Legal and regulatory update

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This section is intended to be a synopsis of recent legal developments and is not intended to be exhaustive. If any issue referred to in this section is to be relied on, specific advice should be sought. Please contact:

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NOTES FROM THE EU

The future of the EPLA

At the end of 2006, the prospects for the formation of a central European Patent Court by way of the European Patent Litigation Agreement (the 'EPLA') seemed slim when it became clear that the EPLA was set to be blocked by member states, with France leading the opposition.

One of the French government's principal objections was that the EPLA proposed a central European Patent Court under the control of national patents judges. The French felt that this was unsatisfactory in that it would lead to a multiplication of courts in Europe having jurisdiction over patent litigation that could lead to conflicting decisions. The latest French proposal to try to overcome their objection is a Community-based solution that builds on the existing jurisdictional structure of the European Union while still reflecting the framework of the EPLA. This would require international agreement between member states to attribute a new competence to the Community jurisdiction.

The proposal would also require the creation of a specialist judicial panel to hear such patent cases. The French propose that specialist judicial panels would be situated in member states and that specialist national judges would sit as part-time Community judges. A further specialist panel would also be created to hear appeals and such appeals would be to the Court of First Instance. The French proposal also envisages that the applicable law would include the relevant provisions of the European Patent Convention.

The French proposal has not met with universal support. Commenting recently on the proposal, the Internal Market Commissioner, Charlie McCreevy, said that 'In essence, it is a question of putting forward a credible proposal and gradually building an agreement around it. Not having a number of competing ideas on the table at once.'

Germany holds the rotating presidency of the EU until June of this year. As a supporter of the EPLA, the German Government is keen to push the issue of reform of Europe's patent system up the agenda before Portugal takes over the presidency on 1 July. At the end of January, the German Federal Minister of Justice, Brigitte Zypries, said that 'It is my belief that we should focus on completing the initiatives already underway, namely the London Protocol and the uniform dispute settlement system offered by the EPLA.'

At the beginning of February, however, the EPLA suffered perhaps a further setback. In an interim legal opinion, the European Parliament's legal service has stated that member states do not have the right, whether acting singly or collectively, to set up the European Patent Judiciary necessary to implement the EPLA. The opinion concludes that the Community has the exclusive competence for matters governed by the EPLA.

On 29th March, 2007, the European Commission issued a communication which explains why in its view a European Patents Court is necessary and why there is a lack of agreement on how to implement the EPLA among EU states. The Commission concludes that it will seek a consensus among the EU states on how to implement the EPLA and will then put forward its legislative proposals.

UK: House of Commons Science and Technology Committee's report on the regulation of hybrid and chimaera embryos

On 5th April, 2007, the House of Commons Science and Technology Committee (the 'STC') published a report on the Government's proposals for the regulation of animal/human hybrid and chimaera embryos for use in research. The report focuses on the proposed legislation in this area as set out in the White Paper 'Review of the Human Fertilisation and Enbryology Act: Proposals for revised legislation' (published

on 14th December, 2006), and on the impact of these proposals upon stem cell research in the UK.

The backdrop to the STC's enquiry was the proposal by the Government that the creation of human–animal chimaera and hybrid embryos for research purposes be prohibited for the time being, notwithstanding that any new law should contain a power enabling regulations to set out circumstances in which the creation of hybrid and chimaera embryos may be allowed under licence in the future. The Government's proposal was in response to the need to update the Human Fertilisation & Embryology Act 1990 ('HFE Act 1990'), which did not specifically address the creation of animal–human hybrid or chimaera embryos. The STC also considered such an enquiry to be urgent on the grounds that the Human Fertilisation and Embryology Authority ('HFEA') was expecting imminent licence applications from a number of academic research organisations for licences falling within the area covered by the White Paper. In January 2007, the HFEA decided to defer consideration of such applications in light of the Government's proposals.

The STC noted that there had been much progress in the area of embryology since the HFE Act 1990 came into force and revised legislation was now appropriate. In stark contrast to the White Paper however, the STC concluded that the creation of human–animal chimaera or hybrid embryos (specifically cytoplasmic hybrid embryos) is both desirable and necessary for research into, for instance, the genetic basis of disease and the use of stem cells in future cell-based therapy. Such use could be of particular importance in drug discovery, thereby leading to a reduction in the use of animals for toxicity testing. The STC also stressed the importance of public education and understanding in this area of research, particularly in light of the profound ethical issues raised.

Despite concluding in favour of the creation of human–animal chimaera and hybrid embryos, the STC remain of the view that development of such embryos past the 14-day stage should remain prohibited, as should the possibility of implanting such embryos into a woman. Finally, the STC was critical of both the HFEA for delaying consideration of the licence applications to create cytoplasmic hybrid embryos, and the Government for inadequately setting out the research areas intended to be covered by the White Paper proposals.

The full STC report can be found at: http://www.publications.parliament.uk/pa/cm200607/cmselect/cmsctech/272/272i.pdf

UK: OFT launches study into the distribution of medicines in the UK

Following proposed changes to the model by which UK pharmaceuticals companies distribute their medicines, the OFT has launched a short market study into the distribution of medicines in the UK.

Pharmaceuticals companies have traditionally distributed their medicines through a range of competing wholesalers but in March 2007, Pfizer broke the mould by starting to distribute prescription drugs exclusively through one wholesaler, Unichem. Other suppliers are now considering following suit despite concerns raised by pharmacists, doctors and competing wholesalers.

This potential shift in distribution models used by the pharmaceutical industry has concerned the OFT sufficiently to warrant a market study into its potential implications. The areas that the OFT will focus on include competition aspects as well as the possible direct effects such a change may have on the NHS, pharmacists, dispensing doctors and patients in terms of the efficiency and cost of medicine provision. More than £10bn is spent each year by the NHS on prescription medicines and for this reason, significant changes in the way such medicines are distributed need to be carefully considered. The study will also consider the potential effects of the 'direct to pharmacy' distribution.

