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

Paediatric regulation enters force

Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12th December, 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 was published on 27th December, 2006 and came into force on 26th January, 2007. The provisions of the Regulation, which introduce a complex regime of requirements and incentives to take into account paediatric use in drug development, were described in a previous legal and regulatory update.[1] Different aspects of the regime will take effect over the new two years to allow sponsors to make appropriate arrangements to comply with the new requirements.

The European Commission has also issued draft guidance[2] on which clinical studies will count towards the incentives that are available when they are conducted in accordance with a paediatric investigation plan (PIP). Depending on the intellectual property and regulatory status of the product, these include additional market exclusivity or additional patent term extension. Where the studies are completed prior to 26th January, 2007, no incentive is available, although the studies can be included in the PIP. Where they were commenced prior to that date, but not completed until afterwards, the results will form the basis for one of the incentives available if the studies are considered to be 'significant'. The Commission draft guidance gives examples of the types of studies that would normally be considered significant, although it also states that the assessment is made on the merits of each case. The types of study, which should normally cover all paediatric patient subsets, include efficacy, dose-finding, prospective clinical safety and age-appropriate formulation studies. The guidance also sets out the content of PIPs together with procedures for seeking a deferral or waiver from the PIP requirement.

Progress with proposed advanced therapy medicinal products regulation

The proposed EU Regulation on Advanced Therapy Medicinal Products was first proposed by the European Commission in the autumn of 2005[3] and came before the European Parliament for consideration in the summer of 2006. The aim of the Regulation is to provide a specific, pan-EU regulatory framework to govern tissue engineering, gene therapy and somatic cell therapy medicinal products and fill perceived gaps between the current medicinal product and medical device regimes. The system would be superimposed on the current medicinal product regime and would create a new Committee on Advanced Therapies within the EMEA as well as amend the Clinical Trials Directive and provide a legal basis for product-specific guidelines for novel therapies.

The European Parliament's Committee for the Environment, Public Health and Food Safety has now recommended the approval of the draft Regulation with certain amendments. These include stricter pharmacovigilance and post-marketing follow-up requirements, support for sponsors that do not fully meet Commission criteria to qualify as SMEs and further fee reductions for scientific advice and marketing authorisation fees payable to the EMEA.

The committee had previously rejected the proposal because certain members had sought to introduce provisions intended to restrict the use of chimeras and human embryonic stem cells in the discovery and manufacture of novel medicinal products. The committee also rejected an amendment mandating a ban on the commercialisation of human body parts.

The proposal is expected to be considered by the full parliament in March of this year with possible agreement by the Council of Ministers in May. The current presidency of the European Council, Germany, is said to be keen to prioritise this proposal. This means that the new Regulation may be adopted by end of 2007 if the Commission accepts changes made by the Parliament and the Council of Ministers.

WHO review the international non-proprietary names (INNs) for biologics

The emergence and increasing importance of biosimilar medicines in European and other markets has highlighted the issue of whether biosimilars should be assigned INNs which are distinct from the INNs attached to the original reference products. The World Health Organization (WHO) met in November 2006 to discuss this issue. Originator companies were firmly of the view that these two products should be distinguished by using different INNs; however, generic manufacturers did not agree. A number of submission have therefore been made to enable the WHO to reach a view on the issue.

It is often said that with biologics, the product is the process. As such, biologics cannot necessarily be exactly replicated and generic versions cannot be created in the same way as traditional, small molecule medicines. There are subtle differences in the manufacturing processes used by different suppliers of even the same biologic. As a result the typical manufacturing process consists of 250 or more in-process controls to ensure that these differences do not impact on the safety and efficacy of the biologic.

