

# Legal and regulatory update

## ReedSmith

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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 to be relied upon, specific advice should be sought. Please contact:

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## NOTES FROM THE EU

### European Court of Justice confirms ruling on supplementary protection certificates for combination products

Following its decision last year in Case C-431/04 *Massachusetts Institute of Technology* that a supplementary protection certificate (SPC)<sup>1</sup> is only available to extend a patent covering an active ingredient of medicinal product and not an excipient that aids the pharmacological effect of the medicinal product,<sup>2</sup> the European Court of Justice (ECJ) has recently ruled in *Yissum R&D Company of Hebrew University of Jerusalem* that the available protection is also limited such that a patent merely covering a second medical use cannot be extended by means of an SPC.<sup>3</sup>

In this case Yissum was holder of a European patent entitled ‘Cosmetic and dermatological compositions containing l-alpha-hydroxycholecalciferol’. It concerned in particular a composition, for use in topical treatment of skin disorders, containing a compound of l-alpha-hydroxycholecalciferol or of 1-alpha, 25-dihydroxycholecalciferol, commonly known as calcitriol. The patent also covers the same composition in conjunction with a carrier suitable for the manufacture of a cream, an ointment or a lotion; in other words, a second medical use. A product consisting of calcitriol as active ingredient, and liquid paraffin, white soft paraffin and alpha-tocopherol as carriers was authorised in the UK in December 2001. The ointment is authorised for ‘topical treatment of plaque psoriasis (psoriasis vulgaris) with up to 35% of body surface area involvement’. Yissum subsequently applied to the UK Patent Office for an SPC for calcitriol either

solely for calcitriol or alternatively for a combination of calcitriol with an ointment base.

The UK Patent Office refused that SPC application on two grounds:

- the authorisation to place the product on the market on which Yissum was relying was not the first such authorisation for that product as a medicinal product,<sup>4</sup> as required by Article 3(d) of the SPC regulation;
- an ointment base cannot be considered to be an active ingredient and, consequently, dismissed Yissum’s SPC application in so far as it concerned a combination of active ingredients including an ointment base.

Yissum appealed to the English High Court, which referred the matter to the ECJ for a preliminary ruling as to the meaning of ‘product’ for the purposes of the SPC regulation, in particular whether a product authorised for a different use could constitute a different product and hence qualify for an SPC.

The ECJ confirmed the principle that ‘product’ meant active pharmaceutical ingredient and the particular use for the product did not ‘form an integral part’ of the definition. Consequently in defining what the product is for the purposes of the SPC regulation, one must discount the carrier used in preparing the ointment leaving only calcitriol. It follows that an SPC is not available because an SPC has already been issued covering calcitriol and furthermore the second medical use patent cannot qualify as a basic patent for the SPC regulation because it does not cover the product *per se*.

The decision is interesting in that it was delivered by the ECJ without first receiving an opinion from its advocate-general, which happens where on written submission from the parties, the outcome is already clear to the court. It was felt that the reasoning in the MIT case (which was decided after the Yissum case was referred to the ECJ) gave an obvious answer to the issues raised. It will of course be observed that the court's reasoning gives a very narrow interpretation to the scope of the SPC regulation.

### **European Union adopts advanced therapy medicinal products regulation**

The regulatory framework for novel therapies in the EU, such as stem cell-based treatments and tissues engineering products with the adoption of the Advanced Therapy Medicinal Product Regulation<sup>5</sup> (the 'ATMP Regulation'). By way of reminder, this defines advanced therapy medicinal products ('ATMP') as the following:

- a gene therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC;
- a somatic cell therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC;
- a tissue engineered product as further defined below.

A tissue-engineered product means a product that:

- contains or consists of engineered cells or tissues; and
- is presented as having properties for, or is used in or administered to human beings with a view to, regenerating, repairing or replacing a human tissue.

One of the key elements of this definition is the word 'engineered'. The ATMP Regulation considers a product to be

engineering if it falls within one or both of the following points:

- The cells or tissues have been subject to substantial manipulation, so that the biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement, are achieved.
- The cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor.

It is clear, therefore, that the ATMP Regulation will include stem cell-based therapies and other therapies where precursor cells are caused to differentiate into cells for implantation.

The consequence of this is that firstly stem cell-based therapies will be subject to the clinical trials regime under the 2001 clinical trial directive, which require that a clinical trial is authorised by the competent authority in each member state (in this case obtaining 'positive' rather than 'negative' approval) and has been subject to ethical review and that it is conducted in accordance with GCP using investigational medicinal product manufactured in accordance with GMP. Furthermore, the ATMP Regulation requires that a marketing authorisation will need to be obtained to market the ATMP in the EU in the same way that, for example, novel biologics must follow the centralised procedure, which requires completion of clinical trials and submission of appropriate safety, efficacy and quality data.

