Legal and regulatory update

UK and European content is compiled and written by Bird & Bird
an international law firm which specialises in advising clients in:

- Life Sciences
- Intellectual Property
- Information Technology
- E-Commerce
- Communications
- Aviation
- Sport
- Media
- Banking and Financial Services

Bird & Bird has offices in Beijing, Brussels, Düsseldorf, Hong Kong, London, Milan, Munich, Paris, Stockholm and The Hague.

US content is compiled and written by Cooley Godward LLP
a US-based firm with headquarters in Palo Alto, California, and with attorneys and affiliates throughout Europe and Asia. Cooley Godward LLP is an established provider of strategic litigation and business transaction services, and a recognised leader in the representation of high-growth private and public companies, venture capital firms and non-profit organisations.

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 upon, specific advice should be sought. Please contact:

John Wilkinson,
Bird & Bird,
90 Fetter Lane,
London EC4A 1JP, UK
Tel: +44 (0)20 7415 6000
Fax: +44 (0)20 7415 6111

Frederick J. Dorey,
Cooley Godward LLP,
5 Palo Alto Square,
3000 El Camino Real,
Palo Alto,
CA 94306-2155, USA

Legal and regulatory update

NOTES FROM THE EU
Proposed revision of EU medical devices legislation

The European Commission has launched a public consultation on its proposed amendments to the Medical Devices Directive (MDD) (Dir 93/42/EEC). The aim of the European Commission's proposals is to improve the coherence, transparency and effectiveness of the legislation governing medical devices in line with the recommendations of the report produced in 2002 by the European Commission's Medical Device Experts Group. This report recommended that the requirements for clinical evaluation of medical devices be clarified, transparency be increased by amending post-market surveillance requirements and that the decision making process be improved by empowering the European Commission to make binding decisions where individual national opinions differ on whether a product falls within the definition of 'medical device'. The report also recommended that the three directives governing medical devices (the MDD, the Active Implantable Medical Devices (AIMD) Directive 90/385/EEC and the In-vitro Medical Devices (IVDD) Directive 98/79/EC) should be made more consistent with each other.

For now, the Commission's public consultation centres on the MDD Directive, although it has also proposed amending text to bring the AIMD Directive into line with its proposals for the MDD Directive and to include the application of Directive 2000/70/EC on Medical Devices which incorporate stable derivatives of human blood or plasma. Amendments are also proposed to the Biocides Directive (89/8/EC) to make it clear that IVDD are excluded from its scope.

The European Commission has explained the key proposed amendments. The first is in the area of conformity assessment and the aim is to clarify that, as part of their quality assessment, the notified bodies must assess the design documentation for a selection of the medical devices being manufactured. Changes are also proposed to the requirements for clinical data items and how they are to be evaluated. The possibility of creating a central European databank of data from clinical evaluations has also been considered. Another proposal relates to Article 13 (which concerns requests submitted to the European Commission by member states asking for measures to be taken), so that the European Commission may make binding decisions on whether products are medical devices. To make it clear that a product may be both a medical device and an item of personal protective equipment, which are regulated by Directive 89/686/EEC, it is proposed to delete the reference to that directive in Article 1 (which sets out definitions and the scope of the MDD).

The European Commission also proposes to make certain information that is currently treated as confidential (the registration of persons responsible for placing devices on the market, vigilance reports of the competent authorities and data relating to certificates) available to the public. New Article 20b (cooperation) is proposed in order to foster cooperation between the various national authorities. Finally, it is proposed to clarify the roles of the notified body and relevant authority in order to deal with the conformity assessment of medical devices that incorporate as an integral part a medicine or a stable derivative of human blood or plasma.

The closing date for submission of comments on the proposed amendments was 25th June, 2005, so the outcome of the consultation is expected in the near future.

ECJ has no jurisdiction to hear Greek Competition Commission's referral

On 31st May, 2005, the European Court of Justice (ECJ) published its decision in the case of *Syfait & Others v. GlaxoSmithKline* (Case C-53/03) in response to the Greek Competition Commission's request for a preliminary ruling concerning parallel trade in the pharmaceutical industry. The ECJ held that it did not have jurisdiction to answer the questions referred.

Under Article 234 EC, the ECJ's jurisdiction to provide a preliminary ruling is limited to references made by courts or tribunals of member states. According to the ECJ, the Greek Competition Commission lacks certain characteristics necessary for it to be classified as such a body, namely independence and the fact that its questions would not ultimately lead to a decision of a judicial nature.

