Legal and Regulatory Update

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

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NOTES FROM THE EU

EU: Patent settlements under the authorities' magnifying glass

Drug prices are currently a key area of discussion in many countries around the globe. Agreements that limit price competition in the pharmaceutical sector can have severe adverse effects on public health and national budgets. Given the current political debate in the United States on health-care reform and the downward pressure on health-care budgets in general, competition authorities are scrutinizing any kind of agreement that would limit price competition (for example, by delaying entry of generic competition).

In its final report on the Pharmaceutical Sector Inquiry, delivered last July, the European Commission underlined its concerns regarding patent settlement agreements between originator and generic companies. According to the report, about half of the 207 assessed settlement agreements limited the generic companies' ability to market their products.

Since then, the first competition cases against originator and generic firms have been opened.[1] In addition, it has been reported that the Commission is currently contemplating requesting copies of all the patent settlement agreements of pharmaceutical companies entered into between July 2008 and December 2009, in order to review their legality.

On the other side of the Atlantic, patent settlements have also come to the attention of the US antitrust authorities, who have stated as their enforcement priority those agreements aimed at delaying the entry of generic drugs onto the market. The recent *Solvay* and *Cephalon* cases brought by the Federal Trade Commission (FTC) before American courts confirm this trend. Political support for such enforcement is now emerging strongly, with draft legislation being introduced in the US Congress to establish a rebuttable presumption of illegality of patent settlements that include any value transfers to the generic company involved. This has limited exceptions, such as authorization to market the product or sums to cover litigation expenses.

As the European Commission has not yet provided clear criteria on how it will evaluate patent settlement agreements, the development of US legislation is no doubt of great interest in assessing the different options for antitrust enforcement.

Given this current trend on both sides of the Atlantic, any life science company potentially involved in patent settlement agreements should assess the legality of past agreements and the drafting future agreements with utmost care.

New Commission Regulation (EC) No. 668/2009 on certification of quality and non-clinical data relating to advanced therapy medicinal products

Article 18 of Regulation (EC) No. 1394/2007 on Advanced Therapy Medicinal Products (ATMP) provides that Small and Medium-sized Enterprises (SMEs) developing an ATMP may submit to the European Medicines Agency (EMEA) all relevant quality and, where available, non-clinical data required in accordance with modules 3 and 4 of Annex I to Directive 2001/83/EC on the Community code relating to medicinal

products for human use, for scientific evaluation and certification.

Provisions for the evaluation and certification of such data have been laid down by the European Commission in its Regulation (EC) No. 668/2009, published on 25 July 2009 in the Official Journal of the European Union.

The certification procedure aims at giving the SMEs an incentive to develop ATMPs regardless of any future application for marketing authorization. It could, nevertheless, facilitate the evaluation of any future application for a clinical trial authorization or a marketing authorization application, provided that these applications are based on the same data.

Requirements

In order to be eligible for this new procedure, *applicants* must be (i) a micro, small or medium-sized enterprise, within the meaning of Recommendation 2003/361/EC, (ii) developing an ATMP and (iii) established in the Community.

To be valid, an *application* must contain:

(a) all information necessary to demonstrate that the applicant meets all the requirements set out above;
(b) indication as to the type and nature of the data submitted;
(c) reference to any applications for certification previously submitted for the same product and related information;
(d) the relevant fee as provided for in Council Regulation (EC) No. 297/95. According to the EMEA Rules for the implementation of Regulation (EC) No. 297/95, the fees for this procedure will amount to €56 600 for the evaluation of an application relating to quality and non-clinical data and €37 700 for the evaluation of an application relating to quality data, respectively;
(e) the data referred to in module 3 of Part I of Annex I to Directive 2001/83/EC, which is submitted for certification; and
(f) where the application relates to both quality data and non-clinical data, the data referred to in module 4 of Part I of Annex I to Directive 2001/83/EC, which is submitted for certification.

In case of applications for certification relating to combined ATMP, additional requirements will apply in relation to the conformity of the medical device or active implantable medical device contained in the combined product with the essential requirements laid down in the relevant EU legislation.

