



Pharmaceutical

Law Insight

News and analysis of developments in pharmaceutical law

European Commission launches attack on drugs industry

Anti-trust action looms against major drug companies after the European Commission accused pharmaceutical firms of costing Europeans €3bn between 2000 and 2007 in healthcare costs by delaying the release of generics.

Neelie Kroes, European Commissioner for Competition, attacked major pharmaceutical producers in a preliminary report following a year-long investigation into the industry.

The Commission said it had found documents during the investigation that contained admissions from brand-name companies that they had tried to stop generics. It also found evidence of obstacles being placed in the way of less expensive competitors.

Kroes listed a 'toolbox' of strategies that pharmaceutical firms use to stifle the generic drug market in Europe. This included 'patent clusters' where hundreds of patents could be filed for one drug. In one case, no less than 1,300 patents were filed for a single drug medicine. There were also nearly 700 cases of reported patent litigation, lasting on average nearly three years, with generic firms ultimately prevailing in more than 60% of cases. This, said the Commissioner, was a strategy that drug makers used to tie generic producers up in litigation so as to delay the release of generic drugs. There were also more than 200 settlement deals between brand-name and generic companies, of which more than 10% limited the entry of generics and provided for payments from the originator to the generic firms.

'It is still early days, but the Commission will not hesitate to open anti-trust cases

against companies where there are indications that the anti-trust rules may have been breached,' Kroes said.

The breadth of evidence presented by the Commission is damning, said Jonathan Radcliffe, intellectual property partner at law firm Nabarro LLP in London. 'From a patent lawyer's perspective, this is raw data, and in my experience as a lawyer for over 20 years this gels very much with what I've seen on the ground,' he said. 'It has been long suspected that by using the outlined strategies, big pharmaceutical firms delay generics by up to three years at a huge profit to itself. The extreme example given by the commission was of one company making US\$300m as a result of these strategies. All of that benefits shareholders at a cost to members of the public.'

Brian Sher, competition partner also at Nabarro, agreed but said the report falls short in some respects. 'What you don't get in this report is an analysis of how to deal with the problems identified under competition rules,' said Sher. 'They've clearly uncovered a lot of smoking gun evidence, and a lot of documents they uncovered in raids. What interests me is that what do you do with that? On the one hand they accuse brand-name pharmaceutical firms of making agreements with generic firms to delay the release of drugs. It will be easier to take action on this front because all they need to prove is that these agreements had anti-competitive goals. I think what will be more tricky will be tackling the unilateral action of pharmaceutical firms. Strategies that everyone knows go on, such as tying up

IN THIS ISSUE

News

- 1 **European Commission launches attack on drugs industry**
- 2 **Myriad wins appeal for controversial cancer test patent**
- 3 **Consumer group seeks US ban for Glaxo diabetes drug**

Pfizer drops bid for over-the-counter Viagra

Analysis

- 4 **Is the MRP now a tactical choice for generics?**
- 7 **Patentability and prior disclosure: boundaries defined**
- 9 **Ryan Haight law: paper tiger or real change?**
- 11 **No guarantee of data protection for European pharmaceuticals**
- 14 **US: the year in review**

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ISSN: 1747-4981

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Published 10 times a year by:
Informa Law, Telephone House,
69-77 Paul Street, London EC2A 4LQ
tel 020 7017 5532 | www.informaprofessional.com

Printed by: Premier Print Group, London

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Registered Office:
Mortimer House, 37-41 Mortimer Street, London W1T 3JH.

Registered in England and Wales No 1072954.

This newsletter has been printed on paper sourced from sustainable forests.

firms in litigation and attempting to file new patents for old drugs. The question is where do you draw the line? That will be the key challenge. These are industry-wide practices, and how you tackle industry-wide practices is not going to be easy.'

Drug makers, however, have countered the EC's findings by saying that the real reason that the generic drug market in Europe is only 40% of the total pharmaceuticals market, even though in the US it is closer to 60%, is because of the regulatory framework. In the US, for example, there is much more emphasis on competition, and rules such as 180 days exclusivity for generic manufacturers actively encourage the generic industry.

Indeed, large pharmaceutical firms are under a great deal of pressure, particularly from the generics market. The makers of branded drugs face a decline in revenue starting in 2011 when products generating US\$150bn a year will be hurt by generic competition as patents for blockbuster drugs expire. The industry is struggling to protect this revenue with the creation of new drugs. Only 28 new types of drugs were launched from 2000 to 2004, far fewer than the 40 that hit the market from 1995 to 1999.

Bernardine Adkins is partner and head of the anti-trust team at law firm Wragge & Co. She says the Commission has failed to

ask key questions that are needed in an investigation of this kind. 'What I find interesting is that there is no examination of the profits of the pharmaceutical companies,' says Adkins. 'If pharmaceuticals were doing what they are accused of, surely they would have excess profits. That is the line of enquiry the Commission did not take. A lot of what the pharmaceuticals are accused of doing is fundamental to a properly functioning intellectual property system. They are accused of going into litigation, but of course they are, they have to, to protect their legitimate intellectual property rights.'

Launched in January, the Commission probe gathered evidence from Pfizer, GlaxoSmithKline and Sanofi-Aventis, the world's three biggest drug makers. The week in which the report was published also saw raids at the offices of Teva Pharmaceuticals – the world's biggest generic drugs manufacturer. The action was partly triggered by the EU's 2005 action against AstraZeneca in which the company was fined €60m for filing misleading information to patent offices to delay generic versions of its ulcer drug Losec (omeprazole) for most of the 1990s.

It is expected that enforcement action will be taken against some of the pharmaceutical firms targeted, though it is not yet clear as to what form this enforcement will take. ■

Myriad wins appeal for controversial cancer test patent

The European Patent Office has upheld Myriad Genetics' breast and ovarian cancer test patent, which had initially been refused over Myriad's licensing policy.

The patent, first granted in Europe in 2001, had been revoked in May 2004 after complaints by various parties, including several French and UK research institutes. The patents were criticised for being too broad and requirements that blood samples needed to be sent back to Myriad's laboratories in the US at considerable expense raised privacy concerns. Several public health officials also raised concerns that Myriad's tight controls of the test would lead to higher costs in handing over the testing to Myriad's laboratories.

The patent upheld on appeal is smaller in scope, meaning that it only covers diagnostic

testing methods 'caused by a specific group of mutations of the gene'. Myriad will continue to be able to resist the widespread licensing of its technology, however. The company said that it would still require clients to send blood samples to its own laboratories for testing. 'Sub-licensing the analysis to others would be impractical, if not impossible, while holding quality standards where they need to be, due to the extremely sophisticated nature of the test and its interpretation,' said a Myriad spokesman.