All that remains is the formal adoption and publication of the ATMP Regulation. At the time of writing, the English text is being translated into the other official EU languages and so formal adoption is anticipated by mid-November 2007. The regulation is then published in the Official Journal, probably by the beginning of December 2007. It will then enter into force 20 days after publication and will apply one year after entry into force; in

other words, for all practical purposes, the regulation will become relevant from the end of 2008.

### **New EU GMP guide for the manufacture of biological medicinal products for human use**

The GMP Guide for the manufacture of biological medicinal products (Bio-GMP) for human use was much in need of updating for several reasons. The first of these is that the guide needed to keep pace with the breadth of biological products and biological product types that are now available and in use. The second reason is that the GMP guide as a whole has been restructured and a new active substance GMP added, and the Bio-GMP needed to take account of these. The third reason is that there is the adoption of the ATMP Regulation described above.

The European Commission and EMEA have issued a proposal for a new Bio-GMP guide has increased the specific manufacturing activities covered by the guide.<sup>6</sup> It now covers the following different types of source material:

- animal (transgenic and non-transgenic)
- human
- plant (transgenic and non-transgenic)
- fermentation
- virus bioreactors/cell culture
- biotechnology: fermentation and cell cultures.

Whereas the previous Bio-GMP guideline did not include detailed requirements for specific classes of biological products, the new guide includes in section B specific guidance on: allergen products, animal immunosera products, vaccines, recombinant products, monoclonal antibody products, gene therapy products, somatic and xenogeneic cell therapy products, transgenic animal products and transgenic plant products. A separate section on tissue engineered products is still in the process of being written and will be added at a later date.

The common themes within the GMP requirements for the specific classes of biological products include:

- the quality of the source material, including monitoring the health of human, plant and animal sources both before and after extraction of biological materials with look-back procedures for conditions not apparent at the date of harvest;
- traceability from sources to recipients (with the proviso that the individual's privacy is respected);
- the consistency of the products in each batch and the demonstration of the consistency between batches;
- ensuring the stability of materials through the establishment of and adherence to procedures for the proper storage and handling of the particular biological materials concerned.

Of particular concern is the health and safety of those handling biological materials. The Bio-GMP guideline requires special measures to be taken where there are particular hazards associated with these products. Live and genetically modified organisms, including vaccines and particularly those with a higher biological safety level (such as smallpox) require particularly safe handling. The importance of this has been unfortunately underlined by the outbreak of foot and mouth disease in the UK where the source was a government laboratory handling the virus material.

The Bio-GMP in its section on general guidance also contains additional requirements. Among these new requirements is the consideration of various steps to avoid cross-contamination by dedicating equipment and internal space to an individual product, as well as carrying out production on a campaign basis and the use of closed systems.

Personnel working with biological materials are to be given consideration for their own safety, but also the potential for them to

contaminate or cross-contaminate products. Suggestions include special clothing and changing facilities, training and education requirements (including practical experience) and obtaining specialist advice on how personnel should ensure the safe handling of the particular materials. Furthermore, there are new requirements for dealing with spillages of biological materials and validated decontamination measures need to be established for each organism.

The draft document is open for consultation until 14th March, 2008.

### **UK National Institute of Health and Clinical Excellence guidance on treatment of Alzheimer's disease upheld by court**

As reported in the previous Legal and Regulatory Update,<sup>7</sup> Eisai with the support of Shire Pharmaceuticals has been seeking to challenge guidance issued by the UK National Institute of Health and Clinical Excellence (NICE) in January 2001 that restricts the availability of certain Alzheimer's drugs belonging to the class of acetylcholinesterase inhibitors, namely donepezil, rivastigmine and galanthamine, to certain categories of patient only.<sup>8</sup> One of the functions of NICE is to publish clinical appraisals of whether particular treatments should be considered worthwhile by the UK National Health Service (NHS). These appraisals are based primarily on cost-effectiveness. The guidance issued by NICE must generally be followed by prescribers and purchasers within the NHS in areas that have been subject to NICE review.

Prior to issuing the guidance, NICE had undertaken a consultation following the preparation of a technology assessment report prepared by an independent academic centre included an economic model (in the form of an Excel spreadsheet). The model was sent to consultees, including Eisai and Shire. The proposed guidance recommended the use of acetylcholinesterase inhibitors for those with Alzheimer's disease of moderate severity only,

as determined by their scores in a mini mental state examination.

Following an unsuccessful appeal against the decision of NICE's appraisal committee to the tribunal established within NICE to hear such challenges, the NICE guidance was published and then Eisai applied for judicial review of the NICE decision-making process. Judicial review is not an appeal as such, but rather considers the procedural regularity of the process. The court does not have the power to order NICE to recommend the drugs for particular indications or to make findings of fact on which the recommendations can be made. The case represented the first occasion on which NICE has faced a judicial review of its decision-making.

Eisai's grounds for seeking judicial review and the court's response were as follows:

The process was procedurally unfair on the basis that NICE refused to disclose the full cost-effectiveness model that was used to determine the value of treatment in patients with mild Alzheimer's disease.