The OFT describes possible outcomes of the study as including: (i) giving the market a clean bill of health; (ii) encouraging a consumer code of practice; (iii) making

recommendations to the Government or sector regulators; (iv) a market investigation reference to the Competition Commission; and (v) enforcement action against companies suspected of breaching consumer or competition law.

The OFT has welcomed submissions on this topic from interested parties by Friday 1st June, 2007 and intends to have completed its study by the end of the year.

UK: Office of Fair Trading Report on the Pharmaceutical Price Regulation Scheme

On 20th February, 2007, the Office of Fair Trading ('OFT') published a 120-page report on the regulation of the price of branded pharmaceutical products under the voluntary scheme that is periodically re-negotiated between the industry and the Department of Health, the Pharmaceutical Price Regulation Scheme ('PPRS'). The OFT report concludes that the PPRS does not provide value for money for the NHS. The current PPRS basically regulates prices by imposing an overall profit cap on those companies which sell branded products to the NHS – compliance with the profit cap is achieved by price adjustments across a company's product range and/or refunds to the NHS. The OFT says that there is a compelling case for reform of the scheme towards a value-based pricing system that would relate the prices of products to their clinical value relative to existing treatments.

The report considers in some detail supply- and demand-side factors that affect the pricing of pharmaceuticals, including generic substitution, prescribing practices, price competition in supplies to pharmacies and hospitals as well as parallel trade. It considers three alternatives to the current PPRS scheme and concludes that an *ex ante* value-based pricing scheme, in which there would be rapid upfront negotiation of price prior to the launch of a product, is preferable. As to establishing the value of a drug under the proposed scheme, the OFT advocates the Quality Adjusted Life Year ('QALY') measure used by the National Institute of Clinical Excellence ('NICE'). If implemented, the scheme would mean that this type of assessment will be required not only for the purchase of a new drug by the NHS (NICE review) but also for the purposes of fixing a price (DOH price negotiation). This in turn would mean that the development of any new pharmaceutical product should not proceed unless there is a reasonable expectation of achieving a satisfactory QALY measure.

UK: Pfizer/Eisai and Shire to seek judicial review of NICE Appeal Board Decision on treatments for Alzheimer's disease

On 11th October, 2006, the Appeal Board of the UK NICE, whose duty is to perform such functions in connection with the promotion of clinical excellence as the Secretary of State for Health may direct under the National Health Service Act 1977, rejected appeals by a number of parties including Eisai and Shire Pharmaceuticals from guidance issued in January 2001 that the three drugs donepezil, rivastigmine and galanthamine should be made available on the NHS as one part of the management of some people with mild and moderate Alzheimer's disease.

The appellants argued, *inter alia*, that other categories of patients suffering from Alzheimer's disease, including new mild patients, would not thereby be able to receive these drugs under the NHS. Pfizer and Eisai (who jointly market Aricept (donepezil)) and Shire Pharmaceuticals (who market Reminyl (galanthamine)) announced their intention to seek judicial review of the decision of the Appeal Panel and the Institute's decision to issue the guidance.

Until now there have been few attempts to seek judicial review of NICE guidelines, one reason being that they can be viewed as recommendations to the Secretary of State for Health, rather than determinations or decisions capable of being judicially reviewed. In substance however, it is clear that the process as a whole, in which the Secretary of State seeks guidance from NICE and decisions made by NICE in

providing 'guidance' are adopted by the Secretary of State (which must then be followed by Primary Care Trusts) is a decision-making process. This much now appears to be recognised by NICE in that the Appeal Panel informed the parties that they would appeal the decisions by the Institute and its Appeal Panel by way of judicial review. It is possible that in inviting appeals, NICE was seeking judicial endorsement of the process.

On 26th March, 2007, following a joint application from Eisai and Pfizer, together with the Alzheimer's Society as an interested party, the High Court gave permission to launch a judicial review to challenge the Appeal Board's decision to reject Aricept. The review will consider the soundness of NICE's decision-making process.

Pfizer and Eisai have appealed on the following grounds:

(i) Procedural fairness on the basis that NICE refused to disclose the cost-effectiveness model that was used to determine the value of treatment in patients with mild Alzheimer's disease.
(ii) Irrationality on the basis that some of the assumptions and conclusions in the Final Appraisal Document were irrational or unsupported.
(iii) Human Rights and Discrimination on the basis that the Mini Mental State Examination scores used in the appraisal discriminated against certain patient groups.

Life Sciences Patent Litigation in the UK – A Summary of Calendar Year 2006

The life sciences sector continued to dominate the court lists in the UK in Calendar Year 2006. Of the 14 patents in issue in fully contested first instance hearings in the English Patents Court on which judgment was given in 2006 (in 12 actions), nine were in the life sciences sector (in six actions). All but one of these patents was found invalid, and the single one that survived (for a formulation of cyclosporin) was found not to be infringed (Table 1). In addition, the Scottish court with first instance jurisdiction over patent matters, the Court of Session, also heard a pharmaceutical patent action, and also found the two patents in issue invalid.