Whether Myriad will be able to enforce these controls remains to be seen. France has amended legislation to give it the right to override the patent, while other countries, including the UK, have conducted tests on sample, and refused to pay royalties. ■

Consumer group seeks US ban for Glaxo diabetes drug

GlaxoSmithKline's diabetes drug Avandia (rosiglitazone) should be banned in the US because it can cause death from liver failure and poses many other life-threatening risks, said consumer group Public Citizen.

The group said it has identified 14 cases of Avandia-induced liver failure, including 12 deaths reported in the US Food and Drug Administration's (FDA) Adverse Event Reporting System. Public Citizen's call for a ban comes on the back of a joint press release from the American Diabetes Association and the European Association for the Study of Diabetes, which advised against the use of the drug.

'The FDA is in possession of clear, unequivocal evidence that [rosiglitazone] causes a wide variety of toxicities,' said Public Citizen. 'Many of these are life-

threatening, such as heart attacks, heart failure and liver failure.'

Rosiglitazone sales have fallen sharply since May 2007, when the issue was first raised in an article linking the drug to the risk of heart attack. In that analysis, cardiologist Steven Nissen of the Cleveland Clinic found that people on rosiglitazone had a 43% higher chance of suffering a heart attack.

In a statement, GlaxoSmithKline said it does not believe there to be any liver toxicity risk related to the drug, and it disputes the claims, saying the drug is safe when taken as directed.

The drug already has a black-box warning, the highest kind for a pharmaceutical in the US. FDA officials have said there is a split within the agency about whether to pull rosiglitazone off the market or allow it to stay but with more stringent controls. ■

Pfizer drops bid for over-the-counter Viagra

Drug maker Pfizer has withdrawn plans to make its anti-impotence drug Viagra (sildenafil citrate) available without a prescription in Europe, following concerns from the EU's European Medicines Agency (EMA).

In a statement Pfizer said it withdrew the application 'recognising that there were some concerns regarding the proposed supply of sildenafil citrate 50 milligram tablets without a prescription in the European Union'.

The decision was taken following comments from the European Agency that the availability of sildenafil over the counter would mean that patients would have no medical supervision over their use of the drug, which could delay diagnosis of possible cardiovascular disease related to erectile dysfunction.

Pfizer does not share this concern and says it believes sildenafil 'is a suitable candidate for non-prescription supply' and 'meets the criteria set out by the European Commission guideline for changing the

classification of a medicinal product to non-prescription'. The firm added that 'millions of men in Europe are currently circumventing the healthcare system when seeking erectile dysfunction medicines, exposing themselves to unnecessary risks of medicines from uncontrolled sources and the missed opportunity to get important health information from a healthcare professional'.

Sildenafil overcomes impotence by blocking an enzyme that limits blood flow to the penis. An over-the-counter version of the drug would have helped Pfizer expand the Viagra brand and protect itself against generic competition before its patent expires in 2012. Pfizer has already suffered from the growth in sales of generic sildenafil on the internet, bought from countries where it does not have the same patent protections as it does in Europe or the US. Through over-the-counter sales, it might have been able to recapture a share of those customers who buy it illegally rather than discussing the matter with their doctor and possibly being refused the drug. ■

Sanofi agrees to allow Allegra and Nasacort generics

UNITED STATES

Pharmaceutical firm Sanofi-Aventis has reached a settlement with Barr Pharmaceuticals and Teva Pharmaceuticals. Barr and Teva have been seeking to bring out generic versions of Sanofi's anti-allergy drugs Allegra (fexofenadine) and Nasacort (triamcinolone). Sanofi said in a statement that its unit in the US had agreed to grant Barr and Teva a licence to certain patent rights, which will allow them to sell generic versions of fexofenadine and triamcinolone in the US in exchange for payment of royalties. Some royalties for past sales will also be paid.

Barr facing suit over generic Oxytrol

UNITED STATES

Watson Pharmaceuticals has filed a suit against Barr Pharmaceuticals in an attempt to prevent the release of a generic version of its overactive bladder drug Oxytrol (oxybutynin). Barr challenged Watson's oxybutynin patent, and filed an Abbreviated New Drug Application with the US Food & Drug Administration in October 2008. They would be the first company to produce a generic version of the drug. In response, Watson has filed a lawsuit against Barr, an action which formally initiates the patent challenge process under the Hatch-Waxman Act.

Correction

In the October issue of *Pharmaceutical Law Insight*, Neil Hoffman was referred to as an associate in Kilpatrick Stockton's Corporate Department when he is in fact Counsel at Kilpatrick Stockton.

Is the MRP now a tactical choice for generics?

Guidance from the European Court of Justice clarifies the operation of the mutual recognition procedure, say **Gareth Morgan** and **Helen Cline** of Taylor Wessing

A recent decision by the European Court of Justice (ECJ) in *R (on the application of Synthon BV) v Licensing Authority*, Case C-452/06 found that a member state being asked to approve a generic product under the mutual recognition procedure (MRP) has only limited powers to challenge the approval granted by another member state. In this case, the UK medicines agency, the Medicines and Healthcare Products Regulatory Agency (MHRA), was liable in damages to generic company Synthon after it refused to recognise the marketing authorisation issued for a Synthon product (Varox) in Denmark.

This article will examine the importance of this case, including a summary of the ECJ's ruling on the operation of the mutual recognition procedure, how it interacts with current law governing the issue of marketing authorisations and its effect on practice within the pharmaceutical industry.

The law

Under European legislation a marketing authorisation is required to market a medicinal product in any European member state. There are now four routes to obtaining a marketing authorisation in the EU:

- the national route which can be undertaken in each member state;
- the mutual recognition procedure (MRP);
- the decentralised procedure (DCP); and
- the centralised procedure (CP).

Centralised procedure

The CP is mandatory for all new active substances for the treatment of HIV/AIDS, cancer, diabetes and neurodegenerative disorders, and for orphan-designated substances. Other new active substances can use the procedure, as can medicinal products that constitute a significant therapeutic, technical or scientific innovation.¹ However, the definition of the phrase 'significant therapeutic, scientific or technical innovation' is not entirely clear. The application

procedure is administered through the European Medicines Agency (EMA).