The court rejected this ground, noting that the process followed by NICE was a consultation, albeit a highly structured one and not for example a statutory or judicial process. It did not therefore follow that there was any right for consultees to 'quality assure' the model, nor was there any obligation on the institute to allow them to do so, whether explicitly or implicitly. Furthermore, the court found that Eisai had not been denied access to significant information nor deprived of the opportunity to make an intelligent response to the invitation to take part in the consultation. There was a clear policy in relation to the receipt and release of models, which was on the basis that it was in confidence and subject to the intellectual property rights of the provider.

The decision made was irrational on the basis that some of the assumptions and conclusions in the Final Appraisal Document were irrational or unsupported.

It was also found that the appeal panel had not erred in its consideration of the rival arguments relating to the assumption in the model that patients receiving acetylcholinesterase inhibitor treatment would derive no additional benefits after having received six months of treatment, nor those relating to a long-term study which showed no long-term benefit from acetylcholinesterase inhibitor treatment. The court further found that the decisions of the appeal panel in relation to the measurement of carer benefit and carer costs could not be characterised as irrational.

The guidance infringed human rights and was discriminatory on the basis that the mini mental state examination scores used in the appraisal discriminated against certain so-called atypical patient groups (i.e. ethnic minorities and those for whom English is not a first language).

Eisai was successful on this more limited point since the court decided that the issue of atypical groups was dealt with in an unsatisfactory manner in the guidance. The approach of the appeal panel and the subsequent guidance was flawed in that no proper consideration was given to the NICE's duties as a public authority to promote equal opportunities and to have due regard to the need to eliminate discrimination.

The result is that while NICE has been forced to review its advice as regards the atypical patient populations, the process followed by NICE in reaching its recommendations was not otherwise found to be defective.

### **Greater onus on UK trade-mark owners to monitor competing trade-mark applications**

Changes in the procedure for examining new applications at the UK Trade Marks Registry mean that trade-mark owners will have to take positive steps to ensure that conflicting marks do not find their way onto the register.<sup>9</sup>

The Registry has always examined new applications to see whether they should be refused on 'absolute grounds', for example, for lack of distinctiveness or due to various policy considerations. Prior to 1st October, 2007 it would also refuse registration on 'relative grounds'. Relative grounds are grounds for refusal that are based on conflicts with existing marks on the register. If the new mark was (1) identical to an existing mark, (2) similar to an existing mark and likely to cause confusion, or (3) likely to take unfair advantage of or cause detriment to the distinctive character or repute of an existing mark, the application could be refused (depending on the specification of goods and services applied for).

This procedure meant that all trade-mark owners had to do to stop conflicting marks from being registered was to sit back and wait for the Registry to cite their mark against the new application. However, from 1st October, 2007 the Registry stopped examining on relative grounds. Applications may still be refused on relative grounds, but in order for this to happen, mark owners must take active steps to oppose them.

When looking at new applications, the Registry will still search the register for the potential conflicts, but instead of refusing registration they will simply send a list of potentially conflicting marks to the applicant. The applicant then has three choices:

- withdraw the application;
- restrict the specification to try to overcome any conflict; or
- continue with the application.

If the applicant continues with the application, the Registry will automatically notify the owners of any potentially conflicting UK marks, and it will be up to those owners to oppose the new registration. Owners of potentially conflicting Community Trade Marks will *not* be notified automatically. They have to 'opt in' to receive notifications at a fee of £50 per mark for three years.

The changes mean that the UK Registry procedure is now in line with that of the Community Trade Mark Office (known officially as the Office for Harmonization in the Internal Market or OHIM) procedure for the examination of Community Trade Marks. It would never have been practical to refuse registrations on relative grounds in the OHIM due to the vast number of Community registrations.

By aligning its procedures with OHIM's, the UK Registry may hope to attract more business. It is likely to be easier to push an application through to registration in the UK if refusal based on relative grounds is not automatic, and new registrations will not be prevented by 'dead' marks (ie marks which remain on the register but are no longer valued or enforced by their owners). However, a UK registration is arguably of less value now. Owners will need to invest more time and money in monitoring new applications and opposing them where necessary. Larger corporations will no doubt take this in their stride, but the losers may be small and medium-sized businesses who are not aware of the need for action or who do not have the resources to allocate to these processes.

#### **UK Mark owners**

Owners of existing UK trade-mark registrations should take the following practical steps:

- Ensure the contact address for your mark is up to date so that you receive notifications of conflicting applications.
- Make sure you keep the address up to date if you move.
- Put in place a system to ensure that notifications are passed promptly to a person who is qualified to assess whether new applications should be opposed.
- If following a notification you decide you do wish to oppose, ensure that you monitor the application so that you can oppose as soon as it is published (there is

only a three-month window in which you can oppose).

- Consider setting up a watching service for new applications as a backup to the notification procedure (until it becomes more established, it is not clear how efficient the notification procedure will be).

#### **CTM owners**

The following steps should be considered in addition by owners of Community Trade Marks:

- Ensure you opt in to receive notifications and renew your opt-in every three years.
- Follow the steps for UK mark owners as set out above.