Table 1 omits other matters heard by the Patents Court such as interim and procedural applications, entitlement disputes, appeals from the UK Patent Office and enquiries into damages. Of the pharmaceuticals patents in issue at first instance in 2006 none were for new chemical entities, but they were instead all 'second generation' patents such as new formulations (as in the cyclosporine cases) or allegedly new physical forms or purities (as in the Scottish tibolone cases). Of these first instance decisions the judgment in *Conor* v *Angiotech* has already, earlier in 2007, been upheld by the Court of Appeal, although in other actions the equivalent patent in The Netherlands has so far survived such attack. Only one appeal in a life sciences matter got

Table 1: Outcomes of UK Patents Court Trials in 2006—Life Sciences

Date	Parties	Subject matter	Judge	Infringed?	Valid?
17.02.06	*GE (Amersham)* v *PerkinElmer*	Scintillation proximity test	Kitchin J	NA	No – Obvious
24.02.06	*Conor* v *Angiotech*	Drug eluting stent	Pumfrey J	NA	No – Obvious
10.04.06	*Ivax* v *Chugai*	Nicorandil	Kitchin J	NA	No – Obvious
19.05.06	*Mayne Pharma* v *Debiopharm*	Oxaliplatin	Pumfrey J	(1) No (2) NA	(1) No – Obvious (2) No – Obvious
22.05.06	*Ivax* v *Akzo*	Tibolone	Lewison J	NA	No – Obvious
15.09.06	*Arrow* v *Organon, Organon* v *Norton*	Tibolone	Lord Glennie	(1) NA (2) NA	(1) No – Anticipated (2) No – Anticipated
16.10.06	*Novartis* v *Ivax*	Cyclosporine	Pumfrey J	(1) No (2) No	(1) Yes (2) No – Obvious
30.10.06	*Merz Pharma* v *Allergan*	Botulinum toxin	Kitchin J	NA	No – Anticipated, Obvious, Added Matter

to the Court of Appeal in 2006 – that in *Ranbaxy* v *Warner Lambert* where the court upheld the decision of the Patents Court that the basic patent was infringed, but that the later calcium enantiomer patent was anticipated.

Sweden: Application for registration constitutes patent infringement

In a recent decision by the District Court, it was held that the request for pricing of a generic medicine in conjunction with an application to the Pharmaceutical Benefits-register (the 'FBR') for registration, was to be considered as an 'offering' of that generic product.

The Act on Pharmaceutical Benefits (2002:160) (the 'Act'), states that the government shall cover all pharmaceutical expenses for individuals over a certain amount (approximately EUR 400). The Act only applies to expenses for pharmaceuticals that are registered in the FBR. In order to register a pharmaceutical with the FBR, an application for registration is made to the Swedish Pharmaceutical Benefit Board (the 'PBB').

STADApharm AB ('STADA') is the manufacturer of the anti-depressive pharmaceutical Sertralin STADA, which is a generic version of Pfizer's product, Sertraline, for which Pfizer had a supplementary patent protection that expired in October 2005.

STADA applied to the PBB in April 2005 for the registration of the generic version in the FBR and also requested a pricing for it. Pfizer filed a complaint with the District Court claiming that the application and request for pricing was an 'offering' of the generic, and accordingly constituted an infringement of the (at the time) valid patent.

Under Article 3 of the Swedish Patent Act (1967:837), the patent holder has the exclusive right to 'offer' ('bjuda ut'), put on the market or use a product protected by a patent or import or possess such a product for these purposes.

STADA claimed that it had not 'offered' the generic product since no sales had occurred and PBB does not purchase or sell pharmaceuticals; it only decides at first instance which pharmaceuticals to register in the FBR.

The District Court held that the definition of 'offering' in the Patents Act must be interpreted in a wide manner. The definition would therefore include such types of use that indicated an intent to offer an infringing product for commercial purposes. With regards to this, it is not relevant whether the offering later results in actual sales of the product or if the delivery of the product occurs after the expiry of the patent.

The District Court further stated that there could not be any other purpose than a commercial purpose for STADA's application to PBB, and so the application must therefore be considered as 'offering' in accordance with the Patents Act. Pfizer's patent was therefore infringed.

The District Court delivered its decision on 1st June, 2006 (Case T 22250-05). The decision has been appealed.

Italy: The 2007 Italian Budget Law narrows down the use of 'off-label' medicinal products

Under Article 3.1 of Legislative Decree no. 23/1998, a doctor, when prescribing medicinal products to patients, must follow the therapeutic indications, methods and the routes of administration provided in the Marketing Authorisation granted by the AIFA.

Nevertheless, under Article 3.2 of the Decree, a doctor may, under his own responsibility and after having acquired the prior informed consent of the patient, prescribe a medicinal product for therapeutic indications, methods and routes of administration different from those actually authorised. This 'off-label' use is permissible whenever the doctor considers that the patient cannot be usefully treated with the registered indications and provided that this 'off-label' use conforms to guidelines or scientific literature at an international level.

Article 1 (paragraph 796, letter z) of Law no. 296/2006 (the 2007 Italian Budget Law) has narrowed down the 'off-label' use of medicinal products in Public Hospitals and

Healthcare Institutions. Article 3.2 of the above Decree will no longer apply to the systematic use in Public Hospitals, Healthcare Institutions, etc of pharmacological therapies funded by the Italian Health Service ('HIS'). Moreover, the 'off-label' use cannot be made outside the terms and indications authorised by the same HIS as a therapeutic alternative for patients suffering from pathologies for which pharmaceutical products containing specific indications for treatment have been authorised. Such therapies will be allowed solely in the ambit of the clinical trials.

By 28th February, 2007, the Regions must adopt provisions relating to Local Health Authorities, Hospital Authorities and other health authorities aimed at the identification of those persons liable for implementing the provisions mentioned above and also with regards to administrative liability for damages to the Inland Revenue Service. Until the regional dispositions come into force, such liability is attributed to the Healthcare Director of Local Health Authorities, Hospital Authorities, etc.

Germany: Federal Supreme Court of Germany decides on second medical use claims that relate to dosage recommendations

In the decision Carvedilol II (file X ZR 236/01), the Federal Supreme Court had to deal with the validity of the German part of a European patent that was defended with a main claim, the essential part of which reads as follows:

> Use of Carvedilol for the manufacture of a medicament […], wherein the medicament is administered in an initial dose of 3.125 mg […], daily for a period of 7–28 days […].