As with the DCP and MRP discussed below, the timelines for the centralised application procedure are strict and the procedure is designed to be a fast and effective way of obtaining a marketing authorisation throughout the Community. However, any issues raised during the application procedure may cause delay for the entire authorisation in every member state.

National and mutual recognition procedure

The DCP and MRP are European authorisation procedures that involve one member state assuming responsibility for driving the application procedure. Such states are known as reference member states (RMS).

Under the MRP procedure a company first makes a national application for a marketing authorisation in one member state.² When this marketing authorisation is granted, the MRP can be used sequentially in other member states to expand cover as and when required. Article 28 of Directive 2001/83/EC (as amended), provides the legal basis for the marketing authorisation holder to initiate the MRP process. The member state designated as the RMS sends the updated product documentation to the concerned member states (CMS) which then validate the application.

The process then follows the general timeline of:

- day 50 – CMS submit comments to the RMS and the applicant;
- day 60 – applicant responds;
- day 68 – RMS sends assessment of applicant's response;
- day 90 – after further discussion, the CMS, RMS and applicant attempt to reach consensus on the application and, if this is not possible, the points of disagreement are referred to CMD(h)³ within seven days of day 90;

- day 150 – if consensus cannot be reached at CMD(h), the application is then referred to CHMP⁴ for arbitration.

Whatever the way in which the application is closed, if consensus has been reached, national product authorisations are granted within 30 days of the closure of the MRP provided the applicant provides sufficient product-related document translations to the satisfaction of each CMS.

This route has the advantage that there will be a marketing authorisation in place when expanded cover is applied for. Therefore, post-marketing data may be available to assist in answering the concerns of any of the CMS.

Decentralised procedure

The DCP creates a streamlined application and assessment procedure that has the potential for significantly shortened approval times compared with the MRP. It should be used where a medicinal product has not yet received a marketing authorisation in any member state. It allows simultaneous parallel applications to selected CMS using the RMS to drive the process forward. It might be advantageous for companies who do not require marketing authorisations in all member states, who do not have a presence in every member state, or who cannot or do not wish to take advantage of the CP. The DCP can be used across all member states. As with the CP, however, it is possible that issues raised by CMSs during the application process could delay the grant of a marketing authorisation in all the designated states.

As with the MRP, the precise procedure followed depends upon whether it is the member state or the applicant initiating the procedure. It can end at different stages depending on the degree of harmonisation of the original summary of product characteristics, the quality of the dossier and the assessment report. If consensus is reached between the member

states it would be possible to end the procedure and recommend marketing authorisation at day 105.

The general principles and post-application administrative time line for the DCP involves:

- day 70 – the RMS forwards a preliminary assessment report to CMS and the CMS have until day 100 to feed their comments on this report back to the RMS;
- day 105 – the RMS, CMS and applicant attempt to reach consensus on the assessment report and any issues raised;
- clock stop – there then follows a period of up to three months where the applicant agrees a final response document and also possibly supplements its dossier in order to address questions raised;
- day 106–120 – the RMS then updates the preliminary assessment report and prepares a draft assessment report and other product associated documentation that is then sent to the CMS
- if consensus between CMS, RMS and applicant is not reached then, the application must be discussed at the CMD(h) with the potential to refer any matters not resolved to CHMP for arbitration;
- following consensus, the national grant of product authorisations must be determined within 30 days.

The options for obtaining marketing authorisation can give rise to tactical choices and careful regulatory strategic decisions.

The case

Synthon, a generic pharmaceutical company, was granted a marketing authorisation for its product Verox under the abridged procedure in Denmark, on the grounds that it was ‘essentially similar’ to the already authorised product, Seroxat. Verox and Seroxat contain different salts of the same active pharmaceutical, paroxetine.

The drug, paroxetine, used to treat depression, had been originally marketed, by Smithkline Beecham, in the form of its hydrochloride hemihydrate salt. Both Synthon BV and Smithkline Beecham discovered that a different salt, paroxetine methanesulfonate, has better pharmaceutical formulation properties. Synthon obtained a Danish marketing authorisation for its

product from the Danish Medicines Agency on the basis that the two salts were ‘essentially similar’. SmithKline Beecham challenged that decision on the ground that the active principals were not the same, and so there could not be essential similarity. The ECJ ruled in favour of essential similarity. In the meantime Synthon had applied to the MHRA, via the MRP, for recognition of its Danish approval, and was initially refused marketing authorisation in the UK. In fact, MHRA refused even to validate the application.

The MHRA believed it was entitled to refuse to recognise Synthon’s Danish authorisation because it considered that different salts of the same active moiety had a different qualitative and quantitative composition. However, the Commission then issued guidance indicating that different salts of the same active moiety should generally be regarded as being ‘essentially similar’, and this was subsequently confirmed by the ECJ when reviewing Synthon’s Danish authorisation (*SmithKline Beecham* [2005] Case C-74/03, ECR I-595).

Synthon was eventually granted a UK marketing authorisation for Verox in 2006, but nevertheless continued its action in England for judicial review of the initial MHRA decision and for damages. The English court felt that the case raised issues of general importance in European law and asked the ECJ to issue guidance on the correct approach to the MRP and to clarify when damages may be an appropriate remedy for breach of Community law by an EU member state.

Although we will report the court’s

decision on the damages claim, it is the ECJ’s ruling on the operation of the MRP that will have the greatest effect on practice within the pharmaceutical industry.

ECJ guidance on MRP

The ECJ decided that there should be no difference under the MRP procedure founded in art 28 of Directive 2001/83 EC (‘the Directive’) whether one is considering full applications under arts 6 and 8 or abridged applications under art 10. The submissions of the MHRA and SmithKline Beecham had urged the ECJ to decide differently on the grounds that member states, when in receipt of an application under the MRP that had proceeded via the abridged procedure, had the right to conduct their own assessment of ‘essential similarity’ for the purpose of granting an authorisation under the abridged procedure. The ECJ stressed that one of the objectives of the Directive had been to abolish all barriers to the free movement of medicinal products.⁵ The court thought that to proceed as suggested by the MHRA and SmithKline Beecham would be to deprive arts 28 and 29 of the Directive of most of their effect.

The ECJ highlighted that art 29 does permit member states to object to marketing authorisation applications under the MRP, but that these grounds are limited to reasons of risks to public health and, to invoke such a provision there is a particular procedure that needs to be adhered to. What constitutes ‘a risk to public health’ was not within the scope of the questions the ECJ had been asked to answer.

The options for obtaining marketing authorisation can give rise to tactical choices and careful regulatory strategic decisions.