This case concerned an alleged breach of Article 82 by GlaxoSmithKline, which had stopped supplying Greek wholesalers with its products because a large proportion of their orders were exported to other EC member states where prices were much higher. Although GlaxoSmithKline subsequently reinstated supply to wholesalers, it did so only in limited quantities. The wholesalers brought the case before the Greek Competition Commission, who asked the ECJ whether and in what circumstances a dominant pharmaceutical company could, in order to restrict parallel trade in its products, refuse to meet orders received from wholesalers.

In October 2004, Advocate General Jacobs gave his opinion to the effect that a pharmaceutical undertaking that holds a dominant position does not necessarily abuse that position by limiting the supply of its products, merely because in doing so it intends to restrict parallel trade. He commented that normal conditions of competition do not apply in the pharmaceutical sector, owing to high levels of regulation by the European Commission and EU member states. Furthermore, given the specific economic characteristics of the pharmaceutical industry, a requirement to supply would not necessarily promote either free movement or competition and might harm the incentive for pharmaceutical undertakings to innovate.

The ECJ's refusal to accept jurisdiction in this case will no doubt be extremely disappointing for the pharmaceutical industry. However, the Advocate General's opinion, although nonbinding, will continue to provide some guidance in this area.

Term of SPCs: The ECJ'S decision on the Liechtenstein–Switzerland issue

In the joined case of Novartis and Millennium Pharmaceuticals (C-207/03 and C-252/03) of 21st April, 2005, the ECJ held that the calculation of the terms of supplementary protection certificate (SPCs) must take into account marketing authorisations granted in Switzerland even though Switzerland is not part of the European Economic Area (EEA), since such marketing authorisations are recognised by Liechtenstein. This decision will have far-reaching consequences for the pharmaceutical industry, as it may result in several products benefiting from market exclusivity for a shorter period than expected.

SPCs confer on the holder the same protection provided by a patent in respect of a specific medicinal product or plant product for a period of up to five years. SPCs are intended to compensate the relevant pharmaceutical or agrochemical companies for the delay between their filing of a patent application for a new drug or plant product and the grant of an authorisation to put the product on the market. In accordance with European Regulation 1768/92, which governs SPCs for medicinal products, and European Regulation 1610/96, which governs SPCs for plant products, the holder of an SPC is entitled to an overall

maximum of 15 years of protection from the date he or she obtains first authorisation to put the product on the market. Article 13 of European Regulation 1768/92 provides more specifically that an SPC takes effect at the end of the lawful term of the patent, that its term should end no more than 15 years from the first marketing authorisation to put the product on the market in the EEA was granted and that its term cannot exceed five years.

The SPC Regulations apply to the member states of the EEA, which encompasses the European Community and Norway, Iceland and Liechtenstein. Accordingly, a marketing authorisation granted in any of those countries will start the clock for the calculation of an SPC's term. The ECJ's decision of 21st April, 2005, effectively adds Switzerland to this list of countries as a result of the special relationship that exists between Switzerland and Liechtenstein. Liechtenstein does not grant its own marketing authorisations, but recognises automatically the ones granted by the EU and by Switzerland.

As a result, some patent offices in the EEA, such as the UK and the Luxembourg patent offices, argued that a Swiss marketing authorisation should determine the duration of an SPC when it was granted by any EEA country. This position was challenged by Novartis and Millennium Pharmaceuticals with the result that the issue was referred to the ECJ. The ECJ confirmed the UK and Luxembourg patents offices' interpretation that a marketing authorisation granted in Switzerland (and therefore recognised by Liechtenstein) constitutes an authorisation to place the medical product on the market in the EEA for the purposes of the SPC regulations. Consequently, if a marketing authorisation is granted in Switzerland before it is granted anywhere else in the EEA, the term of a SPC should be calculated by reference to the Swiss authorisation. In effect, that means that a Swiss marketing authorisation will determine the duration of the SPC when it was granted earlier that any EEA authorisations.

This decision may result in several marketed products having a shorter market exclusivity period than expected. Furthermore, if the terms of SPCs already granted in the EEA without reference to Swiss authorisations have to be rectified (this issue was not considered by the ECJ), such rectification is likely to reduce the terms of several existing SPCs.

Another likely consequence of this decision is that pharmaceutical companies will try to have their marketing authorisations issued in the EEA before Switzerland. As a result, the Swiss SPC, which is also valid in Lichtenstein, will end after the EEA SPC, resulting in Liechtenstein having a longer period of exclusivity than any other member of the EEA.