The Court dealt with Art. 52 (4) of the European Patent Convention according to which methods for treatment of the human body are not regarded as inventions which are susceptible to industrial application. The Court concluded that the determination of a therapy plan for a patient which includes the prescription and dosing of medicaments is a distinctive part of the activity of a medical doctor and therefore a method excluded from patentability pursuant to Art. 52 (4) EPC. The Court did not decide whether the claim as a whole is excluded from patentability, but concluded that the dosing recommendation specified in the claim cannot be considered for the assessment of novelty and inventive step of the claimed subject matter. Consequently, novelty and inventive step were evaluated as if the feature relating to the dosage regimen was absent. The claim was finally rejected for lack of inventive step.

As an auxiliary request, the patentee defended the patent with a claim in which the passage 'whereby the medicament is administered […]' was replaced by 'whereby the medicament is prepared for an administration […].' According to this auxiliary request, the dosage regimen was defined as a feature of the medicament as such ('is prepared for administration') and not as part of an administration scheme ('is administered,' see claim 1 of the main request). In the Court's view, the patent claim of the auxiliary request did not conflict with the regulations of Art. 52 (4) EPC. The claim drafted in the 'is prepared for administration' language was regarded as relating to the design of the medicament for this use, for example by designing a suitable size of the tablet, by adding an imprint on the package or on the package insert. Although the court was of the opinion that the claim complied with the requirements of Art. 52 (4) EPC, it was also rejected for lack of inventive step.

In summary, it should be concluded that features related to dosage regimens as such might not be considered in Germany for assessing novelty and/or inventive step of the subject matter of a second medical use claim. If the claim is, however, redrafted to specify that the medicament is designed to be useful in a specific administration scheme, dosage features linked to the medicament will be taken into account.

France: Updated version of the French Charter on communications on the internet for pharmaceutical companies

In December 2001, the French Agency of Sanitary Safety of Health Products

('AFSSAPS') adopted a Charter on communications on the internet for pharmaceutical companies. The aim of the Charter was to assist pharmaceutical companies established in France in creating their websites in compliance with the French regulations on the advertising of medicinal products.

This Charter was revised on 26th October, 2006 and is now available on the AFSSAPS' website (http://agmed.sante.gouv.fr/htm/5/recopub/indrepub.htm in French only).

As a general obligation, websites must:

(i) identify the company advertising its products, including its postal address;
(ii) state whom the website is aimed and the kind of information that will be provided; and
(iii) clearly identify any information for foreign countries (language being an insufficient indication in that respect).

Furthermore, it must clearly identify which pages have informational content and which are merely promotional.

According to the Charter, advertising on the internet aimed at consumers is only possible for non-reimbursable and non-prescription medicinal products, subject to meeting the Direct to Consumer advertising regulations. Internet advertising aimed at professionals is also possible, but access to corresponding web pages must be limited by a personal code.

The following are not considered to be advertising and can be accessed by consumers on the internet (they must, however, be in the same part of the website):

- institutional information regarding the company;
- summaries of product characteristics ('SPC');
- the European Public Assessment Report on products given a marketing authorisation through the Centralised Procedure;
- the information leaflet on the product;
- information regarding reimbursement; and
- if fixed according to the regulations, the maximum price which can be charged to the public for the product.

The revised version of the Charter includes new requirements and implements some of the new provisions of Directive 2004/27 modifying Directive 2001/83. For example:

- Regarding advertising streamers (banners), two recommendations dated 26th March, 2001 have been incorporated in the Charter: one intended for 'Direct to Consumer' advertising and the other for advertising to professionals. The Charter implements the new Article 89.2 of Directive 2001/83 as modified which provides that: 'Member States may decide that the advertising of a medicinal product to the general public may, notwithstanding paragraph 1, include only the name of the medicinal product or its international non-proprietary name, where this exists, or the trademark if it is intended solely as a reminder.'
- The 'Request of information via Internet' contact form has been excluded from the scope of the Charter, as it is a type of correspondence that is not defined as 'advertising.' This contact form must not contain any pre-established list of documents that can be requested.
- Domain names are considered as communication and promotion tools and must therefore comply with the advertising regulations. Consequently, a domain name can be constituted by a trade mark only for medicinal products for which a prescription is optional and which are not reimbursed, as well as for vaccines, subject to obtaining the necessary prior advertising authorisation.
- Finally, activities of medical representatives can be carried out via the internet provided that a number of specific requirements are first met, including:
  - the persons are qualified to carry out such activities in accordance with Article L.5122-11 of the Public Health Code;

- access to the website is limited by a single-use code;
- the Charter's guidance on medical representatives' activities is followed; and
- the documents listed in Article R. 5122-10 of the French Public Health Code are mailed following the visit (ie SCP, the opinion of the Transparency Commission regarding reimbursement and pricing).

NOTES FROM THE US

Teva/Novartis decision opens the door for generics to bring declaratory judgments against branded drug companies

In *Teva Pharmaceuticals USA, Inc.* v *Novartis Pharmaceuticals Corp.*, No. 06-1181, slip op. (Fed. Cir. March 30, 2007), the United States Court of Appeals for the Federal Circuit ('CAFC') interpreted the Supreme Court's ruling in *MedImmune* v *Genentech*, 127 S. Ct. 764, 774 (2007), to necessarily require the overruling of the reasonable apprehension of suit test followed by the CAFC. The reasonable apprehension of suit test requires a declaratory judgment plaintiff to prove that it faces a reasonable apprehension of imminent suit by the patent holder prior to bringing suit against such patent holder. The Teva decision moves away from such a requirement and allows generics to only establish a lower threshold that an 'actual controversy' exists making it easier for such generics to get into court and obtain such declaratory judgments against their branded counterparts.

The Supreme Court evaluated the CAFC's reasonable apprehension of suit test in the MedImmune decision. In footnote number 11 of the MedImmune decision, the Supreme Court noted that the reasonable apprehension of suit test violated Supreme Court precedent. Specifically, the Supreme Court, in its prior decision in *Altvater* v *Freeman*, 319 US 359, 365 (1943), held that a licensee should not be forced by the courts to choose between paying certain royalty payments or committing wilful patent infringement, risking treble damages. The CAFC's reasonable apprehension of suit test requiring that a breach of contract must exist before the courts could have jurisdiction over declaratory judgment suits that seek to invalidate patents clearly flies in the face of the Altvater decision.