In summary, the *Synthon* case establishes that:

- Under EU legislation there is no distinction as to the scope or effect of marketing authorisations granted under the ordinary or abridged procedure.
- A CMS being asked to approve a generic product under the MRP has only limited powers to challenge the approval granted by another member state and must follow the prescribed procedures.
- It is not open to the regulatory authority being asked to approve a generic under the MRP to refuse to validate/accept the application on the grounds that it was debatable whether the generic product in question was ‘essentially similar’ to its reference product. That was only open to the member state considering the original application under the abridged procedure – in this case, Denmark.
- The regulatory authority in the country where mutual recognition is applied for must rely on the assessment carried out by the RMS otherwise each member state could reopen the issues which would nullify the intended advantages of the MRP.

Decision on damages

It is already established in case law⁶ that where a breach of EU law by a member state is attributable to a public authority, an individual is entitled to damages if three conditions are fulfilled:

- 1) The rule infringed is intended to confer rights on them
- 2) The breach is serious
- 3) There is a causal link between the breach and the damage sustained.

The English court in this case asked the ECJ to give guidance on the second of these conditions.

The ECJ held that it is for the individual member states to determine if there has been a serious breach and that it could only give guidance as to what might amount to a serious breach. The ECJ considered that the following factors were relevant in considering if there had been such a manifest and grave disregard by the member state for the limits set on its discretion as to amount to a serious breach:

- 1) Clarity and precision of the rule infringed.

- 2) The discretion given to the national authorities by that rule.
- 3) Whether the infringement or damage caused was intentional or unintentional.
- 4) Whether any error in law was excusable or inexcusable.
- 5) The fact that the position taken by a Community institution may have contributed to the adoption or maintenance of national measures or practices contrary to Community law.

The ECJ decided that the MHRA has a limited discretion under the legislation and its failure even to validate the Danish approval on the grounds that essential similarity between the generic and its reference product was not established did constitute a sufficiently serious breach of EU law, capable of rendering the MHRA liable in damages to Synthon for the time it had been kept out of the market. Articles 28 and 29 of the Directive were sufficiently clear, the MHRA had no evidence that a risk to public health existed, nor had it attempted to invoke the procedure set out in art 29.

Tactical choices

The case clarifies why in many cases it may be advantageous for generic companies to follow the MRP. The ECJ has now clarified that there are only very limited grounds (where there is a risk to public health) on which a member state can object to recognition of a marketing authorisation granted by a RMS under the MRP.

The DCP creates a streamlined application and assessment procedure, which has the potential for significantly shortened approval times compared to the MRP. However, under the DCP the nominated RMS is required to circulate its draft assessment report to the regulatory authority of all countries in which a marketing authorisation is sought under the DCP. Any member state who has objections or questions may raise them during the 90-day mutual recognition phase. The applicant then must satisfactorily address such a consolidated list of objections/questions in order for the application to be granted. Although a similar consultation process exists for the RMS’s preliminary assessment report for

the MRP, a marketing authorisation will already exist in a member state, generally in the RMS, for the product.

The post-marketing data generated under this authorisation may be valuable in overcoming any objections raised by CMSs and avoid the possible delays that may be incurred under the DCP or CP if further data is needed to satisfy these objections. One additional advantage of using the MRP is that the post-marketing data generated from the initial authorisation could ensure that, at least initially, the commercial and safety risks of any serious adverse reaction are minimised.

This ruling gives companies the opportunity to proceed with applications in single member states in the knowledge that, if successful, that authorisation must then be recognised throughout Europe via the MRP (absent the establishment of a risk to public health). The post-marketing data generated in the initial member state may mean that costly delays in getting approval under the DCP or CP are avoided. Tactically, companies may therefore decide that the certainty of dealing with one regulatory authority and then applying for mutual recognition of that authorisation is preferable to dealing with the consolidated list of questions under the DCP.

1 Article 3 (2), reg 726/2004

2 In practice, the applicant often informs the relevant competent authority that the national authorisation will be used as a basis for the MRP when the initial application is made.

3 Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human

4 Committee for Medicinal Products for Human Use

5 Further, see recitals 12 and 14 of that Directive

6 See *Brasserie du Pecheur* and *Factortame*

Gareth Morgan is a partner in Taylor Wessing’s intellectual property department. He has experience in all areas of contentious and non-contentious intellectual property law with a particular focus in the life sciences and healthcare sector, and also advises on medicinal regulatory law.

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Patentability and prior disclosure: boundaries defined

The ruling in *Dr Reddy's v Eli Lilly* may lead to greater patent protection for pharmaceutical companies, explain **Gregory Bacon** and **Andrew Bowler** of Bristows

The recent decision of the English High Court in *Dr Reddy's Laboratories v Eli Lilly* [2008] EWHC 2345 (Pat)¹ clarifies the tests for novelty and inventive step of a patent for a pharmaceutical compound where there has been prior disclosure of a class that includes that compound. The decision of Mr Justice Floyd is also of interest as he provides his comments on the status of 'selection patents' in English law.

Background

The patent in suit was the result of Eli Lilly's drug development programme into novel treatments for schizophrenia known as atypical antipsychotics, resulting in the discovery of olanzapine, which is now one of the leading treatments for schizophrenia. The patent claimed olanzapine and its various salts. Dr Reddy's applied to revoke the patent.

The traditional treatments for schizophrenia were known to be associated with a number of significant side effects, in particular a group of motor side effects known as extra pyramidal symptoms (EPS). Some of these motor side effects are described as tardive, as they only manifest themselves some time after exposure to the drug, and may continue even after discontinuation of the treatment.

A significant breakthrough in treating schizophrenia was the discovery of clozapine. Clozapine is as effective as the classical antipsychotics, but is not associated with EPS. It was therefore termed an atypical antipsychotic. Clozapine was not the panacea hoped for, however. Its use was curtailed by the incidence of agranulocytosis, a lethal suppression of white blood cells, in a significant proportion of patients. Although clozapine could still be administered in carefully monitored patients, there was an obvious desire to discover further atypical antipsychotics, ie those that could treat schizophrenia without causing EPS, but that would not lead to agranulocytosis.