There is a growing number of biosimilar medicines in development as patents protecting the original biological medicinal products begin to expire. The launch of biosimilar medicines will, generic manufacturers argue, provide patients and physicians with cheaper and alternative treatment options. Biosimilars which have been given marketing authorisation can be sold on the European market after appropriate testing to ensure their safety, quality and efficacy. The active substance of a biosimilar must be similar in molecular and biological terms to that in the reference product. Analytical and preclinical tests are, however, not sufficient to demonstrate whether two biological products are similar, and hence whether they effect the human body in the same way. This gives rise to concern when issuing same INN to the original reference product and to a biosimilar.

The current INN system was designed for small molecule medicines and their generic copies. It is a cataloguing system which allows the international use of a common name for the active ingredient. As such it clearly identifies the active ingredient and communicates the pharmacological class (drugs from the same pharmacological class have names with the same stem, for example simvastatin and atorvastatin, so that the name indicates the class notwithstanding the fact that they may be different molecules).

The US Biotechnology Industry Organisation (BIO) has highlighted that current requirements for naming and labelling could lead to assumptions regarding the 'sameness' and interchangeability of biological medicines. Biologics are too complicated, it is argued, to allow biosimilars to be substituted for brand biologics by pharmacists. Each biologic is unique, and biosimilars unlike traditional generic drugs, are not identical to, or interchangeable with, the reference product. As a result patients could respond differently to the original reference product and the biosimilar one. In the event of an adverse consequence with a biological medicine, it is imperative that the manufacturer can be traced quickly. For these reasons, it has been recommended by BIO that all biological medicines are assigned a distinct INN. PhRMA[4] has stated in addition that 'this change is made necessary by the significant advances of biotechnology, including the development of multiple products in the same class by multiple innovators and the advent of follow-on biologics'.

In a joint position paper submitted to the WHO, BIO, EBE,[5] EFPIA,[6] EuropaBio, IFPMA,[7] and PhRMA asked the WHO to insist upon the implementation of different INNs for biosimilars. They recommended

that each biotechnology-derived therapeutic protein produced by a given manufacturer be given a name composed of a common stem with a unique qualifier to maintain the class identity while indicating the unique nature of the active ingredient. The addition of a suffix such as 'alpha' or 'beta' was suggested. This paper went further to suggest that each biological medicine should have an original label. This would mean that biosimilars could not copy labels from the original reference products. EuropaBio, the European Association for Bioindustries, has also suggested that each biosimilar medicine should have its own specific label.

Given that many physicians use the INN when prescribing products as an indication of interchangeability, it would be sensible to provide physicians with specific information, so that they are able to make an informed decision regarding the use of different products. It has been suggested that separate INNs for biologics and their biosimilars are therefore necessary for an informed and effective medical practice, pharmacovigilance and to protect and promote the public health. Similar conclusions were drawn at the WHO meeting where it was decided that although the current system is useful, there are inconsistencies when naming some products. Therefore, it is possible that the WHO INN committee may come up with a new proposal in the future that will take into account the views expressed by regulators and the industry. A new policy would have a significant impact but is deemed necessary to reflect recent technological advances. Bearing this in mind, any new policy should aim to be consistent but also as flexible as possible to accommodate any future developments and changes in scientific technology.

Review of UK intellectual property system

The Gowers Review of Intellectual Property was delivered on 6th December, 2006 as part of the government's Pre-Budget Report.[8] The Review comprehensively scrutinised the UK's intellectual property regime and concluded that the current regime was performing satisfactorily but that some improvements are necessary for UK companies to prosper in the modern world where economic competitiveness is increasingly driven by knowledge-based industries, innovation and creativity.

In total, the Review made 54 recommendations of which ten will be of special interest to the life sciences sector.

Patent rights

The Review acknowledges concerns that the current patent system may not provide incentives to innovate in new areas of technology such as software or genetics. Fast-paced industries such as these create new products quickly; however, many companies are unable to recoup costs or make a profit due to the length of time it takes to receive patent protection. Nevertheless, the Review recommends that the present policy is maintained and rejects the idea of a 'utility patent', which would offer a second tier of patent protection for inventions which can be obtained quickly and at lower cost. The author examined countries that have a track record of innovation and concluded that there was no correlation between the existence of a 'utility patent' and strong innovation.