With the MedImmune decision, the Supreme Court has also shown its support for the congressional amendments to the Hatch–Waxman Act passed as part of the Medicare Modernization Act of 2003. The Hatch–Waxman amendments attempt to alleviate certain risks that generics take when they decide to launch products, even if a branded drug company does not sue a generic within 45 days of the generics filing a Paragraph IV Certification. By way of background, when filing an abbreviated new drug application ('ANDA'), a generic has to make what is known as a Paragraph IV Certification which requires the generic to certify that the patents of the branded drug company will not be infringed by the manufacture, use or sale of the generic's drug product. After a Paragraph IV Certification is made, a branded drug company has 45 days to bring a suit against the generic and can thereby obtain a 30-month stay of the FDA's approval of the ANDA. Prior to these Hatch–Waxman amendments, if a branded drug company decided not to invoke its right to sue within such 45-day window, generics could open themselves up to potential patent infringement liability if they decided to launch the product anyway. To solve this problem, the Hatch–Waxman amendments allow generics to bring declaratory judgment actions regarding a branded company's patent 45 days after the generic files its Paragraph IV Certification. The CAFC, however, essentially eviscerated this right with its decision in *Teva* v *Pfizer*, which held that declaratory judgment jurisdiction did not exist irrespective of these Hatch–Waxman amendments until Teva had proven a 'reasonable apprehension of imminent suit.'

The CAFC clearly has taken notice of the MedImmune decision with its recent decision in *Teva* v *Novartis*. In this *Teva* case, Teva filed an ANDA and filed five Paragraph IV Certifications with respect to Novartis' compound and method of use patents for the

drug Famvir®. Novartis brought an infringement suit against Teva asserting that Teva would only be infringing on Novartis' compound patent. Teva brought a declaratory judgment action with respect to the other four patents. Given the MedImmune decision, the CAFC ruled in this Teva case that the reasonable apprehension of suit test was overruled and that a plaintiff in a declaratory judgment suit now needs to show that 'an actual or imminent injury caused by the defendant [exists] that can be redressed by judicial relief' which is of 'sufficient immediacy and reality to warrant the issuance of a declaratory judgment.' In addition, the CAFC stated that 'all the circumstances' would be considered when reviewing whether such injury exists. In particular, the CAFC found that an actual controversy existed in this case when Novartis listed its patents in the Orange Book, Teva listed the Novartis patents in its Paragraph IV Certifications and Novartis sued Teva on the one compound patent.

Although the Teva case seems to open up the doors for generics to bring declaratory judgment suits against branded drug companies, this case and the MedImmune decision have other implications for patent holders, and likely licensors, of drug compounds. In the wave of cases allowing and opening up the ability for would be declaratory judgment plaintiffs, it will be even more important for licensors to negotiate covenants not to sue into their license agreements. This will act as a measure to prevent at least the licensees, as was the case in MedImmune, from bringing declaratory judgment suits against the licensors.

Recent developments with respect to HIPAA

Although it has been 11 years since the passage of the Health Insurance Portability and Accountability Act 1996 ('HIPAA') and four years since compliance with HIPAA's first set of administrative simplification requirements was due, those HIPAA requirements continue to impact the day-to-day operations of healthcare providers, health plans and other healthcare entities. One of the key elements of HIPAA is a set of regulations referred to as the Privacy Rule that establishes a category of protected health information ('PHI'), which may be used or disclosed to others only in certain circumstances or under certain conditions. PHI includes a patient's personal health information, such as information in a patient's medical records or a patient's test results, when that information is held or transmitted by a covered entity. PHI also includes identifiable health information about subjects of clinical research gathered by a researcher who is a covered healthcare provider.

The Privacy Rule applies to individually identifiable health information created or maintained by a covered entity. Covered entities include healthcare providers that transmit health information electronically in connection with certain defined HIPAA transactions, such as claims or eligibility inquiries. Clinical trial sponsors and CROs who are not themselves covered entities, or who are not workforce members of covered entities, may be indirectly affected by the Privacy Rule if covered entities supply their data in the course of a study.

A covered entity may use or disclose PHI for research in the following situations in each case in accordance with HIPAA requirements:

- if the subject of the PHI has granted specific written permission through an Authorisation;
- for reviews preparatory to research with certain representations obtained from the researcher;
- if the covered entity receives appropriate documentation that an IRB or a Privacy Board has granted a waiver of the Authorisation requirement;
- if the covered entity obtains documentation of an IRB or Privacy Board's alteration of the Authorisation requirement as well as the altered Authorisation from the individual;
- if the PHI has been 'de-identified';
- if the information is released in the form of a limited data set, with certain identifiers removed and with a data use agreement between the researcher and the covered entity;

- under a 'grandfathered' informed consent of the individual to participate in the research, an IRB waiver of such informed consent, or Authorisation or other express legal permission to use or disclose the information for research as specified under the HIPAA transitional provisions.

The Privacy Rule permits covered entities, without Authorisation, to make a number of other disclosures of PHI, including disclosures for adverse event reporting to certain persons subject to the jurisdiction of the FDA (eg clinical trial drug sponsors).[1]

The following provides a brief update of regulatory, case law and enforcement developments on the HIPAA administrative simplification front.