## **NOTES FROM THE US**

### **United States Supreme Court rules on the test for 'obviousness' in patent law**

On 30th April, 2007, the Supreme Court of the United States issued its decision in *KSR Int'l Co. v Teleflex, Inc.*<sup>10</sup> Depending on perspective, the decision either simply clarified existing law or significantly altered the standard for denying or overturning patent grants based on the 'obviousness' of the claimed invention. The Supreme Court itself stated that it was simply reiterating and clarifying the existing law of *Graham v John Deere Co. of Kansas City*, 383 US 1, 17–18 (1966). In *Graham*, the Court set out a series of factors (the 'Graham factors') to be considered in determining whether an invention was obvious: the scope and content of the prior art; the difference between the prior art and the claims of the patent; the level of skill of one of ordinary skill in the relevant art; and any secondary considerations such as a long felt need in the art; the failure of others to develop the invention and the commercial success of the invention. Although the technology forming the subject

matter of the patent comes from the mechanical sciences, the principles enunciated are of general application in all fields.

Long before KSR the United States Court of Appeals for the Federal Circuit developed its own test and, essentially, only paid lip service to the Graham factors. The Federal Circuit test, rigidly applied, was the so-called 'teaching, suggestion, motivation' ('TSM') test. The application of the TSM test precluded a finding of obviousness unless there existed in the prior art a teaching or a suggestion or a motivation to combine two or more prior art references. While the Supreme Court did not wholly abandon the TSM test in KSR, it unequivocally determined that it was not the only test for obviousness. Moreover, the Supreme Court did not provide its own rigid test. Rather, it requires an 'expansive and flexible' approach to the analysis of obviousness based, in the first instance, on the Graham factors.

In reaching its conclusion, the Supreme Court reiterated the need for caution in granting patents based upon combination of old elements found in the prior art and unambiguously rejected the application of any rigid rule on obviousness, including the TSM test. The guidelines proposed by the Supreme Court take into consideration inferences and common sense creative steps that a person of ordinary skill in the art would employ. Still, after years of applying the easily understood TSM case, inventors, patent lawyers and owners of patents are concerned that these guidelines fail to provide any sense of an easily measurable or consistent test for obviousness.

In setting aside the TSM test, the Supreme Court criticised it on three principle grounds. First, it concluded that the TSM test limited examiners and courts to consideration only of the specific problem attempted to be solved by the inventor and, on the flip side, that an inventor would only be led to consider prior art specifically designed to solve the problem presented. Instead of limiting the prior art to only that related to the problem

addressed by the inventor, the Court reasoned that any need or problem known in the field and addressed by the patent can provide a reason for combining the elements in the manner selected.

Secondly, the Supreme Court found fault with the TSM test for failing to consider whether the combination of elements was 'obvious to try'. The Court elaborated that when a work is available in one field, design need or market pressure will prompt variations of it whether in the original field or another. It reasoned that if there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. Success in such circumstances is likely the product of common sense not of innovation of ordinary skill.

Finally, the Supreme Court's decision challenged the Federal Court's concern of possible hindsight bias of examiners and counts because it led to rigid appreciation of the TSM tests and 'denied fact finders recourse to common sense'.

The 'common sense' theme ran throughout the Court's opinion and its invocation has led to some confusion. Here the Court considered 'common sense' at two levels. The first of these is the common sense knowledge of one of ordinary skill in the art. The second is the common sense of the fact finder in evaluating the conclusions and inferences that would have been drawn by one of ordinary skill.

So far the Federal Circuit has only addressed the 'common sense' standard once since KSR. In *Leapfrog Enterprises, Inc. v Fisher-Price, Inc.*, 485 F.3d 1157, 1161 (Fed. Cir. 2007), it confirmed that the 'common sense' standard was applied as to the common sense of the person of ordinary skill in the art and may be used to 'demonstrate... why some combinations would have been obvious where others would not'.

Despite the multiplicity of guidelines addressed, the net-net of the Supreme



Court's opinion can be found in a single sentence:

Therefore, in formulating a rejection under 35 U.S.C. §103, based upon a combination of prior art elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed (Emphasis added).

In other words, there must be a rational explanation provided by the examiner to deny a patent based on obviousness. There have been subsequent Federal Circuit cases but enough to determine yet whether the Federal Circuit will have its own gloss on the KSR guidelines. Still, the Federal Circuit does appear to be focusing on the requirement of finding a 'reason' that would have prompted an allegedly obvious combination. See for example, *In Re Trans Texas Holdings Corp.*, 2007 WL 2377009, CA No. 2006-1599, 2006-1600 (Fed. Cir. August 22, 2007) (finding obviousness where the 'reason' was that it would have been 'obvious to try'); and *Lakeda Chem. Indus. Ltd. v Alphaharm Pty., Ltd.*, 492 F.3d 1350, 1358-59 (refusing to find obviousness where the prior art did not identify any predictable solutions but instead disclosed a broad selection of compounds any one of which could have been selected for further investigation).