Those investigating novel atypical antipsychotics included Eli Lilly. During the course of its research, Eli Lilly developed a number of lead compounds, including olanzapine (although olanzapine was not the first lead identified by Eli Lilly). In parallel, Eli Lilly also filed an application for a patent (before that in suit) claiming a wide class of novel compounds that were stated to have 'useful central nervous system activity'. The class was defined by reference to a general formula with a number of substitution positions, often referred to as a 'Markush' formula. The total number of compounds encompassed by the formula ran to some 10 billion billion. Some preferred substituents were provided, giving a preferred group of some 86,000 compounds. The specification of the application then listed 100 specific examples by name, although no physical properties were given for these 100 examples, and 15 synthetic examples for a selection of compounds. Olanzapine was not one of the 100 compounds, nor the subject of any of the synthetic examples. However, the necessary substituents for olanzapine did fall within the narrower range that gave the 86,000 preferred possibilities. Dr Reddy's cited this earlier patent application against the patent in suit.

Dr Reddy's also cited other prior art documents, but none of these specifically included olanzapine as an example. These related to disclosures of similar compounds, and discussed the rationale for various substituents based upon structure-activity relationships, in particular, electron distribution across the compound.

Novelty

Floyd J reviewed both English and EPO case law on whether a claim for an individual compound is novel if it is selected from a prior disclosed class. He referred to *Synthon v SmithKline Beecham* [2005] UKHL 59, and in particular, the requirement for anticipation that the prior art disclose subject matter

which, if performed, would necessarily result in an infringement of the patent in suit. He concluded from this general principle that a generic disclosure does not normally take away the novelty of a subsequent claim to a member of a class.

In determining whether a Markush formula could be considered as one such generic disclosure, such that a subsequent disclosure of a particular compound falling within that formula could be novel, Floyd J reviewed a number of EPO Technical Board of Appeal decisions, and in particular, the case of *Draco Xanthines*, Case T-7/86. In that case, the board had held that the disclosure of a general structural formula did not specifically disclose each of the individual compounds that could be obtained from all the possible variants at each substituent position.

Furthermore, in *Hoechst Enantiomers*, Case T-296/87, the Technical Board of Appeal held that the prior disclosure of a racemic mixture did not mean that the enantiomers were disclosed in individualised form and therefore the novelty of a patent to the enantiomers was not destroyed by the disclosure of the racemate (although this only applied where the disclosure of the racemate did not also specifically name enantiomers which could be produced).

In the Court of Appeal in *Generics v Lundbeck* [2008] EWCA Civ 311, Lord Hoffmann had specifically approved this reasoning, and Floyd J accepted that a general Markush formula would not normally take away the novelty of a subsequent claim to an individual compound unless that compound was disclosed in individualised form, eg, by disclosure as a specific example of the wider class of compounds. In this case, a claim to olanzapine had not been anticipated by the prior Eli Lilly patent application.

Selection

Although not ultimately required to do so, as the patent in suit was held to be valid in any event, Floyd J also reviewed the case law on

In this case, a claim to olanzapine had not been anticipated by the prior Eli Lilly patent application

selection inventions. He referred to the classic espousal, in the case of *IG Farbenindustrie* (1930) 47 RPC 289, of the doctrine of allowing patents to old or obvious inventions where the invention lay in the selection from a class. In that case, a three-step test had been set out by Mr Justice Maugham for a selection patent to be valid: (1) the patent must be based on a substantial advantage secured (or disadvantage avoided) by the selection; (2) the whole of the selected members must possess the advantage; and (3) the advantage of the selection must essentially be peculiar to the selected group.

Mr Justice Floyd reasoned that the judge in *IG Farbenindustrie* had not set out an exception to the law of novelty, which still fell to be decided by the principles elucidated in the relatively recent case of *Synthon*. Instead, the test could be relevant to whether there was subject matter in a selection patent which could support inventive step. Despite the decision in *IG Farbenindustrie* surviving the House of Lords' decision in *Du Pont* [1982] FSR 303 and that of the Court of Appeal in *Hallen v Brabantia* [1991] RPC 195, Floyd J, relying on EPO jurisprudence (some of which is referred to above), considered that the three-step test would not assist in overcoming a finding that a compound was specifically disclosed in a prior document. A claim to that compound would lack novelty.

The judge instead stated that if a compound is selected from a disclosure of a general class wherein it has not been individualised, such that it is novel (as set out above), the advantage described in the three-step test may assist with inventive step. However, satisfaction of the three-step test is not a prerequisite for inventive step in such cases. Mr Justice Floyd therefore appears to suggest that the three-

step test is like many such tests in patent law: more helpful in some cases than others, but never mandatory. However, his reasoning is interesting, particularly in light of the support for selection patents by the House of Lords in *Du Pont* and the Court of Appeal in *Hallen v Brabantia*, and it remains to be seen whether an appellate court would agree with his finding that, in light of the decision in *Synthon* and the EPO jurisprudence, the 'selection patent' test has only the limited application elucidated in this case.

Inventive step

Having identified that the patent in suit was novel in the classical sense, ie in that novelty was present without having to rely on selection, Floyd J applied the familiar structured approach to obviousness, as restated in *Pozzoli v BDMO* [2007] EWCA Civ 588. The existence of an advantage possessed by the selected example that was novel in the conventional sense did not need to be demonstrated, although it was relevant to the overall assessment of obviousness.

In this case, the judge referred to the fact that knowledge of structure-activity relationships as an important tool in developing lead compounds was common general knowledge at the priority date of the patent in suit, but that there were no rigid rules as to how this should be done. Synthesising novel compounds and testing them would be required to develop knowledge of the particular structure-activity relationship, and this would involve a substantial amount of work. On the evidence, the judge concluded that the patented invention involved an inventive step. In particular, he stated that the prior art did not provide sufficient leads in the direction of olanzapine.

Insufficiency

The claimant also sought to invalidate the patent in suit on the basis of insufficiency. The claimant argued that the patent could only be valid as a selection patent over the prior art, and that the patentee had failed to disclose the surprising advantage that olanzapine was alleged to possess over the previously disclosed class. Thus, the invention was not disclosed with sufficient clarity and completeness. Mr Justice Floyd agreed that the special case of selection patents, as they were previously understood, might require a disclosure of the advantage of the compound over the prior art to avoid a finding of insufficiency.

However, as described above, the judge held the patent in suit to be novel in the classical sense and not obvious (without having to rely on any doctrine of selection patents). Accordingly, the patent was sufficient on the basis that it disclosed the novel compound olanzapine, and its use in treating schizophrenia.

Conclusion

The decision is helpful to those in the life sciences industry embarking on large research and development projects. Further patent protection may now be available in the UK should original leads and fallback compounds fail in development, so long as the new compounds are not 'individualised' in earlier patents. However, once such an 'individualised' disclosure of a compound has been made, it now appears that at least one respected High Court judge doubts that a patent to the selection of that compound on the basis of an advantage enjoyed by that compound over the wider class would be novel.