State Courts look to HIPAA as standard

While HIPAA does not provide a private right of action, compliance with HIPAA is being noted by courts in assessing state privacy claims. Two recent examples:

- In a recent Illinois case, compliance with HIPAA standards helped to defeat respondeat superior claims against Illini Hospital. The plaintiff patient in *Bagent* v *Blessing Care Corporation*, 244 Ill.2d 154 (2007), asserted that subsequent to her undergoing a blood test at the hospital, a phlebotomist employee revealed in a social setting that the patient was pregnant. The patient's allegations of breach of patient confidentiality, invasion of privacy and infliction of emotion distress were made against the phlebotomist, and also against the hospital on the theory of *respondeat superior*. In a reversal of the appellate court's denial of the hospital's motion for summary judgment, the Illinois Supreme Court reviewed evidence that the hospital provided HIPAA privacy training to its employees, including the phlebotomist, and that the phlebotomist understood from the training that patient information should not be disclosed. The court's conclusion that the phlebotomist's disclosure of the patient's information was not the kind of conduct she was hired to perform was, in large part, based on the evidence that Illini Hospital had provided HIPAA training to its employees.
- In *Acosta* v *Byrum*, 638 S.E.2d 246 (N.C. Ct. App. 2006), a psychiatric patient brought claims of invasion of privacy and infliction of emotional distress against a psychiatrist and office manager who allegedly improperly accessed and disseminated the patient's health information. The plaintiff alleged that the psychiatrist improperly permitted the office manager to use the psychiatrist's medical records access code in violation of hospital rules and regulations and in violation of HIPAA. The trial court had dismissed the case, in part on the grounds that HIPAA does not provide a private right of action. In reversing the trial court's dismissal of the claims against the psychiatrist, the North Carolina Court of Appeals found that the plaintiff had not made an HIPAA claim, but found instead that HIPAA provided a standard of care in determining whether the physician defendant properly maintained the privacy of a patient's confidential medical records.

Both the Bagent and Acosta cases demonstrate that HIPAA compliance is not simply a federal regulatory matter. In assessing state privacy claims, courts are now looking to HIPAA as a standard of care for protecting the privacy of health information.

First HIPAA conviction at trial

In the first HIPAA violation case to go to trial, on 24th January, 2007 a Fort Lauderdale jury convicted Fernando Ferrer, Jr. of computer fraud, conspiracy to defraud the United States, aggravated identity theft, and the wrongful disclosure of protected health information under HIPAA. The case involved the theft and transfer of Medicare patient information from the Cleveland Clinic in Weston, Florida. Ferrer purchased the patient information from a former Cleveland Clinic employee, who pleaded guilty to similar charges and testified against Ferrer. The theft resulted in the submission of more than $7m in fraudulent Medicare claims. In addition to a maximum sentence of 20 years for the

non-HIPAA counts, Ferrer faces up to 10 additional years in prison for wrongfully disclosing protected health information.

Enforcement notes

According to the Department of Health and Human Services, as of 31st December, 2006, the Office for Civil Rights ('OCR') received a total of 24,000 HIPAA privacy complaints. Of those complaints, more than half were not investigated because (1) the complaints were not filed in time, (2) the OCR did not have jurisdiction over the covered entity named in the complaints, or (3) the allegations did not constitute violations of the Privacy Rule. OCR has investigated and closed approximately 6,000 complaints, and took informal enforcement action in 4,025 of those cases. As of the end of 2006, OCR had referred more than 300 cases to the Department of Justice.

HHS Security Guidance on portable devices and remote access

The Centers for Medicare and Medicaid Services ('CMS') recently published additional guidance for compliance with the HIPAA Security Rule ('Security Guidance') in order to reinforce some of the ways in which a covered entity may protect electronic protected health information ('EPHI') when it is accessed or used off-site or remotely. Because of the growing number of reported security incidents and increased vulnerability associated with the use of certain portable, remote access, or off-site devices and tools ('off-site devices'), CMS targeted the Security Guidance to a covered entity's use of off-site devices that store, contain, or are used to access EPHI. The Security Guidance lists the following off-site devices as particularly vulnerable to security incidents: laptops; home-based personal computers; PDAs and Smart Phones; hotel, library or other public workstations and Wireless Access Points (WAPs); USB Flash Drives and Memory Cards; floppy disks; CDs; DVDs; backup media; e-mail; Smart cards; and Remote Access Devices (including security hardware).

Although CMS acknowledged that many situations warrant the off-site use of or access to EPHI, CMS cautioned that such use or access is appropriate only after a covered entity has conducted a risk analysis that (1) examines its business activities to determine the necessity of the off-site use or access; and (2) determines whether its policies, procedures, workforce training, and permitted access to EPHI are consistent with the requirements of HIPAA's privacy and security rules. After a covered entity conducts its risk analysis, the Security Guidance states that the security policies and procedures required by HIPAA should be revised to include appropriate authorisation for remote access to EPHI, security requirements for storing EPHI beyond the covered entity's physical control and transmission processes that ensure the integrity and safety of EPHI that is exchanged both directly and remotely accessed over applications hosted by the covered entity. CMS indicated in the Security Guidance that a covered entity's workforce training should, at a minimum, include clear and concise instructions for accessing, storing, and transmitting EPHI. CMS further indicated that, if applicable, training programmes should include password management procedures, prohibitions against leaving devices in unattended cars or public thoroughfares and prohibitions against transmitting EPHI over open networks or downloading EPHI to public or remote computers.

Security incident procedures must specify the actions workforce members must take in the event that EPHI is lost via portable media; such actions may include securing and preserving evidence, managing the harmful effects of improper use or disclosure of the EPHI and providing notice to affected parties. In developing sanction policies so that workforce members understand the consequences or noncompliance with policies on remote access to and off-site use of EPHI, CMS urged covered entities to consider requiring employees, as a pre-requisite to employment, to sign a statement of adherence to security policies and procedures.

CMS reminded us in the Security Guidance of its delegated authority to enforce HIPAA's security standards; CMS further stated that it may rely on the Security

Guidance to determine whether the actions of a covered entity are reasonable and appropriate for safeguarding the confidentiality, integrity and availability of EPHI and that the Security Guidance may be given deference in an enforcement hearing.