Now the United States Patent and Trademark Office (USPTO) has issued its 'Examination Guidelines for Determining Obviousness Under 35 U.S.C. § 103 in View of the Supreme Court Decision in *KSR Int'l Co. v. Teleflex, Inc.*'.<sup>11</sup> The USPTO still requires examiners to look to the Graham factors in the first instance (as required by the Supreme Court) to determine whether an invention would have been obvious. Following the instructions of the Supreme Court, however, the USPTO has clarified that 'obviousness cannot be sustained by mere conclusory statements' and requires examiners to provide a clear articulation of the reasons

for finding obviousness. Possible rationales can include:

- combining prior art elements according to known methods to yield predictable results;
- simple substitution of one known element for another to obtain predictable results;
- use of known techniques to improve similar devices (methods or products) in the same way;
- applying a known technique to a known device (method or product) ready for improvements to yield predictable results;
- 'obvious to try', that is to say, choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;
- known work in one field of endeavour may prompt variations of it for use in either the same field or a different one based on design incentives would have been predictable to one of ordinary skill; and
- some searching suggestion or innovation in the prior art, that would have led one of ordinary skill to the invention.

The hallmark of these guidelines is predictability of results. They will not be limited only to the USPTO but should work their way into district court decisions as well as Federal Circuit opinions. Thus depending on whether one is arguing for or against an obvious finding, it will be critical to present evidence on these factors. As the last factor confirms, the TSM test has not been rejected completely, but now there are other 'reasons' for finding an invention to be obvious.

### **United States Patent and Trademark Office rule changes claims and continuations rules summary and considerations**

To reduce the growing backlog of unexamined patent applications, the US Patent and Trademark Office (USPTO) announced a new set of rules on 21st August,

2007.<sup>12</sup> In particular, these rules limit the number of continuation applications that an applicant may file without justification, limit the number of claims that may be submitted in a patent application without having to provide a detailed analysis, as well as, affect related applications containing patentably indistinct claims. The new rules entered effect on 1st November, 2007. Many of the new rules, however, apply to already pending applications.

### ***Continuation practice***

Traditionally, continuation practice has been a useful tool for keeping a patent application alive when confronted with a 'final rejection' or when pursuing broader claims than the patent examiner initially allows. Under the previous rules, an applicant was permitted to file an unlimited number of continuation applications based on a parent application either in parallel or in series. The new rules limit an applicant to two continuing applications (either continuation or continuation-in-part applications) plus one request for continued examination (RCE) in a 'patent family'. Any additional continuing applications or RCEs will require justification in the form of a petition showing that an amendment, argument or evidence could not have been submitted during the prosecution of the prior-filed application. According to the new rules, a divisional application filed as the result of a restriction requirement can serve as a parent application for two continuing applications plus one RCE.

The change in continuation practice will also impact all patent families with pending applications. In particular, the USPTO will permit an applicant to have 'one more' continuing application after 21st August, 2007, regardless of the number of continuing applications that may have been filed before 1st November, 2007.

### ***Claims***

Under the previous rules there was no limit on the number of claims that an applicant could submit in a single application. The new

rules limit an application to no more than five independent claims and 25 total claims (5/25 rule). The 5/25 rule applies equally to all new applications and pending applications that have not received an Office Action on the merits before 1st November, 2007.

If an application exceeds the 5/25 rule, the applicant will be required to either cancel the excess claims or file an extensive 'examination support document' (ESD). An ESD will be required to include a pre-examination search statement, a listing of the references most closely related to the subject matter of the claims, an identification of all of the claimed subject matter disclosed in the references, a detailed explanation of why each claim is patentable over the cited references, and a show of support in the application's specification for each limitation presented in the claims. The ESD must be filed prior to the first Office Action on the merits.

Applicants will be given a two-month period following a notice from the USPTO to comply with the 5/25 rule.

### ***Concurrent filings***

The USPTO has also revised the rules with respect to filing multiple applications that may contain patentably indistinct claims. Under the new rules, the applicant must identify all related applications filed within two months of each other if they name at least one inventor in common and are commonly owned. Applications that are having the same filing or priority date and contain substantially overlapping disclosures will be presumed to have patentably indistinct claims. Unless this presumption can be overcome by successfully arguing the claims are distinct, the total number of the claims among the commonly owned and concurrently applications will be limited by the 5/25 rule.

### ***Considerations***

The new rules are a significant change in USPTO procedure made in an attempt to streamline the examination process by limiting the number of applications and claims an

applicant may file. This process may present new challenges to obtaining patents and likely increase the expense of obtaining a patent. If an applicant is unable to adequately protect an invention under the 5/25 rule, the applicant will be required to file a burdensome ESD potentially resulting in undesirable admissions in the prosecution history.

Since the rules apply to already pending application, all applications that have not received an Office Action on the merits by 1st November, 2007, will be required to comply with 5/25 rule by either cancelling excess claims or filing an ESD. Applicants who have already filed two continuations before 21st August, 2007, may file 'one more' continuation in that patent family without having to file a petition. In compliance with the 'concurrent filing' rule, applicants may be required to report common filings for pending applications by 1st February, 2008.