¹ Available at www.bailii.org/ew/cases/EWHC/Patents/2008/2345.html

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Ryan Haight law: paper tiger or real change?

Ned Milenkovich, Pharm D, JD, asks whether the US Ryan Haight Online Pharmacy Law will make a genuine change to controlled substances internet prescriptions

Internet pharmacies will once more feel legal pressure on their drug-dispensing activities, this time resulting from new attempts by the US government to eliminate online distribution and dispensing of controlled substances unless certain requirements can be met.

In an ongoing effort to reel in and curb illegal sales of controlled substances from taking place within the internet pharmacy sector, the US Congress recently passed legislation, and President Bush signed the legislation into law, on 16 October 2008, having the effect of amending the federal Controlled Substances Act (CSA).

The amendments are intended to prevent rogue pharmacies from dispensing controlled substances via the internet into and throughout the US. The Ryan Haight Online Pharmacy Law, named after a teenager who died from an overdose of narcotic drugs that he obtained via the internet, contains language that amended the CSA and placed restrictions on online pharmacies. The legislation comes hot on the heels of recent Drug Enforcement Administration (DEA) enforcement actions regarding internet pharmacies and distribution of controlled substances to those pharmacies.

The Ryan Haight law permits the DEA to register only those pharmacies that are able to successfully demonstrate their ability to meet specific criteria to dispense controlled substances to consumers via the internet. In short, this law prohibits dispensing of controlled substances by way of the internet unless:

- 1) the patient is in receipt of a 'valid prescription';
- 2) the DEA has taken the necessary steps to modify the pharmacy's current DEA registration to also permit it to dispense controlled substances via the internet (it remains undetermined whether the DEA would require Internet pharmacies to first register as a pharmacy and then obtain a modification to the existing registration

or if 'online pharmacy' will be a separate category on the registration application the basis of which a valid registration would be issued by the DEA);

- 3) the pharmacy meets specific reporting obligations to the Attorney General respecting the quantity of controlled substances dispensed via the internet, ie, when either dispensing 100 prescriptions or 5,000 or more dosage units in any given month;
- 4) the pharmacy provides notice to the Attorney General and applicable state board of pharmacy 30 days before offering to sell, delivering, distributing or dispensing controlled substances via the internet;
- 5) the name, address, telephone number, professional degree, and states of licensure of any practitioner who has a contractual relationship to provide medical evaluations or issue prescriptions for controlled substances, through referral from the pharmacy website or at the request of the owner or operator of the website, or any employee/agent;
- 6) the pharmacy certifies that it complies with the Ryan Haight law and posts its name, address, telephone number, email address, and pharmacist-in-charge professional degree and state licensure information on its internet homepage, among other things; and
- 7) a statement on the website stating that the pharmacy will only dispense a controlled substance upon receipt of a 'valid prescription' including a description of what that means.

The Ryan Haight law also provides states with the ability to bring civil action in federal district court to enjoin internet pharmacies from further activity and has the effect of increasing penalties for the illegal distribution of schedule III-V controlled substances.

Of significance, it also makes it illegal for controlled substances to be 'delivered, distributed or dispensed by means of the

internet without a valid prescription'. 'Valid prescription' is defined as 'a prescription that is issued for a legitimate medical purpose in the usual course of professional practice by ... a practitioner who has conducted at least one in-person medical evaluation of the patient ... or a covering practitioner'. An 'in-person medical evaluation' is a 'medical evaluation that is conducted with the patient in the physical presence of the practitioner, without regard to whether portions of the evaluation are conducted by other health professionals'. The Ryan Haight law also defines a 'covering practitioner' as 'a practitioner who conducts a medical evaluation (other than an in-person medical evaluation) at the request of a practitioner who ... has conducted at least one in-person medical evaluation of the patient or an evaluation through the practice of telemedicine, within the previous 24 months ... and is temporarily unavailable to conduct the evaluation of the patient'.

To 'deliver, distribute, or dispense by means of the internet' refers, respectively, to any delivery, distribution, or dispensing of a controlled substance that is caused or facilitated by means of the internet.

According to the Ryan Haight law, an online pharmacy is an entity or internet site that 'knowingly or intentionally delivers, distributes, or dispenses, or offers or attempts to deliver, distribute, or dispense, a controlled substance by means of the internet' while excluding: (i) registered manufacturers or distributors who do not dispense to unregistered individuals or entities; (ii) registered non-pharmacy practitioners; (iii) hospitals or medical facilities operated by US agencies; (iv) 'mere advertisements that do not attempt to facilitate an actual transaction involving a controlled substance'; (v) a person, entity, or internet site that is not in the US and does not facilitate the delivery, distribution, or dispensing of a controlled substance by means of the internet to any

person in the US; or (vi) a registered pharmacy 'whose dispensing controlled substances via the internet consists solely of 'filling or refilling schedule III-V prescriptions'. The law also addresses the new requirements for telemedicine and provides the US Attorney General with the authority to issue registrations to practitioners who practice telemedicine.

Notwithstanding its current standing as approved legislation, there are several areas of the Ryan Haight law that will need to be clarified. For example, the law defines what a 'valid prescription' is intended to be, although historically federal laws and DEA regulations have deferred to the individual states for purposes of defining a valid prescription since the states are traditionally relegated the duty of protecting the public against this type of harm. Including this definition raises several questions. A 'valid prescription' is defined as one 'issued for a legitimate medical purpose in the usual course of professional practice by ... a practitioner who has conducted at least one in-person medical evaluation of the patient ... or a covering practitioner'.

DEA regulations have long required that for controlled substance prescriptions to be effective they 'must be issued for a legitimate medical purpose by an individual practitioner acting in the usual course of professional practice'. The DEA has previously already addressed the issue of internet pharmacies and stated that a bona fide physician/patient relationship must be present for a prescriber to issue a prescription in the usual course of professional practice and that the prescriber must have conducted a physical examination to establish such a relationship. The new Law requires an 'in-person medical evaluation'. The question becomes whether an 'in-person medical evaluation' is the same as a 'physical examination'. It is likely that DEA will take the position that an 'in-person medical evaluation' is synonymous with a 'physical examination'. However, it is possible that undertaking an 'in-person medical evaluation' might involve diagnosing a patient without physically examining them, such as through a questionnaire, while a physical examination seems to include some form of hands-on physical evaluation

that might involve listening to lungs or heart or palpating an organ such as the liver, for example. In short, the DEA will need to better characterise what is meant by 'in-person medical evaluation' in light of its prior use of an arguably different term for such purpose.