DOJ/FTC report on antitrust law enforcement

On 17th April, 2007, the United States Department of Justice and the Federal Trade Commission (collectively, the 'Agencies') released a report entitled Antitrust Enforcement and Intellectual Property Rights: Promoting Innovation and Competition[2] (the 'Report'), which sets out the Agencies' current views on various types of licensing agreements involving intellectual property. The Report generally concludes that most licence agreements will be subject to the more liberal 'rule of reason' analysis (allowing for efficiency-based justifications) unless the agreement results in naked restraints of trade.

Extending patent rights beyond the statutory term

The Report addressed the propriety of agreements that allow patent holders to extend a patent beyond the statutory term, specifically through contractual arrangements allowing patent holders to collect royalties beyond the patent's statutory expiration.

While such arrangements traditionally have been challenged under the doctrine of patent misuse, the Agencies now hold the view that these types of arrangements in fact may benefit competition, for example by amortising the legitimate royalty payments over time and thereby decreasing the 'deadweight loss' to licensors. Accordingly, the Agencies review agreements that extend patent market power beyond the statutory expiration using a rule-of-reason analysis. The first steps in this analysis are the determination of whether the patent confers market power upon the patent holder, and if the arrangement extends the market power beyond the patent's legal life. If so, then in order to avoid or limit antitrust scrutiny, the entire royalty should be predicated on pre-expiration use, regardless of the length of the term for such payment. Specifically, agreements are more likely to raise antitrust concerns if the methodology for calculating royalties beyond the statutory term is predicated on the licensee's volume of sales beyond the statutory term, which could allow the licensor to maintain market power and deter competition. If market power is not present or if the arrangement does not extend such market power, then royalty terms are at the discretion of the patent holder, short of naked restraints of trade analysed under *per se* rules (which do not require any market power evaluation). It is important to appreciate that few cases, by the Agencies or otherwise, have been pursued in recent years to challenge these types of arrangements.

Tying and bundling of intellectual property rights

The US Supreme Court originally deemed tying to be *per se* unlawful as far back as the 1940s. In 1984, however, the Supreme Court slightly qualified this position by acknowledging that 'tying may have pro-competitive justifications that make it inappropriate to condemn without considerable market analysis.' Thus, the current view of tying and bundling allegations involves a *per se* 'lite' analysis, for example *per se* treatment if market power in the tying product can be shown, and efficiency justifications do not outweigh anticompetitive effects. Although the likelihood of enforcement on a tying/bundling arrangement may be small, a life sciences company must be mindful of the expense and risk of litigation, particularly in the context of a patent infringement cases where tying/bundling counterclaims are commonplace. Life sciences companies considering tying or bundling arrangements involving intellectual property are less likely to arouse the Agencies' scrutiny if they offer the tied product or service separately as an individual component, as well as through a tied or bundled arrangement.

Unilateral refusals to license patents

The Agencies set forth the general view that the Patent Act, 35 U.S.C. § 271(d)(4), does not create antitrust immunity for refusals to

license a patent, but also conclude that the antitrust laws should be applied in the same manner to intellectual property as they are applied to other property. There exists a long line of cases holding that a mere refusal to license a patent, without more, does not constitute a violation of the antitrust laws, and the contrary decision in *Image Technical Services, Inc.* v *Eastman Kodak* did not persuade the Agencies to change that view.

However, The ability to refuse to deal, however, does not logically permit the imposition of any conditions on a license that a patent holder desires. Certain 'conditional' agreement to license patents likely will attract antitrust scrutiny by the Agencies if the terms imposed by patent owners in licensing agreements, such as mandatory tying arrangements or downstream resale price restrictions, and should be avoided.

Cross-licensing and patent pools

Bilateral cross-licensing agreements and patent pools often arise in industries in which the patent rights necessary to commercialise products are multiple, and in turn are held by multiple separate entities (often called a 'patent thicket'). It is not uncommon to see cross-licensing agreements used as settlement tools in life sciences patent infringement cases. While patent pools are not yet common in the life sciences arena, they could become more mainstream as effective patent thickets crop up, particularly in the biotechnology area.

The Agencies generally recognise that cross-licensing agreements and patent pools have pro-competitive benefits. Despite the general benefits to innovation (eg cleaning out patent underbrush to enable development) and substantial transaction efficiencies, such licensing arrangements are also fraught with potential pitfalls for the unwary.

First, cross-licensing and – particularly – patent pools potentially provide a forum for illicit collusion that is subject to *per se* analysis by the Agencies, that is no efficiency defence is permitted to justify such conduct. Accordingly, participants in such licensing arrangements should exercise extreme caution in drafting the agreements to explicitly discourage and avoid any exchange of information that could later be construed as facilitating coordination of pricing and market allocation among competitors. Provisions for retention of individual patent licensing (ie the pool license is non-exclusive), availability of the pool to all interested licensees, and avoidance of grant backs that unduly limit access to downstream innovation are recommended.

Secondly, the Agencies are least likely to challenge patent pools that contain only purely complementary patents. Conversely, however, pools composed of patents that can be substituted for each other (eg patents covering technologies that compete with each other, from which pool licensees can choose), or patents that are not essential to bring a product to market, raise the potential for collusion and invite scrutiny by the Agencies. One way to alleviate scrutiny is for a patent pool to hire an independent expert to administer the patent pool by determining whether the pool's patents are complementary and essential to enable product development, and by limiting participants' access to competitively sensitive information.

Antitrust principles applied to intellectual property licensing practices

The Agencies generally accept, as enhancing efficiency and innovation, specific types of intellectual property licensing agreements, non-assertion (or 'non-challenge' clauses), grant backs, and reach-through licensing agreements. In particular, non-assertion clauses have become popular in life sciences licence agreements, but are problematic if they are used to protect invalid patents, or to extend a patent beyond its statutory life.