In the Committee for Advanced Therapies (CAT) Draft Procedural Advice (DPA) on the certification procedure, currently under consultation, further guidance on the procedure, timelines and dossier structure that SMEs should fulfil in order for the EMEA to issue its appropriate certificate is provided. According to this document, before the submission of the application for certification, the SME's status shall have been obtained by the applicant and a letter of intent, stating the reasons for the product being classified as ATMP, shall have been sent to the EMEA (that is CAT Secretariat) at the latest 4 months before submission.

Scope

The CAT is responsible for evaluating applications for certification. Interaction between the EMEA and the relevant notified bodies may be necessary in cases of combined ATMPs, which in some cases may also lead to an 'extension' of the ordinary time frame for such a procedure (that is, 90-days procedure to be possibly extended, via a clock-stop, in case additional information is needed). The possibility for the CAT to request site visits of the premises where the ATMP concerned is being developed has also been provided. If the applicant accepts the conduct of a site visit, it shall be carried out by inspectors from the member states who hold the appropriate qualifications.

According to the DPA, the evaluation performed under Article 18 of the ATMP Regulation is intended to certify that each submitted study complies with the relevant scientific and technical requirement set out in the Annex I to Directive 2001/83/EC, and adequately follows state-of-the-art scientific standards and guidelines.

For these reasons, the scientific and technical requirements followed by the CAT when assessing the data submitted for certification will be the same applicable to the evaluation of a marketing authorization. Not all sections as defined by part I of Annex I to Directive 2001/83/EC may however be completed for the application for certification.

Moreover, in order to distinguish between this new procedure and existing procedures (namely, scientific advice procedure), it is provided that the certification procedure will focus only on scientific evaluation of existing experimental data (quality/non-clinical). No advice as to further development of the product will be provided. In case the latter information is needed, the appropriate procedure will have to be applied for (that is, scientific advice).

In the same vein, a certificate is not intended to conclude either on the benefit/risk profile of the product or on the adequacy of the studies submitted for the product to be further developed in a clinical trial. The latter is a separate procedure, under the responsibility of the National Competent Authorities where the clinical trial will be conducted.

The Commission Regulation does not provide for any time limit for an application for certification to be submitted. An application for the certification can therefore legally be submitted at any time of the development of an ATMP. However, the DPA appears to be more restrictive in this regard when providing that a minimum quality and, where available, non-clinical data package will have to be submitted to allow for certification.

Outcome

If appropriate on the basis of the evaluation, the EMEA will issue a certificate identifying the quality and, where applicable, non-clinical data submitted and the corresponding testing methodologies followed by the applicant, which have been found acceptable in terms of regulatory compliance and scientific robustness. This certificate will not be binding with regard to any future regulatory procedure and all relevant data, even if already certified, and should be submitted again for the purpose of any future regulatory procedure.

In principle, the certificate should help EU SMEs to increase profits out of the R&D performed (for example, by selling their early-stage products at a more profitable price or by attracting interested investors).

In practice, the actual value of the Certificate will mostly depend on: (i) the stage of development of the ATMP at the time when the Certificate was issued and (ii) any additional changes introduced to the ATMP after the Certificate was firstly issued.

In this regard, the DPA addresses a clear reminder to applicants that if a certificate is granted during early development its relevance/validity is likely to be limited.

Applicants may wish to follow the DPA of the CAT, according to which the optimum time point to apply for the certification procedure is when the ATMP has reached a level of sufficient development with respect to quality and non-clinical data.

Indeed, although from a legal point of view nothing prevents applicants from requesting certification of their data very early in the development of their products and to 'update' their certificate as much as they might consider it necessary, the fee requested for each procedure as well as the 'minimum' data requirements could act as serious deterrents to use this procedure too soon or too recurrently.

Furthermore, the fact that a list of 'issues' as regards compliance with the above-mentioned

scientific and technical requirements for future consideration by the applicant may be included in the evaluation report attached to the certificate, as well as the possibility for the EMEA to issue a 'refusal letter' whenever the opinion is negative, might also have an impact on the decision of a company as to if and when an application for certification should be submitted.