The research exception

Research exceptions grant researchers the freedom to conduct research on patented inventions for the purposes of understanding and improving the products and processes forming the invention. This plays an important part in reducing a company's costs, as some experiments may involve the use of many patented products and having to obtain licences for all the patented products would be prohibitive.

The Review notes that there is no clear definition of what constitutes 'experimental use'. There is only limited guidance on what amounts to experimental use and no guidance is provided on what comprises a divergence from the original use. The Review recommends clarifying the research exemption in order to encourage research without damaging the interests of rights-holders and cites the Swiss research exemption as a model. The Swiss system sets out a series of activities that are exempted from patent infringement: acts to necessary to obtain a marketing authorisation for a medicinal product, acts

intended to further knowledge about a product including possible other uses, the use of the invention in education and teaching and private, non-commercial experiments.

International development

Though the review is UK-focused, it investigates a number of areas where the government can aid international development. The UK Patent Office should help African countries to take advantage of the flexibilities which exist within the Trade Related Aspects of Intellectual Property Rights Agreement (TRIPS). The government is encouraged to lobby the international community to review the TRIPS status of the least developed countries prior to 2016 and consider whether a further extension for reaching TRIPS compliance would be appropriate. Furthermore, the UK should lobby World Trade Organisation to ratify amendments to TRIPS which make the importation of drugs easier and cheaper.

'Business to Business' agreements

In order to reduce the time and costs associated with licensing, Recommendation 29 calls for the Patent Office to develop a 'Business to Business' model IP licenses through industry consultation. The model is intended to provide a fair and transparent contractual arrangement for both parties.

Community patent & London agreement

Gowers calls for the establishment of a single Community patent, although in reality this seems unlikely. The European Commissioner in February 2006 spoke of 'one last push' for a Community patent but since then there has been scant progress.

The Review advocates that the government should support the London Agreement which has yet to be ratified. This Agreement provides that an application filed in any of the official languages of the European Patent Office (English French or German) need not be translated into any other language to take effect in a country which has ratified the Agreement.

Litigation

The Review recognises that IP litigation is slow, complicated and expensive. Currently, there is a fast track for any litigation for disputes under £15,000; however, the majority of IP claims exceed the limit and do not benefit from any of the advantages of the fast track system, such as restricted costs and shorter trials. Recommendation 53 calls on the Department for Constitutional Affairs to review the issue of IP litigation and the fast track process so that claims process can be made more timely and cost-effective.

Disputes

Recommendations 25a and 25b seek to improve the speed that companies can place their products on the market. The Patent Office should introduce an 'accelerated grant process' for patents as well as a fast track registration for trademarks.

Unfair competition

To combat the concern among businesses about the 'copycat' packaging of products, Recommendation 37 suggests that the success of current measures to combat unfair competition in cases relating to IP should be monitored and if they are found to be ineffective the government should consult on appropriate changes. 'Copycat' packaging has led to customer confusion, reduced goodwill and has proved both costly and difficult to litigate.

Revisions to UK model clinical trial agreement

The UK Department of Health in conjunction with Association of the British Pharmaceutical Industry and the BioIndustry Association has launched a revised version of the model clinical trial agreement for use where companies undertake clinical trials as National Health Service (NHS) sites in the UK.[9]

The purpose of this document and its predecessor is to provide a standard form document for industry-sponsored trials at NHS sites that is well-balanced and reasonable to both site and sponsor thereby streamlining the process of setting up trials and also saving cost through the removal of the need for NHS sites to obtain legal review of the document. The review was prompted both by experience from the previous version and

also the establishment of quasi-autonomous foundation trusts within the NHS which have greater responsibility for their budgets and financial liabilities.