Certain situations may, however, draw attention from the Agencies, particularly where an agreement bears the likelihood of limiting incentives for downstream innovation. For example, the Agencies may take notice if an agreement includes restrictions on licenses that have not yet been issued or filed, or if the agreement is larger in scope or longer in duration than that governing the technology licensed in the original agreement. Accordingly, life sciences companies engaging in these forms of intellectual property licensing agreements

should take special care to avoid these circumstances through the express language of the licensing documents, and generally by ensuring that the agreements continue to allow for competition and innovation outside the confines of the agreements.

FDA discusses evaluation of follow-on biologics

A recent article published by FDA staff[3] has provided a useful insight into the FDA's viewpoint and discusses specific FDA actions with respect to follow-on biologics. As Congress and the FDA continue to work towards establishing a regulatory pathway for the approval of follow-on biologics, the article provides valuable guidance as to the FDA's views towards these products.

Background

The FDA generally approves new drugs, as distinguished from biologics, under Section 505 of the Food, Drug, and Cosmetic Act (FDCA) and licenses biologics under Section 351 of the Public Health Service Act (PHSA). Unlike the FDCA, the PHSA does not contain an abbreviated approval pathway whereby applicants can rely on FDA's analysis of a previously approved product. As a result, biologics have not traditionally been eligible for follow-on or generic approvals.

Owing to a regulatory anomaly, certain biological products are regulated pursuant to the FDCA rather than the PHSA, and are therefore eligible for follow-on approval. FDA has approved various abbreviated applications filed pursuant to Section 505(b)(2) of the FDCA. The publication provides examples of FDA's review of these follow-on biologics and illustrates some of the factors that have influenced the amount and type of data required to support marketing approval for these products.

FDA review of follow-on biologics

The FDA explains that it evaluates each follow-on biologic application on a case-by-case basis, and the amount and type of data required to support marketing approval varies from product to product. Although specific requirements will vary depending on the product, the Agency highlighted the following factors as important in its review of all follow-on biologics:

- evidence of integrity and consistency of the manufacturing process;
- conformance of manufacturing standards to existing regulations (if any);
- demonstrations of a product's consistency with appropriate reference standards or comparators (using relevant assays), including comparative pharmacokinetic and pharmacodynamic data;
- the extent to which the existing body of clinical data and experience with the approved product can be relied on.

Following is an overview of FDA's analysis for the follow-on biological products addressed in the guidance:

Albumin

FDA's evaluation of follow-on Albumin, a naturally occurring human protein obtained from human plasma, relied primarily on evaluation of manufacturing standards and performance of small safety trials. Additional clinical data were considered unnecessary because the mechanism of action was well understood; there was extensive clinical experience for the product; and albumin products are purified using well-established and consistent manufacturing methods.

Standardised allergenic extracts

FDA's evaluation of follow-on standardised allergenic extracts – which are derived from natural sources such as pollens or insects – focused on the integrity of the manufacturing process. FDA stated that clinical data would not be required for such follow-on applications if the product is demonstrated to be consistent with established reference standards.

Mammalian testicular hyaluronidase

FDA approved follow-on versions of hyaluronidase based on assay data showing that the product has enzymatic activity consistent with the United States Pharmacopeia-National Formulary (USP-NF) standards, clinical data assessing the immunogenicity of the product, and information establishing that the manufacturing

process ensures consistency of the original drug product. Clinical testing of immunogenicity was considered important because products derived from different sources may be more or less immunogenic.

DigiFab (digoxin)
The DigiFab follow-on biologic, which consists of digoxin-specific antibody fragments obtained from sheep, was approved based on a small study demonstrating its safety and effectiveness; an understanding of its mechanism of action; and data indicating that its pharmacodynamic and pharmacokinetic parameters were comparable to the original product.

Glucogen
The FDA approved a follow-on version of Glucogen, a product originally derived from bovine and porcine pancreas, based on data bridging the follow-on version to the clinical data supporting the approval of the original product. Data included structural characterisation, pharmacokinetic and pharmacodynamic data, and a favourable safety profile.

Fortical (Salmon calcitonin nasal spray)
FDA approved a nasal spray dosage form of salmon calcitonin based on comparative data including physiochemical characterisations demonstrating sameness of amino-acid sequence and secondary structures; pharmacodynamic data from a 24-week study indicating comparable effects on bone resorption; a similar safety profile; pharmacokinetic data regarding bioavailability; animal pharmacokinetic/pharmacodynamic and toxicology data demonstrating comparability; and immunogenicity data indicating comparability.

Omnitrope (somatropin) – Human growth hormone
The follow-on approval relied on physiochemical, pharmacokinetic, pharmacodynamic and clinical data comparing the follow-on to the original approved product. Clinical comparative data came from two controlled trials (six-month and three-month) in 86 paediatric patients. FDA also reviewed non-clinical pharmacology data; a controlled study supporting the safety and efficacy of reformulated Omnitrope for injection; and safety data from a 24-month uncontrolled trial of 51 subjects.

Eprex (erythropoietin)
Approval of the follow-on product was based on information indicating that the manufacturing process for the follow-on and original product was sufficiently similar; demonstrate structural similarity; were pharmacokinetically and pharmacodynamically similar; and have a similar clinical safety profile.

Recombivax HB (hepatitis B vaccine)
Approval of the follow-on product was based on safety and immunogenicity data compiled for 1,200 healthy volunteers and clinical efficacy studies involving a total of 289 subjects.

Avonex (interferon)
The follow-on version of Avonex required a change in the cell line used to produce the original product. FDA reviewed physiochemical testing, multiple bioassays, and pharmacokinetic data that demonstrated that the follow-on version was sufficiently similar to the original product.

Conclusion
Scientific and technological advances have created new opportunities for the characterisation and evaluation of protein products and have led to increased interest in establishing a regulatory pathway for approval of follow-on biologics. The article illustrates FDA's scientifically based, case-by-case approach to evaluating follow-on biologics and provides an insight into FDA's views and concerns with respect to the review of follow-on biologics.

References and Notes

1. See further National Institutes of Health guidance at http://privacyruleandresearch.nih.gov/clin_research.asp.
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