European Commission consultation on a community regulatory framework on advanced therapies

The European Commission recently made its latest move towards establishing a comprehensive regulatory framework for novel biotechnology therapies involving the use of human tissues and cells including both gene therapy and somatic cell therapy as well as human tissue engineering. Although the former categories have been considered to fall within the Community medicinal products regime since at least 1998,[1] the status of the latter category has been uncertain for some time. This uncertainty has been recognised by the European Commission such that human tissue engineering products (hTEPs) have been the subject of two previous consultations, in 2002 and 2004, and also a study by the Commission Joint Research Centre. However, the Commission has now gone further and put forward for consultation a draft proposal for a Regulation on Advanced Therapies.[2]

Indeed the fact that it is a Regulation (rather than a Directive) that is being

considered is significant since it implies a legal framework that applies directly across the EU as a whole or, in other words, a centralised authority and procedure. This in turn is expected to ensure consistency of application of the new regime and will enable a pooling of scarce expertise in this relatively new sector. In addition, it is hoped this will ensure a level playing field by harmonising market access conditions, promoting a high level of health protection and creating legal certainty for those entering the market. This centralised framework has been advocated by industry representatives for some time and was a conclusion emerging from the European Commission's 2004 consultation.

The most significant feature of the new proposal is the creation of a broad category of 'advanced therapy medicinal products', which covers both hTEPs as well as gene therapy and somatic cell therapy products. The underlying philosophy is to provide a complete bridge over the perceived regulatory gap between medical devices (falling under Directive 93/42/EEC) and medicinal products (covered by Directive 2001/83/EC).

The proposed Regulation on Advanced Therapies would in fact supplement the provisions of these two pieces of legislation together with those of the cells and tissues directive (Directive 2004/23/EC) and the European Agency for the Evaluation of Medicinal Products (EMEA) regulation (Regulation (EC) No.726/2004), thereby providing a legal basis for dealing with certain features peculiar to these advanced therapies.

The definition of hTEP which has been put forward is 'any product for autologous or allogeneic use which: (a) contains or consists of engineered human cells or tissues; and (b) is presented as having properties for, or is used in or administered to human beings with a view to, regenerating, repairing or replacing human tissue.' Furthermore, engineered human cells or tissues are defined as 'cells or tissues removed from a human donor and manipulated via a manufacturing process, so that their normal biological characteristics, physiological functions or structural properties are substantially altered.' It should be noted that these definitions have changed somewhat from those previously proposed in 2004 and are rather more expansive than previously drafted. It can be seen, however, that the draft Regulation does not, for example, cover a one-off product made on a non-industrial basis for a specific patient.

Also of interest is the fact that the previous proposal for treating autologous and allogeneic products differently, with national authorisation of the former being possible, has been abandoned. Instead, there is a compulsory centralised procedure administered by the EMEA for all advanced therapy medicinal products, which is in line with the desire to pool scarce scientific expertise wherever possible.

Supplementing this primary legal framework will be legally binding technical requirements for specific product classes laid down by a so-called 'comitology' procedure (a committee of member state representatives chaired by the European Commission) together with guidance documents on detailed issues arising from time to time. This structure recognises that while, on the one hand, these products do for one reason or another fall to be considered as medicinal products as defined in Directive 2001/83/EC, on the other hand, the safety, quality and efficacy of advanced therapy medicinal products cannot necessarily be assessed by reference to the same technical standards relevant to chemical compounds, for example. The aim is to apply the same regulatory principles as for more conventional therapeutics (including more established biologicals), but also recognise that the technical requirements will be different and may require additional consideration of factors, such as viability of product, proliferation and differentiation of cells and the particular mode of action.

The European Commission also proposes the formation of a Committee for Advanced Therapies (CAT) to work under supervision of the existing Committee for Medicinal Products for Human Use (CHMP) within the EMEA, but with differing members to give access to specialist expertise in the field. In particular, the CHMP would delegate scientific assessment of specific products to the CAT with various mechanisms in place to ensure that there is a consistency of opinion. In addition, where an hTEP contains an element that could be considered to be a medical device, compliance would be assessed by CAT rather than requiring separate compliance with Directive 93/42/EC and CE-marking.

Finally, advanced therapy medicinal products would benefit from the usual incentives to innovate available for other medicinal products, including a period of data protection, the possibility of orphan medicinal product designation and certain proposed additional benefits for small and medium-size enterprises (SMEs), such as 90 per cent fee reduction for scientific advice, deferral of fee until the end of the procedure and assistance with translation of documents such as the summary of product characteristics.

The consultation period ended in June 2005 and it now remains to be seen whether, based on responses to the consultation, the European Commission will press ahead with its proposed Regulation on Advanced Therapies or adopt a different means by which to regulate these therapies. No date has yet been given for when a formal proposal can be expected.