In a subsequent development relating to ATMPs, Commission Directive 2009/120/EC of 14 September 2009 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use as regards ATMPs, published in the Official Journal of 15 September 2009, and to be implemented no later than 5 April 2010, amends Annex I to Directive 2001/83/EC as regards ATMPs. It updates the definitions and detailed scientific and technical requirements for gene therapy medicinal products and somatic cell therapy medicinal products, and establishes detailed scientific and technical requirements for tissue-engineered products, as well as for advanced therapy medicinal products containing devices and combined advanced therapy medicinal products.

Directive 2001/83: Proposal creating legal framework for provision of information from the pharmaceutical industry

Recently, the biggest consumer association in The Netherlands offered a widely supported petition to the Dutch Minister of Health, requesting a ban on disease awareness or symptom awareness advertisement.

Currently, advertising 'prescription-only' medicinal products is subject to the rules set out in Title VIII of Directive 2001/83. However, dissemination of information relating to human health or diseases without reference to medicinal products is excluded from the ban on advertisement, therefore not subject to EU rules.

There can be little doubt that it is in the overall interest of patients and consumers that objective and reliable information on medicines is available. In this context it is important to realize that patient representation groups, hospitals and health-care providers or other parties benefit from this exclusion to communicate about health care and diseases for educational or counselling purposes outside of a treatment relationship. In addition, a complete prohibition as suggested in The Netherlands would be against the fundamental principle of freedom of speech. All in all there seems to be no reasonable justification to exclude the provision of objective and unbiased information on medicinal products to consumers, regardless of the source of information. However, the European Court of Justice (ECJ) recently decided[2] that dissemination of information about a specific medicinal product by an independent third party may be regarded as advertising even when the third party is acting on his own initiative.

Owing to a lack of description as to what constitutes information as opposed to unlawful advertisement, divergent interpretations exist throughout the member states of the EU. The mere fact that information about diseases is being communicated by the pharmaceutical industry should, as such, not make such information promotional of character. However, in some member states that is the overall assumption. In other member states the content of information provided is determinative.

From the *Report on current practices with regard to the provision of information to patients on medicinal products* it has become clear that restrictions on what information can be available and by which sources vary greatly among the EU member states. The European Commission considers access to reliable information on medicines important, as it will help EU consumers to make more informed decisions while being protected against hidden advertisement.

As part of the 'pharmaceutical package', a proposal for the amendment of Title VIII was issued. While maintaining prohibition of

direct-to-consumer advertising the proposal seeks to achieve the following aims:

- to lay down clear rules on information provided by pharmaceutical companies,
- to ensure a high level of quality, objective, reliable and non-promotional character of information,
- ensuring (and limiting) the use of appropriate distribution channels,
- ensuring compliance by pre- and post-monitoring and enforcement measures.

Important changes allowing far wider possibilities for marketing authorization holders to communicate about their products include the following:

- Information that presents the medicinal product in the context of the condition to be prevented or treated will be allowed.
- Information may not be distributed via (web) television or radio.
- The information shall not include comparisons between medicinal products.
- The source of information must be revealed, as well as statements indicating the prescription-only status and that the information is not intended to replace health-care contact.
- Initiating direct consumer contact is not allowed. However providing written answers to unsolicited questions is permitted. Notably, information must include contact details allowing consumers to send comments to marketing authorization holders. Maybe, this route of contact also provides a platform for wider direct communication with consumers.
- Content is subject to prior approval by national competent bodies, whose control may also be executed on the basis of self-regulation by self-regulatory bodies. Further, internet websites are subject to approval by the national competent authorities where the website is registered. The principle of mutual recognition applies insofar that translated information disseminated in other countries is the same as the approved information.

It is likely that this proposal will be further discussed in the first quarter of 2010.