### **Washington University v Catalona: Old law settles new science of tissue ownership**

The United States Court of Appeals for the Eighth Circuit has resolved a contentious dispute over research ownership of tissue and DNA samples by turning to the ancient legal doctrine of *inter vivos* gifts.<sup>13</sup> Examining the intent of tissue donors the court found that the samples had been donated, with very few limitations, as a gift to a researcher's institution. In making this finding the Court rejected the effort by the researcher to have thousands of samples transferred to his new academic institution. The lesson for both is this: be very careful in crafting the informed consent language to make clear the donor's ownership intent.

Dr William Catalona, a renowned urologic specialist and researcher, worked for the University of Washington in Missouri for more than 27 years. During that time he became interested in researching the genetic causes for prostate cancer. In 1983 he began to collect a variety of biological samples from

his patients. His repository became the Genito-urinary Biorepository which, in the words of the Court was 'the world's largest storage facility for biological samples... collected for prostate cancer research'. The trial court highlighted the fact that Washington University housed the research and storage facilities. Indeed, the University provided the majority of funding for the centre's maintenance. The University, not Dr Catalona, was named as the grantee of private and public grants.

When patients were told about the research before their treatments they were given a variety of informed consent forms as well as a brochure. Each was to be read and signed. Critical to the Court's unanimous decision were the following:

- The biological samples were called a 'donation' to a University physician.
- The forms advised the patient that the samples 'maybe used for research with our collaborators at [the University], other institutions or companies'.
- Each patient waived any claim or right he might have to the donated tissue as well as the right to any proprietary development from the tissue.
- Each patient abandoned all rights to designate the particular destination.
- The brochure advised the patient that the tissue would be used by researchers and could be used for studies conducted 10–20 years later.
- Each patient was advised that their only right to the tissue was to have it destroyed upon request.
- 'By agreeing to participate, you are making a free and generous gift of your tissue to research that may benefit society'.

When Dr Catalona moved to another academic institution he attempted to have the samples of more than 50,000 donors transferred from Washington University. He did so by writing to each of them asking them to sign a release authorising the transfer of their individual samples to his new institution.

Washington University responded by filing a declaratory judgment action against Dr Catalona. After a three-day hearing, the trial court entered judgment for the University. On 20th June, 2007, the Eighth Circuit unanimously affirmed this judgment.

A reader of the appellate decision might have anticipated a discourse on intellectual property law or the law of informed consent. Perhaps even a discussion of the well-known California Supreme Court case of *Moore v Regents of the University of California*, 51 C.3d. 120 (1990), that analysed the law of the fiduciary duty of a researcher to his patient as well as the property interests that a patient has in his tissue. The reader, in either case, would be disappointed. Instead, the court began its review with a summary of the state law of *inter vivos gifts*. The state law of Missouri, the state with the controlling law, defines this type of gift as ‘a voluntary transfer of property by the owner to another, without any consideration or compensation as an incentive or motive for the transaction’ (Citing the 1932 decision of *Pilkington v Wheat*, 51 S. W.2d 42, 44 (Mo. 1932) (a case involving the issue of ‘whether certain land which a son owned at the time of his father’s death should be treated as an advancement in a suit for partition’). Thus the University had the burden, under Missouri law that had evolved from a suit in partition of real estate, to prove:

- present intent of the donor to make a gift;
- delivery of the property by the donor to the donee; and
- acceptance of the gift by the donee, whose ownership take effect immediately and absolutely (citing to *Clippard v Pfefferkorn*, 168 S.W.3d 616, 618 (Mo.Ct. App.2005).

There was no dispute that there had been a delivery of the tissue by the donors. The court, looking to the documents given to the patients – the informed consent and brochure – to determine the present intent of the donor and whether the donation had been

immediate and absolute. The court found that the language of the documents was also clear as to the absolute and unconditional grant of, in the word of the consent, the ‘donation’. The court noted too the brochure’s description of the ‘donation’ as ‘a free and generous gift of [biological materials] to research that may benefit society’.

Thus, the first instance court had properly concluded the [donors] made informed and voluntary decision to participate in genetic cancer research, and thereby donated their biological materials to [Washington University] as valid *inter vivos gifts*. This voluntary transfer of tissue and blood samples to [Washington University] – without any consideration or compensation as an incentive for doing so – demonstrates [Washington University] owns the biological samples currently housed in the Biorepository. Whatever rights or interests the [patients] retained following their donation of biological materials, the right to direct or authorise the transfer of their biological materials from [Washington University] to another entity was not one of them.

The lessons for any research institution to take from this decision are:

- Know the law of *inter vivos gifts* in the state in which they practice.
- Ensure that every document given to a donating patient – consent form, brochure, summary and such like – contains words, phrases and sentences unambiguously establishing that it is the donor’s present intent to make the donation as a gift; that the donation is taken as the property of the institution and that the transfer is to take effect ‘immediately and absolutely’.