Proposed changes with regard to the 'teacher's exception' in Sweden

As a main rule, the act on the right to employee's inventions in Sweden (the 'Act') states that employees shall have the same right to their inventions as other inventors. However, under certain circumstances (for example, the employee has made a patentable invention in the course of their employment as a researcher), the employer may be entitled to acquire the right to carry out the invention in their business without hindrance from the employee, although the employee will be entitled to a reasonable remuneration. In the case of research employees, it is possible that the salary and employment benefits that they are already receiving from their employer will constitute such reasonable remuneration. The closer the connection is between the utilisation of the invention and the sphere of activity of the employer, the more extensive is the right of the employer to appear, in whole or in part, as the employee's assignee with respect to the invention. Teachers at universities or other institutes that fall under the educational system are not to be considered employees pursuant to the Act and thus they are excepted from the Act – the so-called 'teacher's exception'.

The Swedish government has appointed a commission to consider various issues including the legal consequences of abolishing the teacher's exception, imposing an obligation on universities to commercialise research results reported by their teachers and whether abolishing the teacher's exception will require an expanded secrecy policy. The commission will also consider the alternative of retaining the teacher's exception but coupling this with an option for the university to acquire inventions, and an obligation on the teachers to report inventions to the university.

The underlying point of the proposed changes is that they may provide for a higher degree of commercialisation of research results, if the university acquires ownership to the inventions. Laws regarding teacher's rights to inventions have already been changed in several countries including Norway and Denmark. The commission will put forward its proposal with regard to the teacher's exception by the end of 2005.

NOTES FROM THE USA
Uses of patented inventions in preclinical research may be exempt from infringement under 35 USC §271(E)(1): Lessons from *Merck KGaA v. Integra Lifesciences I, Ltd*

Introduction

Under US patent law, it is generally an act of patent infringement to make, use, offer to sell or sell any patented invention during the term of the patent. In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act, §202, 98 Stat. 1585, as amended, 35 USC §271(e), which provides an exemption to this general rule:

> It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention (other than a new animal drug or veterinary biological product) . . . solely for uses reasonably related to the development and submission of information under a Federal law which regulated the manufacture, use or sale of drugs. . .

On 13th June, 2005, the US Supreme Court unanimously held that certain uses of patented inventions in preclinical research, the results of which are not ultimately included in a submission to the Food and Drug Administration (FDA) may be exempt from infringement under 35 USC §271(e), 'so long as there is a reasonable basis for believing that the experiments will produce the types of information that are relevant to an IND (Investigational New Drug application) or NDA (New Drug Application).'

Background

Integra LifeSciences I, Ltd, and the Burnham Institute own five patents related to the tripeptide sequence Arg-Gly-Asp, referred to in single-letter peptide notation as the 'RGD peptide'. The RGD peptide promotes cell adhesion by attaching to $\alpha_v\beta_3$ integrins, receptors on the surface of endothelial cells.

In the course of research funded by Merck KGaA, Dr David Cheresh at the Scripps Research Institute discovered that blocking $\alpha_v\beta_3$ receptors inhibits angiogenesis, a process that plays a critical role in many diseases, including solid tumour cancers. In 1994, Cheresh succeeded in reversing tumour growth in chicken embryos by blocking $\alpha_v\beta_3$ integrins on proliferating tumour cells, using a cyclic RGD peptide provided by Merck. The following year, Merck and Scripps entered a collaboration agreement to develop integrin antagonists as angiogenesis inhibitors. Under the agreement, Scripps tested candidate RGD peptides provided by Merck, while Merck performed certain toxicology tests on the primary candidate for submitting an IND application to the FDA.

On 18th July, 1996, Integra accused Merck of infringing five patents relating to the RGD peptide by having conducted tests to measure the efficacy, specificity and toxicity of certain RGD peptides. Merck claimed that its actions fell within the exemption afforded by 35 USC §271(e)(1).

Lower court decisions

At a jury trial in the United States District Court for the Southern District of California, Merck was found liable for infringing the claims of four of Integra's patents. The District Court denied Merck's motion for judgment as a matter of law, finding the connection between the research and FDA review to be 'insufficiently direct' to qualify for the exemption under Section 372(e)(1).

On appeal, a divided Federal Circuit panel affirmed the District Court's denial of judgment as a matter of law, rejected Merck's exemption defence and ruled that Section 271(e)(1) was limited to activities directly related to the submission of data to the FDA. The Federal Circuit concluded that Merck's provision of the patented RGD peptides for research at Scripps was not protected by 35 USC

§271(e)(1) on the grounds that the Scripps research 'was not clinical testing to supply information to the FDA, but only general biomedical research to identify new pharmaceutical compounds,' and hence not 'solely for uses reasonably related' to gathering data for submission to the FDA. The Supreme Court granted certiorari in January 2005.

