe harbour provision in the patent laws that permitted researchers to use certain patented inventions for research purposes without being sued for patent infringement. With the Federal Circuit's August 2008 decision in *Proveris Scientific Corporation v Innovasystems, Inc*, the balance is tipping back toward patent owners. To benefit from the safe harbour provision, researchers need to confirm that they are in strict compliance with its terms.

Under the safe harbour provision, conduct normally constituting infringement is not classed as such if the patented invention is utilised solely for uses reasonably related to the development and submission of information under a Federal law that regulates the manufacture, use, or sale of drugs or veterinary biological products. The Federal Circuit in *Proveris* held that Innovasystems' use of an infringing device is not protected by the safe harbour provision of 35 USC s271(e)(1) because the device was not a 'patented invention' as that term is used in the safe harbour provision.

In reaching its holding, the court conducted an extensive analysis of the policies behind the safe harbour provisions and concluded that neither party is within the category of entities the law was designed to protect, the invention disclosed in Proveris' patent was not a 'patented invention' under safe harbour provisions.

The *Proveris* holding appears to be at odds with prior precedent in *Merck v Integra,* which broadly read 35 USC

s271(e)(1) to protect the infringing user of a patented peptide from liability. The device in *Proveris* related to a research tool for characterising aerosol sprays commonly used in nasal spray pumps and inhalers. Spray characterisation plays an important role in the FDA approval process, but the invention claimed in the patent is not itself subject to FDA approval.

Like the device in *Proveris*, the peptide in *Merck* was not subject to FDA approval. The *Merck* and *Proveris* cases can be distinguished in that the *Merck* court determined that the peptide was not a 'research tool' whereas the Innovasystems' device is arguably a 'research tool'. Given the close question, however, biotech researchers will need to be more cautious when using patented research tools in their research.

A road map for claiming the broadest patent protection for bioactive compounds

The need to file patent applications early and often was the take home lesson for the biotech industry in the case of *In re Alonso*. Biomedical researchers usually focus their research on studying the bioactivity of a single species of a particular genus of compounds even though they know that other species within the genus may very well exhibit the same desired bioactivity or possibly enhanced activity. Therefore, the natural desire is to seek patent protection for the entire genus of compounds. Claiming the genus became more difficult in 2008.

In the case of *In re Alonso*, the researchers claimed a method of treating neurofibrosarcoma (a rare cancer of the sheath of a peripheral nerve) by administering an effective amount of an idiotypic monoclonal antibody secreted in a human-human hybridoma derived from the neurofibrosarcoma cells. The researcher's disclosure only described the preparation of a single monoclonal antibody, but the claim of his application was directed toward essentially all monoclonal antibodies that bind to a neurofibrosarcoma.

The Federal Circuit in *In re Alonso* held that where the researcher disclosed only a single monoclonal antibody capable of recognising one particular patient's neurofibrosarcoma, the applicant's disclosure failed to adequately describe a genus encompassing all human hybridoma-derived monoclonal antibodies capable of recognising any patent's neurofibrosarcoma. The Federal Circuit explained that disclosure of a single monoclonal antibody did not constitute a representative number of species in the genus because two scientific articles in evidence in the case indicated considerable antigenic heterogeneity of tumours between patients and between metastatic sites within a single patient.

Researchers who are aware that there is a great deal of heterogeneity in receptor sites for their compound need to be sure to submit additional data for other species in the genus if they want to claim the entire genus. This may be accomplished by submitting such data in subsequent continuation-in-part patent applications. However, if there is a substantial homogeneity among targeted antigens, then the genus can usually be claimed with some degree of confidence based upon a single species.

Delisting from the orange book remains viable strategy

The Court of Appeals for the District of Columbia gave a boost to the strategy used by patent owners to request delisting of patents contained in the FDA Orange Book.

If a patent holder is not relying upon a particular patent any longer, it can block generic manufacturers from filing an Abbreviated New Drug Application (ANDA) based upon the patented drug. In the case of *Teva Pharmaceuticals USA Inc v Leavitt*, the DC Circuit held that once the FDA officially withdraws a patent claiming a drug from the Orange Book, an ANDA applicant cannot submit a para IV certification to that patent.

In *Teva Pharmaceuticals*, the FDA delisted US Patent No 5,158,952, which claimed Risperdal, from its patent listing database, and soon after updated the electronic version of the Orange Book to reflect this change, but did not update the hardcopy versions. Two months after the delisting, Teva submitted an ANDA, which included a para IV certification directed to the '925 patent. The FDA denied the certification due to the delisting of the '925 patent.

Teva subsequently sued, arguing that Teva's reliance on the hardcopy version of the Orange Book should preclude the FDA from denying Teva's para IV certification. The DC Circuit disagreed, holding that the plain requirements of the statute required a certification to a patent that claimed a drug. Because the patent was already delisted by the time Teva filed its application, no patent claimed Risperdal.

How long this loophole in the ANDA process will be allowed to remain before Congress closes is unknown, but delisting remains an effective strategy for the foreseeable future for patent-holders and an issue that should push generic manufacturers to file ANDAs as soon as possible.

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