The text of the document has been extensively reviewed since the 2003 version and also exists in separate versions for England, Wales, Scotland and Northern Ireland to reflect the different government departments with responsibility for health in those countries. Refinements in the new document include the following:

- Amendments to reflect the implementation of the EU Clinical Trials Directive in the UK.
- Shifting onus to the sponsor of identifying to the NHS site any foreign regulations that must be complied with.
- Generally, the protocol will prevail over the agreement (so enabling consistency of outcome in multi-centre studies); however, where the conflict relates to liabilities or indemnities, confidentiality, data protection, freedom of information, publication or intellectual property, the agreement will now prevail.
- More flexibility regarding steps to be taken to address difficulties in recruiting adequate numbers of subjects.
- Compliance with the Freedom of Information Act (FOIA) and giving sponsor's the ability to be notified of and make representations in relation to any proposed FOIA disclosure by the NHS site.
- Revised intellectual property provisions giving ownership of any trial-related intellectual property and know how to the sponsor, but to the site of any clinical procedures or related improvements attained during the course of the trial. It is also stated that the site of the trial has the right to use any know how obtained during the trials in its normal clinical work.
- The financial liability of the NHS site is much more limited than previously. The NHS site is no longer required to indemnify the sponsor against losses arising from the site's negligence and the site's overall liability under the agreement is limited: where there are wilful and/or deliberate breaches of the agreement or breaches related to confidentiality, data protection and freedom of information, publication and/or intellectual property, liability is capped at twice the 'value of the contract'. Other liability in connection with the study agreement will be capped at the total fees paid to the NHS site.
- More detailed escalation and dispute resolutions provisions.

It should be noted, however, that use of the document is not compulsory although a company sponsoring a trial at an NHS site would have to have good reason for seeking to depart from this template. The new document is also not intended for use in studies involving healthy volunteers.

NOTES FROM THE US

Licensee in good standing is able to challenge licensed patents

In January 2007, the United States Supreme Court in *MedImmune, Inc. v Genentech, Inc.*, US Supreme Court No. 05-608, reversed the Federal Circuit and held that a patent licensee does not have to terminate or be in breach of its license agreement before it can seek a declaratory judgment that the underlying patent is invalid, unenforceable or not infringed. This holding is contrary to the Federal Circuit's decision in *Gen-Probe Inc. v Vysis, Inc.*, 359 F.3d 1376 (Fed. Cir. 2004), that a patent licensee in good standing cannot establish the existence of actual controversy to challenge the validity, enforceability, or scope of the patent because the license agreement 'obliterate(s) any reasonable apprehension' that a licensee will be sued for infringement.

The *MedImmune* decision is currently being digested by the US patent bar and opinions abound, with a broad range of potential ramifications being discussed. The decision does not appear to be nearly as far reaching as some have suggested. Rather, as noted by the Court, the *MedImmune* decision is consistent with the Supreme Court's 34-year-old holding in *Altvater v Freeman*, 319 US 359

(1943), that 'the requirements of [a] case or controversy are met where payment of a claim is demanded as of right and where payment is made, but where the involuntary or coercive nature of the exaction preserves the right to recover the sums paid or to challenge the legality of the claim'.

The decision affirmed that the 'actual controversy' requirement is not bounded by any bright lines, but requires a totality of the circumstances consideration. In *Maryland Casualty Co. v Pacific Coal & Oil Co.*, 312 US 270, 273 (1941), the court ruled that 'the question in each case is whether the facts alleged, under all circumstances, show that there is a substantial controversy between parties having adverse legal interests, of sufficient immediacy and reality to warrant the issuance of a declaratory judgment'.