Generics medicines in France: An unsuccessful legislative attempt for an exemption from trade mark rights of the appearance of substitutable generic drug tablets

On 26 November 2009, the French Senate voted on the law on 'Financing the National Social Security for 2010'. This law was to amend the Public Health Code, and introduce a new article L. 5121-10-3 relating to generics:

> The owner of an intellectual property right that protects the appearance and the texture of oral pharmaceutical forms of a reference product within the meaning of article L. 5121-1 may not prohibit the oral pharmaceutical forms of a generic drug substitutable to this product under article L. 5125-23, from showing a similar or identical texture or appearance.

Accordingly, manufacturers of substitutable generic drugs would have been in a position to freely mimic the shape and colour of the tablets or capsules of the brand-name drug. The legislator's intention was to limit the risks associated with the mistaken identity of a tablet/capsule especially by elderly patients. This provision would have amounted to a significant exemption from trade mark and design right protection. Furthermore, besides an increased likelihood of confusion for the public, difficulties could be expected when attempting to enforce such trade marks or designs by Customs seizures pursuant to EC Regulation 1383/2003, for example against unauthorized generic goods as only *substitutable* generics were intended to benefit from the exemption.

The bill was, however, referred to the Constitutional Council to ensure that it complied with the French Constitution. On 22 December 2009, the Constitutional Council ruled that such provision would have little, if any, effect on health-care costs, and accordingly it did not have any place within a proposed law on the 'financing the social security'. It will therefore not be enacted at this time, at least in this specific context. This legislative proposal, however, clearly was an attempt towards a two-tier system, wherein a name, but not the shape or colour of a tablet, may be used to protect a branded drug.

NOTES FROM THE US

The 'Cabilly' patent saga continues

Genentech (now part of Roche) has collected substantial royalties over the years related to its 'Cabilly patents' (nicknamed for their first-named inventor) on certain methods of producing immunoglobulins. In 2008 alone, Genentech collected approximately US$300 million in royalties derived from Cabilly patent licences to companies that manufacture therapeutic antibodies. The first Cabilly patent issued in 1989 has expired, but US patent no. 6 331 415 ('the Cabilly II patent') remains in force. The Cabilly II patent, co-owned by Genentech and City of Hope, has long been a subject of dispute from licensees who have challenged its validity and enforceability.

The Cabilly II patent was the subject of lengthy litigation beginning in 2003 between Genentech and MedImmune, a licensee of the Cabilly II patent. The litigation led to the landmark 2007 US Supreme Court decision in *MedImmune* v. *Genentech* that made it easier for licensees and potential infringers to seek declaratory relief of patent invalidity, unenforceability, or non-infringement. The litigation settled in 2008, but a re-examination of the Cabilly II patent in the United States Patent & Trademark Office ('USPTO') remained pending.

Two re-examinations were initiated by third parties in 2005 in an attempt to invalidate the Cabilly II patent claims. On 23 February 2009, the USPTO confirmed the patentability of the claims of the Cabilly II patent. Twenty-four of the patent's 36 claims were confirmed unchanged, while the remaining 12 claims were allowed with amendment. According to Roche, the claim amendments are not commercially significant. The USPTO's confirmation of the patentability of the Cabilly II patent claims is a final decision. The Cabilly II patent expires on 18 December 2018.

Despite the USPTO's decision in the re-examination proceedings, the Cabilly II patent remains a subject of dispute. Although US courts give deference to the USPTO's decisions by requiring 'clear and convincing' evidence before finding a patent invalid or unenforceable, courts are not bound by the USPTO's decision in the Cabilly II re-examination proceeding. Thus, licensees and potential infringers continue to challenge the Cabilly II patent.

Litigation related to the Cabilly II patent that was initiated by Centocor Ortho Biotech ('Centocor') in 2008 remains pending. Centocor alleged that the Cabilly II patent is invalid and unenforceable, and that Centocor's products do not infringe the patent. Centocor licenses the Cabilly II patent for Abciximab (ReoPro®), its antibody fragment product that inhibits platelet aggregation, and for infliximab (Remicade®), its antibody product for treatment of certain inflammatory diseases. Centocor has plans to market ustekinumab, a new antibody product to treat certain inflammatory diseases, which is not licensed under the Cabilly II patent. Discovery is currently ongoing in the case.