### **Kickbacks abroad: The Foreign Corrupt Practices Act**

Enacted in 1977 in the wake of the Watergate scandal, the Foreign Corrupt Practices Act (FCPA) was designed principally to prevent

US companies from bribing foreign officials to obtain or maintain a business advantage.<sup>14</sup> However, similar to the federal healthcare programme anti-kickback statute, the FCPA actually covers many types of remunerative arrangements in addition to traditional *quid pro quo* bribes. This, combined with robust enforcement of the FCPA (which is exercised jointly by the Securities Exchange Commission (SEC) and the Department of Justice (DOJ)), signals a need for any US company doing business outside of the US to incorporate the FCPA into its compliance regime.

Healthcare entities, such as biotech, pharmaceutical and medical device manufacturers, which increasingly sell products in foreign countries, need to be particularly aware of the constraints of the FCPA. This is because the FCPA often restricts, and in some instances, prohibits, the provision of anything of value to physicians and other types of healthcare professionals, because such persons often qualify as foreign government officials under the FCPA. The engagement of foreign intermediaries (such as distributors and sales agents) complicates compliance as well. Finally, several recent enforcement actions – which resulted in large settlements – have involved pharmaceutical and medical device manufacturers. In this context, set out below is an overview of the FCPA, followed by a summary of key considerations for US healthcare entities doing business outside the United States.

### **Overview of the FCPA**

The FCPA has two main components: (1) accounting requirements and (2) anti-bribery provisions. In a nutshell, the first component requires publicly traded companies to have internal controls to ensure that corporate assets are properly utilised, and to maintain books and records to support appropriate utilisation. In other words, the accounting requirements are designed to work in tandem with the anti-bribery provisions to eliminate ‘off-the-books’ transactions or ‘under the table’ payments.

Not unlike the US anti-kickback statute, the FCPA’s anti-bribery provisions, in essence, prohibit the payment of any type of ‘kickback’ to a foreign official or political party to secure or maintain a business advantage. ‘Foreign official’ is defined very broadly to include, for example, any employee of a foreign government or any person acting in an official capacity (which, as noted above, potentially covers a variety of healthcare professionals working for a ministry of health, public hospital, or the like). Also, like the anti-kickback statute, the FCPA covers remuneration in any form; there is no *de minimus* exception. Finally, not surprisingly, a company cannot use a third party – often referred to as an ‘intermediary’ – to make an illicit payment on the company’s behalf.

*Exception and affirmative defences.* The FCPA has one exception and two affirmative defences. The exception covers payments made to facilitate or expedite the performance of a ‘routine governmental action’ (or, in other words to ‘grease the wheels’ of commerce). As such, it is commonly referred to as the ‘facilitating payments’ exception. ‘Routine governmental action’ includes only non-discretionary actions that are ‘ordinarily and commonly’ performed by a foreign official in connection with activities such as: obtaining permits or licences; scheduling inspections; providing utility services; and similar activities. Importantly, the term ‘routine governmental action’ does not include: (1) any decision by a foreign official regarding whether to continue or award new business, or (2) any action taken by a foreign official to encourage a decision to continue or award new business.

In addition to the ‘facilitating payments’ exception to the FCPA, there are two affirmative defences to the anti-bribery provisions, which effectively protect: (1) payments that are legal under local law and (2) *bona fide* business expenditures. The former protects the offer or payment of remuneration where such activity is ‘lawful under the

written laws and regulations' of the foreign official's country. The latter, which covers certain business expenses, effectively permits the payment or offer of remuneration made as a 'reasonable and *bona fide* expenditure, such as travel and lodging expenses, incurred by or on behalf of a foreign official', which is directly related to (1) the promotion, demonstration, or explanation of products or services; or (2) the execution or performance of a contract with a foreign government or agent.

*Enforcement.* The FCPA provides for significant civil and criminal penalties. Criminal penalties against an individual for violation of the anti-bribery provisions include a \$100,000 fine, five years imprisonment, or both, per violation. Companies are subject to fines of up to \$2m per violation. Recent cases have resulted in large settlements, reaching as high as \$44m. A range of penalties may be imposed on the civil side, and indictment or conviction under the FCPA may also lead to disbarment (exclusion from participation in federal contracts). Finally, not unlike cases under the anti-kickback statute, many FCPA cases are resolved via settlement, which may include certain contractual compliance requirements akin to a corporate integrity agreement.

#### ***Considerations for healthcare entities***

Efforts to comply with the anti-kickback statute have prepared healthcare companies for compliance with the FCPA. However, the FCPA presents several unique challenges, as outlined below.