Issue presented to the Supreme Court

The question presented before the Supreme Court was whether uses of patented inventions in preclinical research, the results of which are not ultimately included in a submission to the FDA are exempted from infringement by 35 USC §271(e)(1).

Supreme Court reasoning and analysis

On 13th June, 2005, the Supreme Court vacated the Federal Circuit's decision. In rejecting the Federal Circuit's narrow statutory construction, the Supreme Court rested its holding on the plain language of the statute, which 'provides a wide berth for the use of patented drugs in activities related to the federal regulatory process.' First, the Court rejected a restriction of the safe harbour to human clinical trials, finding no basis in the statute for limiting the exemption to particular types of information gathered for FDA submission. The Court noted that preclinical data must be submitted to the FDA in an IND before clinical trials can be commenced, and thus conform with the statutory language. While the Court observed that the FDA's primary objectives in reviewing an IND are patient rights and safety, the Court noted that pharmacological, toxicological and other animal data were also required by the FDA, and concluded that all such data fall within the exemption.

Secondly, the Court rejected a restriction of the safe harbour to experiments whose results are ultimately submitted to the FDA, or that involve drugs that eventually become the subject of an FDA submission. The Court explained that the former limitation is inconsistent with the 'reasonably related' statutory language, while the latter would essentially restrict the safe harbour to generic drug approval. The Court observed that pioneer drug development always involves uncertainty as to whether a candidate drug will survive preclinical studies; the only certain candidates are those identical to drugs that have already been approved.

In reaching its decision, the Court offered only general guidance as to the type of activities that are exempt from infringement liability under 35 USC §271(e)(1). At one extreme, the exemption does not embrace all experimental activity, even if at some point that activity might lead to an FDA submission. As an example, the Court noted that the exemption does not apply to '[b]asic scientific research on a particular compound, performed without the intent to develop a particular drug or a reasonable belief that the compound will cause the sort of physiological effect the researcher intends to induce.' On the other hand, the Court held that 35 USC §271(e)(1) exempts any use of a patented compound in which

> a drugmaker has a reasonable basis for believing that [the] patented compound may work, through a particular biological process, to produce a particular physiological effect, and uses the compound in research that, if successful, would be appropriate to include in a submission to the FDA.

The information need only be of the 'types . . . that are relevant to an IND or NDA.'

The Court remanded the case to the Federal Circuit for a review of the evidence presented at trial under the proper construction of 35 USC §271(e)(1).

Potential future impact

The Merck decision offers potentially expansive protection for testing patented drugs and medical devices for specific

uses. At the same time, the decision limits the enforcement options available to patent holders when they become aware of potentially infringing activity. Following Merck, the key inquiry focuses on distinguishing between researchers who are using a patented compound to develop a specific product or cause a desired physiological effect that may be the subject of a future submission to the FDA (which is activity protected under 35 USC §271(e)(1)) and researchers who are testing the general properties and capabilities of the patented compounds in a manner wholly unrelated to FDA submissions (conduct that constitutes patent infringement).

In the light of the Merck decision, research and development companies seeking to take advantage of Section 271(e)(1) would be well advised to create documentation prior to testing that shows a reasonable basis for believing a compound or device will produce a particular physiological effect through a particular biological process and conduct tests that will produce information that could be submitted (regardless of whether or not it actually will be submitted), or used to develop information that could be submitted, to the FDA. In the post-Merck world, patent holders should focus investigative efforts on determining the intent behind a potential infringer's use of a patented compound as well as on identifying any data accumulated by the potential infringer. That information will be key to determining whether otherwise infringing activities are protected by Section 271(e)(1).

On the other hand, the Merck decision offers little guidance for those who hold patents that cover 'research tools' or researchers who intended to use patented tools. The Court did not address 'whether, or to what extent, § 271(e)(1) exempts from infringement the use of ''research tools'' in the development of information for the regulatory process.' Thus, some caution should be taken before accepting that 'all uses of patented compounds' reasonably related to the submission of information to the FDA are exempted from infringement under Section 271(e)(1). Nor should anyone assume that sales of research tools to those engaged in drug discovery are automatically exempted from infringement under the safe harbour. The Supreme Court has reserved those issues for another day.

References

1. See 'Commission Communication on the Community Marketing Authorisation Procedures for Medicinal Products' (98/C 229/03) and also part IV of annex I to Directive 2001/83/EC as amended by Directive 2003/63/EC.
2. All these documents are available from: http://pharmacos.eudra.org/F2/advtherapies/index.htm.