GlaxoSmithKline ('GSK') on 8 October 2009 initiated an action also alleging that the Cabilly II patent is invalid and unenforceable. GSK also seeks a declaration that its new product, ofatumumab (Arzerra™), will not

infringe the Cabilly II patent. GSK plans to launch ofatumumab, a monoclonal antibody to treat chronic lymphocytic leukaemia, and does not have a licence to the Cabilly II patent. The case is currently in the pleading stage.

Given the 9 years remaining on the term of the Cabilly II patent and the high financial stakes involved, the Cabilly II patent remains the subject of dispute despite the USPTO's recent confirmation of patentability. The biologics industry will likely keep a close eye on the pending litigation involving the Cabilly II patent.

Richard Ting

PATENTABLE SUBJECT MATTER AND ENABLING DISCLOSURE – CASES TO WATCH

One challenge to doing business in the United States is its active and changing legal landscape. The life sciences intellectual property area of the law remains particularly active, and new legal standards and potential reforms have been emerging. Of the many currently pending court cases in this area, at least three merit close attention from inventors, companies and investors in the life sciences space.

As of the writing of this article, the US Supreme Court has heard oral arguments in *Bilski* v. *Kappos*, the Supreme Court's review of the Federal Circuit *en banc* decision of *In re Bilski*, 545 F.3rd 943 (Fed. Cir. 2008) (en banc). This case is testing the outer limits of patentable subject matter for methods and it will likely direct answer whether business methods are still patentable subject matter in the United States. A decision is expected from the Court in this matter during the first half of 2010. Many amici from the life sciences cautioned the Supreme Court to limit its decision to business method patents, yet the Court's recent dismissal of *Metabolite* v. *Lab Corporation of America* as improvidently granted, 548 U. S. 124 (2006), certainly suggests that some of the Justices are eager to review patentable subject matter in the life sciences if and when that issue is properly presented to the Court. Because of that, many are eagerly awaiting a decision on the petition for review by the Supreme Court in the case of *Prometheus Laboratories, Inc.* v. *Mayo Collaborative Services*, No. 2008-1403 (Fed. Cir. 2009). In that case the Federal Circuit upheld the patentability of a claim very similar to that in *Metabolite*. The claim in *Prometheus* covered a method of optimizing therapeutic efficacy by maintaining drug–blood concentrations between two pre-determined limits where the lower limit correlated with minimum efficacy while the upper limit correlated with the onset of undesirable side effects. Between the Supreme Court's decision in *Bilski* v. *Kappos* and potentially with a decision in *Prometheus* v. *May*, if the Supreme Court chooses to hear *Prometheus*, there may well be some changes to patentable subject matter in the life sciences. Significant changes could occur to one's ability to obtain patent protection in the United States for methods of treatment, diagnostic products accompanying therapeutics and other approaches delivering human health care that derive at least in part from correlating and otherwise making such use of efficacy and patient data in directing treatment regimes.

Another case of potentially significant impact to the life sciences industry that should be monitored is the *Ariad Pharmaceuticals, MIT, and Harvard* v. *Eli Lilly* (Fed. Cir. 2009) (en banc). As of the writing of this article, the Federal Circuit *en banc* heard oral arguments in this case and a decision is expected in the first half of 2010. In *Ariad* v. *Lilly*, one of the central facets of the case is whether a written description requirement in a patent should be eliminated as a separate doctrine from the enablement doctrine. How the Federal Circuit resolves this issue could directly impact a number of patents in the biotechnology space, particularly patent claims that extend beyond the embodiments explicitly disclosed in the

patent specification. The decision could impact claims using functional language to broadly claim life sciences products and technologies, especially monoclonal antibodies.

Andres Liivak

REFERENCES AND NOTES

1. Case COMP/39612 – Servier (perindopril).
2. C-421/07, 2 April 2009.