Briefly, the facts in *MedImmune, Inc. v Genentech, Inc.*, are as follows. Genentech is the co-owner of the Cabilly I and Cabilly II patents both of which relate to the use of cell cultures to manufacture human antibodies. In 1997, MedImmune entered into a license agreement for the Cabilly I patent, which by its terms also conveyed a licence to MedImmune under the Cabilly II patent, which had a later expiry date than the Cabilly I patent. After the Cabilly II patent issued, Genentech wrote to MedImmune expressing its belief that a MedImmune product marketed as SYNAGIS® was covered by the Cabilly II patent and that it expected royalty payments beginning March 2002. MedImmune disagreed and did not think royalties were due, believing that the Cabilly II patent was invalid and that Synagis in any event was not an infringing product. Nevertheless, believing that Genentech was threatening to enforce the Cabilly II patent, terminate the 1997 agreement and sue for patent infringement if the royalties were not paid, MedImmune began to pay royalties, under protest, to Genentech and brought a declaratory judgment action to declare the Cabilly II patent invalid and unenforceable.

The 'substantial controversy' standard to be met was whether the dispute was definite and concrete, touched the legal relations of the parties, was real and substantial, and could be conclusively adjudicated. The Court indicated that mere refusal to make royalty payments was not a legal requirement for this case to ripen into a justiciable case where the totality of the facts indicate that it is otherwise ripe for adjudication. In other words, the fact that royalties were being paid did not make the underlying dispute hypothetical and the law does not require MedImmune to take measures that could seriously harm its business interests before seeking a declaration of its actively contested legal rights.

Genentech's case hinged on the applicability of the common-law rule that a party to a contract cannot at one and the same time challenge its validity and continue to reap its benefits. The Supreme Court stated, that the issue is not whether the licensee is reaping the benefits of the license agreement, but whether the agreement itself, properly interpreted, prevents the licensee from challenging the patents and 'does not require the payment of royalties because the patents do not cover its products and are invalid'. In the Court's opinion, under the facts of this case, whether or not the license agreement precludes a suit by the licensee does not defeat the fact that there still exists a genuine contract dispute that meets the 'substantial controversy' test required to bring a suit in the Federal Courts. And that this is so despite the fact that MedImmune's obligation to pay arose out of its voluntary decision to sign a license with Genentech.

Many in the patent bar have raised the fear that the Supreme Court has opened a Pandora's box by appearing to indicate, in a light most favourable to a licensee, that a licensee's reasonable and express belief that its product is not covered by an asserted patent is sufficient, without more, to confer declaratory judgment jurisdiction upon the federal courts. Even if the case does suggest a broadening of scenarios where declaratory judgment jurisdiction will exist, it does not suggest that it will be any easier for licensees to succeed on the merits and overturn existing licenses. Obviously, the Supreme Court's reversal of the Federal Circuit represents a significant change in declaratory judgment practice before the Federal Circuit. Rather than a weakening of patent rights, as some have

suggested, this decision appears to be more of a reminder to the Federal Circuit that patent law fits into the framework of the law as a whole.

FDA proposed regulations regarding expanded access to experimental drugs

On 14th December, 2006 the US Federal Food and Drug Administration (FDA) issued proposed regulations intended to make investigational new drugs more widely available to seriously ill patients with no other treatment options, and to clarify the circumstances and costs for which drug manufacturers may charge for experimental drugs. The proposed regulations are intended to improve patient access to experimental drugs, and increase drug manufacturers' incentive to develop treatments for serious and life-threatening illnesses by permitting manufacturers to charge for a broader range of investigational and expanded access uses than is explicitly permitted under the current regulations.