Additionally, the definition of 'covering practitioner' seems to indicate that 'an evaluation of the patient through the practice of telemedicine' is an adequate substitute for an 'in person medical evaluation'. This, however, should be further clarified by DEA. Finally, a 'valid prescription' has no time limits during which a prescriber is required to conduct a single in-person medical evaluation, but Ryan Haight also requires a practitioner for whom a prescriber is covering to have conducted such an evaluation within the past 24 months.

Also, pharmacies do not typically engage in distribution of controlled substances pursuant to a prescription so it is unclear why the new law prohibits distributing, along with delivery and dispensing, without a valid prescription. 'Distribute' means 'to deliver (other than by administering or dispensing) a controlled substance or listed chemical'. Controlled substances are 'dispensed,' not 'distributed,' pursuant to a prescription. 'Dispensing' is the delivery of 'a controlled substance to an ultimate user or research subject by, or pursuant to the lawful order of, a practitioner'. By prohibiting distribution without a valid prescription the law prohibits something that should not occur in the first place under a pharmacy licence. It is possible that it was really intended to prohibit distribution from a wholesale supplier to an online pharmacy; however, this language should have been better articulated before the passage of the Ryan Haight law. Depending on the intent of using the term 'distribution' the law may need to be amended to better reflect what the legislature had intended.

The Ryan Haight law provides little insight with regards to how any endorsement or modified registration DEA will be provided to pharmacies so they can dispense controlled substances via the internet. As a result, DEA will need to develop a process for 'tagging' those

internet pharmacies that are involved with legitimate dispensing activities. Such a process will assist DEA in tracking the legitimate pharmacies; however, DEA will still need to overcome the hurdles of identifying those pharmacies lacking modified registrations in order to keep them from dispensing via the internet.

The larger question is whether and to what extent the DEA will be able to prevent those illegitimate internet pharmacies that operate abroad from trafficking controlled substances into the US and what methods would be available to the DEA to prosecute those cases internationally, if at all. If the DEA is unable to enforce Ryan Haight across borders, then this mandate may prove to have limited utility with respect to internationally based rogue internet pharmacies who continue to ship illegitimate prescriptions into the US. The modified registration requirements will validate a pharmacy's legitimacy by providing the DEA with verification of an existing internet pharmacy, but in order for the the Ryan Haight law to be effective, the DEA must prevent patients from ordering from pharmacies that have not met the requirements of that law, whether they be in the US or abroad. In the end, the DEA will likely require international cooperation from other governments to curb any illegal activity abroad in order to have any real effect domestically. Signs of this are already occurring. An international cooperation in November, codenamed operation Pangea, witnessed an unprecedented global coordinated sweep of internet pharmacies by Interpol in nine countries. The sweep included dozens of locations in Britain, Germany, Ireland, Israel, New Zealand, Singapore, Switzerland, Canada and the US.

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No guarantee of data protection for European pharmaceuticals

Dr Christian B Fulda, Rechtsanwalt, and Elizabeth Campbell, solicitor, of Jones Day, examine the implications of the German *Plavix* case

Data protection, in conjunction with patent protection, is the central driving force for innovations in the pharmaceutical industry. Whereas patent protection protects only the invention, data protection extends to protect a company's investment in the pre-clinical and clinical research behind the development of the product. Costs for the development of a new pharmaceutical product currently amount to approximately US\$800m, a major part of which is attributable to the data required for the dossiers to put the product on the market. The data, and the investment behind it, are protected by the European regulatory framework.

However, in its decision in the German *Plavix* case the Administrative Court of Appeal (Oberverwaltungsgericht; (Court of Appeal)) of Münster, the Court queried the scope of data protection.

Background

Sanofi-Aventis received approval for its anticoagulant Plavix with the agent clopidogrel sulfate on 15 July 1998. At the same time, Bristol-Myers Squibb (BMS), the US distribution partner and co-distributor in Europe, received the approval for Iscover from the European Medicines Agency (EMA). In Germany, applications for approvals before 30 October 2005 are subject to data protection for 10 years, pursuant to §24a of the German Pharmaceuticals Act (Gesetz über den Verkehr mit Arzneimitteln; (AMG)) before the amendments to this section were incorporated due to Directive 2004/27/EC. The former version of §24a prevents manufacturers of generic pharmaceutical products from applying for approval of generic drugs using the originator's data for 10 years. Therefore, an application for approval of a generic form of Plavix would not have

been expected before 16 July 2008 and, as the average application takes between 10 and 12 months to process, generic drugs would not have been expected on the market before mid-2009.

Therefore, it was surprising that the German Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte; (BfArM)) approved three preparations with the agent clopidogrel besylate on 21 May 2008. The applications for approval were filed for the German companies Ratiopharm and Sandoz. Sanofi-Aventis and BMS lodged an opposition, which led to the approval being suspended pursuant to §80 of the Rules of the Administrative Courts (Verwaltungsgerichtsordnung; (VwGO)).

The Administrative Court (Verwaltungsgericht; (VG)) of Cologne, in its (identical) decisions dated 25 July 2008¹ and 5 August 2008², held that the term of

protection for the original manufacturers had expired on 15 July 2008 and that therefore the data was no longer entitled to protection. As a result of a weighing of interests, an immediate enforcement in favour of the generic manufacturers was ordered pursuant to §80a of the VwGO.

On appeal, the Court of Appeal not only confirmed the opinion of the VG on the restricted validity of data protection regarding 'bibliographic approvals' but also moved away from the accepted European legal position regarding 'generic approvals' in its decisions dated 26 September 2008³ on the complaint of Sanofi-Aventis and BMS.

The approval of the generic clopidogrel applications

The applications for approval of the generic product made reference to the European Public Assessment Report (EPAR) of the EMA for Plavix and Iscover, as well as to

Costs for the development of a new pharmaceutical product currently amount to approximately US\$800m, a major part of which is attributable to the data required for the dossiers to put the product on the market

the summary basis of approval (SAB) of the US Food and Drug Administration (FDA) from the US approval procedure, in addition to the bioequivalence study mandatory for a generic approval pursuant to s24b AMG. The applications were stated to be based in addition on 'published material'. Therefore, the application could be processed via the abridged bibliographical approval procedure pursuant to s22 AMG (also known as the 'well established use' application).