- *Definition of foreign official may include physicians and other healthcare professionals:* As noted above, the definition of 'foreign official' under the FCPA is extremely broad and may encompass many persons in the healthcare industry. In many countries, physicians and other healthcare personnel are employed by public hospitals and are therefore considered

'foreign officials'. Any payment to those physicians by healthcare companies may, accordingly, implicate the FCPA. For example, in a recent FCPA settlement, a medical equipment company agreed to pay a \$2m criminal penalty for paying 'commissions' (a percentage of purchases) to physicians and laboratory personnel employed by government-owned hospitals in China. In another recent case, a medical device company paid \$450,000 to resolve criminal liability under the FCPA for making payments to doctors employed by public hospitals in France, Turkey, Spain and Germany to induce the hospitals' purchases of the company's devices. Understanding the structure of the healthcare industry in each country in which a healthcare entity does business is, therefore, critical to ensuring compliance with the FCPA.

- *Excessive distributor margins may be viewed as a kickback:* In at least one case the DOJ has taken the position that the profit margin provided by a manufacturer to a foreign distributor was sufficiently wide that there was a high probability that at least part of this profit margin would be used for illicit purposes. By failing to make inquiries to discern the purposes for which the funds would be used, the DOJ asserted that the company violated the FCPA. This theory of liability is cause for concern, particularly given that it is common practice for distributors to make a profit. Manufacturers should, therefore, consider whether the government would deem the profit available to distributors on the manufacturer's products to be unreasonably high or excessive.
- *Vetting intermediaries:* Intermediaries of all types, including sales agents, distributors, consultants and other contractors, are frequently used by healthcare companies doing business in other countries. While such intermediaries are often commissioned for their ability to navigate unfamiliar processes and business practices in the local country, they, in turn, may

not be familiar with the restrictions of the FCPA. Because a healthcare company may be liable for actions of its intermediaries, the need for comprehensive policies and procedures for selecting, screening, and monitoring (and possibly training) all intermediaries cannot be understated.

Developing standardised contract terms for each type of intermediary may also facilitate, and enhance, compliance.

- *Remuneration is anything of value, paid directly or indirectly:* Similar to the anti-kickback statute, the FCPA covers a wide-range of remuneration that is paid or offered to gain a business advantage. Charitable donations, gifts, travel and entertainment all potentially implicate the FCPA. In addition, remuneration need not be provided directly to a foreign official to give rise to a violation. For example, a pharmaceutical manufacturer entered into a consent agreement to pay a \$500,000 fine for making charitable donations to a non-healthcare-related foundation in Poland because the government alleged the donations were intended indirectly to induce the director of a Polish health fund to influence the purchase of the manufacturer's products. Finally, the remuneration need not be particularly valuable to trigger an enforcement action. Indeed, the DOJ has pursued cases where the remuneration provided was relatively minimal, as well as cases where the remuneration was never even paid, only offered. Accordingly, healthcare entities should consider developing policies governing the provision of any gifts and entertainment (and other remuneration). Local law should be considered as well, as certain countries have additional restrictions in this regard.

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## References and Notes

1. Pursuant to Regulation (EC) No. 1768/92.
2. *Journal of Commercial Biotechnology* (2006) **12**, 299–311. Reported at [2006] ECR I-4089.
3. Case C-202/05 *Yissum R&D Company of Hebrew University of Jerusalem v The Comptroller-General of Patents* (European Court of Justice, 17th April, 2007).
4. Other medicinal products, such as Calcijex and Rocaltrol, containing calcitriol as sole active ingredient, had already been granted authorisation to be placed on the market before Silkis ointment. Calcijex is a sterile, isotonic, clear, aqueous solution containing calcitriol for intravenous injection and is used for the management of hypocalcaemia in patients undergoing dialysis for chronic renal failure. Rocaltrol consists of soft gelatine capsules, containing calcitriol and various inactive ingredients, and is administered orally to patients with chronic renal failure or post-menopausal osteoporosis.
5. European Parliament and Council Regulation on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 adopted on 31st May, 2007, but not yet published (text accessed on 12th October, 2007 at <http://ec.europa.eu/enterprise/pharmaceuticals/advtherapies/index.htm>).
6. Available at [http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2007/2007\\_09/gmp\\_annex\\_2\\_consultation\\_2007\\_09\\_03.pdf](http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2007/2007_09/gmp_annex_2_consultation_2007_09_03.pdf).
7. *Journal of Commercial Biotechnology* (2007) **13**, 293–308.
8. *Eisai Limited v National Institute for Health and Clinical Excellence, Alzheimer's Society and Shire Pharmaceuticals Limited (interested parties)* (QBD (Administrative Court), 10th August, 2007) [2007] EWHC 1941.
9. The Trade Marks (Relative Grounds) Order 2007, SI 2007/1976.
10. 127 S.Ct. 1727 (2006).
11. 72 Fed. Reg. 57526 (Oct. 10, 2007) available at <http://www.uspto.gov/web/offices/com/sol/notices/72fr57526.pdf>.
12. 72 Fed. Reg. 46716 (Aug. 21, 2007) available at <http://www.uspto.gov/web/offices/com/sol/notices/72fr46716.pdf>.
13. 437 F.Supp.2d 985 (E.D.Mo. Mar 31, 2006).
14. See 15 U.S.C. §§ 78m, 78dd-1 et seq.