The FDA has allowed access to experimental therapies since the 1970s but the existing regulations do not adequately describe the full range of access programmes available. Both critics and the Agency believe the regulations have been applied inconsistently and inequitably.[10] The proposed regulations are intended to ensure broad and equitable access to experimental drugs, and to account for the full range of circumstances in which charging for experimental drugs is permissible.[11]

Expanded access to investigational drugs for treatment use

The proposed regulations set out specific criteria, submission requirements, and safeguards for expanded use of investigational drugs for individual patients, intermediate-size patient populations, and treatment IND or treatment protocols. As a general matter, an investigational new drug may be made available for expanded treatment use if the FDA determines that: (1) the patient's serious or immediately life-threatening disease or condition has no satisfactory approved therapy; (2) the potential benefit for the patient justifies the potential risks; and (3) providing therapy will not interfere with the drug's development.[12]

The FDA would allow an investigational drug to be used to treat an individual patient if a licensed physician determines that the probable risk to the patient from the investigational drug is not greater than the probable risk from the patient's disease or condition, and the FDA determines that the patient cannot otherwise obtain the drug (eg the patient cannot participate in a clinical trial of the investigational drug).[13] As the seriousness of the disease increases, less data will be needed to justify expanded use of the investigational drug. For example, when a patient has an immediately life-threatening condition that is not responsive to available therapy, completed Phase I safety testing in humans, together with preliminary evidence suggesting possible effectiveness, would be sufficient to support expanded treatment use.[14]

The FDA would also allow an investigational drug to be used to treat an intermediate-size patient population when there is enough evidence that the drug is safe to justify a clinical trial of the drug and there is at least preliminary clinical evidence of effectiveness.[15] Expanded access may be appropriate for intermediate size patient populations when a drug that is currently being developed represents the only promising therapy for patients with a certain disease or condition, a drug is being developed but certain patients are unable to participate in the clinical trial, or an approved drug is no longer marketed due to safety or other concerns but the benefits of the drug to a specific subset of patients outweigh the risks.[16]

The FDA would permit widespread treatment IND use of an investigational drug if the drug is being investigated in a controlled clinical trial under an IND designed to support a marketing application for the expanded access use (or such clinical trial or trials have been completed), the sponsor is actively pursuing marketing approval for the expanded access use with due diligence, and there is sufficient evidence of safety and effectiveness to support the expanded access.[17] Such evidence would ordinarily consist of data from Phase III trials, but could consist of compelling data from completed Phase II trials.[18]

While the proposed regulations represent an important step towards granting seriously

ill patients access to experimental drugs, there is concern that the expanded access will hinder clinical trial recruitment. Recruitment efforts may be impeded by, for example, the prospect that patients can get access to experimental drugs without the risk of being part of a control group. The FDA has attempted to strike a balance between authorising access to promising drugs and ensuring the integrity of the drug approval process but it remains to be seen how this expanded access would affect clinical trial recruitment.

Charging for investigational drugs

Under the proposed regulations, a sponsor could charge for expanded access to an investigational drug if the sponsor: (1) complies with the applicable requirements for the type of use for which charging is requested; (2) provides justification that the amount to be charged reflects only those costs that are permitted to be recovered; and (3) obtains prior written authorisation from the FDA.[19] A sponsor who wishes to charge for expanded access must provide reasonable assurance that charging will not interfere with the development of the drug for marketing approval.[20] Unless FDA specifies a shorter period, charging may continue for one year and a sponsor may request that FDA reauthorise charging for additional periods.[21]

The proposed regulations allow a sponsor to recover 'direct costs' of making the investigational drug available and administrative costs directly associated with the expanded access.[22] Direct costs are costs that can be specifically and exclusively attributed to providing the drug for the investigational use and include costs per unit to manufacture the drug, costs to acquire the drug from another manufacturing source, and direct costs to ship and handle the drug.[23]

The FDA acknowledges that providing investigational drugs for treatment use is potentially costly to manufacturers, particularly when the drug is being provided to large patient populations. The proposed cost recovery regulations are intended to offset those costs and encourage drug manufacturers to make investigational drugs available to seriously ill patients. It, however, remains somewhat unclear what costs are recoverable. For example, there is room for interpretation regarding what constitutes a cost 'specifically and exclusively attributed to providing the drug for the investigational use'. In addition, manufacturers may be reluctant to disclose costs associated with providing an investigational drug to avoid making themselves vulnerable to claims that a market price is too high after a drug is approved.

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