The VG stated that it was not a generic approval and rejected the application of data protection with respect to generic drugs on the basis of the reference to the EPAR and SAB. It stated that these reports were not part of the protected documents from the application for approval filed by the original manufacturer. The Court of Appeal indicated that data protection had to be accorded to EPAR and SAB, but in the end left this question open.

a) Protection against generic approval

A reference to the EPAR (or SAB for that matter) comes under the protection of the former version of s24a or 24b AMG, as both reports are based on the data of the original manufacturer. Although the EPAR is published on the EMEA website, any protection of the data created by the

original manufacturer would be meaningless if generics manufacturers could use the summary and assessment prepared by the regulatory authority for their own applications. Therefore, pursuant to the former version of s24a AMG, the EPAR and SAB for Plavix should have been subject to data protection for 10 years beginning on the date of the original approval.

The BfArM had unquestionably granted the approval to the generics manufacturers prior to the expiry of the 10-year term for Plavix and Iscover. The Court of Appeal, however, handed down its decision when the 10-year term had already expired. The Court of Appeal decided that an application for approval referring to data that has not yet expired is allowed. This reasoning fails to protect the investment in data made by originator companies.

With regard to the data protection in relation to generic applications, the Court of Appeal first stated that a reference in the application to the SAB of the FDA for Plavix might trigger data protection against generic applications. The decision does not discuss the reference in the application to the EPAR, however the same consideration would surely apply. Instead, the Court of Appeal held that the

10-year protection period did not prevent an earlier filing and review of the application. It considered the former version of s24a AMG which required that 'the applicant should prove that the first approval of the pharmaceutical ... was issued more than ten years ago'. Even though under both the German and European legislation this would require the applicant to demonstrate that the data-protection period has expired, the Court of Appeal was not able to draw this conclusion. However, it is not possible to demonstrate that the first approval of a pharmaceutical was issued more than ten years ago unless the data protection period has, in fact, expired.

Finally, the Court of Appeals considered the introduction of the '8+2+1' formula in the amendment to s24a AMG amendment based on Directive 2004/27/EC. Again the Court of Appeal found the new rule inconclusive with respect to the interpretation of the previous rule. In the court's view, the '8+2+1' formula, which is the result of a hard-fought political compromise relating to the term of data protection, (only) makes it possible to issue an approval before the expiry of 10 years and allows the authorities to review an application before the expiry of such term (not until the expiry of eight years, however). But, if under the old rule applications could be made before the expiry of the protection period, then in theory the application could have been made from the moment that the original marketing authorisation had been granted. This could not have been what was intended.

b) Bibliographic approval

For a bibliographic approval, an applicant may refer to published scientific material in order to prove the product's safety and efficacy, rather than submitting its own data. This is set out in art 10a of the Community code and in s22 of the AMG. However, an original applicant will not have its data published if it has to bear the risk that competitors can file applications for their products on the basis of such publications.⁴ Therefore, art 10a of the Community code and s22 AMG provide for a 10-year term of protection that allows

The VG stated that it was not a generic approval and rejected the application of data protection with respect to generic drugs on the basis of the reference to the EPAR and SAB

Originators should pay careful attention to the strategy of publishing regulatory data and be aware of the possibility that they may encounter generic competition earlier than expected

the original applicants to publish their results without having to fear that they will be used immediately for the approval of preparations of competitors. The Court of Appeal held that the preamble of Directive 1999/83/EC, by means of which the term of protection was at first introduced, 'indicates' such protection. However, the drafting history not only 'indicates' but explicitly states that data protection is the purpose of the 10-year term.⁵

Further, in keeping with the analysis of the generic approvals process, bibliographic approval should not be reviewed by the BfArM before the expiry of the 10-year term of protection.

Nonetheless, the Court of Appeal held that bibliographic applications are admissible even before the expiration of the 10-year protection period. It referred to the introduction of the '8+2+1' formula for generic applications in and held that a similar structure could have been introduced for bibliographic applications. However, bibliographic applications, according to the European Court of Justice, are supposed to remain an exception, which was why it was not deemed necessary in 2004 to amend the existing protection period for bibliographic applications. In addition, the Court of Appeal raised the concern that an

additional period of protection would be awarded due to the time required for the BfArM to review the application. Because such an additional time period depends in no small measure on the workload of the BfArM and therefore cannot be exactly determined, the court held that the originator is not entitled to an unspecified period for this additional period of protection. While it may be that it is difficult to determine how long this time period will be, this does not mean that the right to protection of data should be denied.

Future considerations

It may be argued that the court did not give the protection intended by the legislator in connection with the data protection pursuant to the former version of s24a AMG with respect to generic approvals, and further, that it failed to grant protection for the duration of the approval procedure, where that procedure extends beyond 10 years, with respect to bibliographic approvals.

Sanofi-Aventis and BMS could still potentially file for main proceedings, although the data protection term has now expired and clopidogrel products may be marketed by the generic competition. A decision in favour of Sanofi-Aventis and

BMS would be relevant for the industry, in particular regarding the data-protection period relating to generic applications. However, by the time main proceedings were concluded, the old rule would have been replaced by the new '8+2+1' rule in any case.

Nonetheless, originators should pay careful attention to the strategy of publishing regulatory data and be aware of the possibility that they may encounter generic competition earlier than expected.

1 Case no 7 L 988/08 and 7 L 1009/08.

2 Case no 7 L 1102/08.

3 Case no 13 B 1169/08, 13 B 1171/08 and 13 B 1202/08.

4 The upcoming US requirement to publish part or all data of trials will have to be addressed accordingly in European legislation. See s801 Public Law 110-85, 27 September 2007, 121 Stat 823.

5 Report from the Commission to the Council concerning the adoption of certain urgent measures intended to facilitate the development and marketing of medicinal products derived from biotechnology and other high-technology medicinal products in the Community (which serves as an explanatory memorandum), COM(84) 437 final, 25 September 1984. See in this respect, Cook, *The Protection of Regulatory Data in the Pharmaceutical and Other Sectors*, 2000 [cited Cook, *Protection of Regulatory Data*], pp 20 et seq and the same, *Regulatory Data Protection of Medicinal Products in Europe*, *Bio-Science Law Review* [cited Cook, *Regulatory Data Protection of Medicinal Products*], available at pharmalicensing.com/public/articles/view/1046957520_3e674dd06906d, last visited on 4 November 2008.

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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 manufacturer'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 patient'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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