The Rhineland Biopatent Gazette

brought to you by Michalski Huettermann & Partner Patent Attorneys - Issue 3/2015

Duesseldorf/Munich, **03 August 2015** The times they are a'changing – particularly in the Biopatent discipline. Biopatent professionals live in a quickly developing world, which is sometimes hard to keep pace with. Michalski • Huettermann & Partner Patent Attorneys have decided to produce relief to this situation, and are proud to present a new information service related to Patent issues in Biotechnology. This newsletter issues on an irregular basis in order to provide information with respect to actual events, as well as in-depth-analyses of long-term developments. Patent Attorneys from our firm explain the meaning of recent developments and decisions affecting the Biopatent community, and provide expert insight into what's going on behind the scenes. In this issue, Dr. Christoph Volpers, Senior Patent Manager in our firm, discusses the Amgen Sandoz case, while MH Partner Dr. Ulrich Storz reports about the patent dispute between Bristol Myers Squibb and Merck&Co regarding their anti PD-1 antibodies.

"Shall" Or Not "Shall" – That Is The Question

CAFC landmark ruling on biosimilar pathway might turn previous strategic considerations upside down

To some extent like Hamlet in his famous monologue on the difficulty of decision making amongst uncertain existential alternatives, patent experts, regulatory attorneys and pharma managers might feel after the US Court of Appeals for the Federal Circuit (CAFC) issued a key ruling in *Amgen Inc. vs Sandoz Inc.* (No. 2015-1499, July 21, 2015) last week, its first decision that relates to the interpretation of key provisions of the Biologics Price Control and Innovation Act (BPCIA).

The BPCIA had been enacted in 2009 in order to pave the way for regulatory approval of biosimilars, generic versions of bio-pharmaceutical drugs, in the US. As part of the Public Health Service Act, the BPCIA established a pathway for submission of an abbreviated biologics license application (aBLA) for such products, defined a procedure for patent dispute resolution between the originator, also termed reference product sponsor (RPS), and the biosimilars manufacturer, and provided for a 12-year marketing exclusivity period in favor of the originator drug. The patent dispute resolution procedure, also casually termed "patent dance", involves a complicated, multi-step patent information exchange process, aiming at a mutually agreed list of patents to be immediately litigated, and triggered by disclosure of the application dossier and manufacturing information to the RPS.

As first application under the BPCIA's pathway for biosimilar products, on July 7, 2014, the FDA accepted to review Sandoz's application to market a biosimilar version of Amgen's Neupogen® (filgrastim, granulocyte colony stimulating factor). As Sandoz refused to disclose its application and to participate in the "patent dance", Amgen sued Sandoz in October 2014, and subsequently appealed the District Court's decision from March 19, 2015, in favor of Sandoz to the CAFC. In the

anti-PD-1 rivalry between BMS and Merck&Co entering hot phase

Merck had clinical advantage, BMS strikes back with patents

Bristol Myers Squibb (BMS) and Merck&Co have both recently received approval for their anti-PD-1 antibodies, Nivolumab (Opdivo®) and Pembrolizumab (Keytruda®), which belong to the class of ravely reviewed immune checkpoint inhibitors. Both antibodies have shown impressive efficacy in melanoma and NSCLC, and analysts are predicting sales figures for the coming years that likely overturn those of the current antibody blockbusters.

Clinically, it appears that Merck had a tiny advantage, because they received approval for Keytruda in the USA already in Sept 2014. BMS is slightly lagging behind, with their first approval for Opdivo in Japan in Dec 2014.

However, BMS is striking back on the patent arena. On Sept 4, 2014, BMS, together with Ono, filed suit against Merck at the Delaware District Court for patent infringement. The claimants alleged that the marketing of pembrolizumab would infringe Ono's US Patent US8728474 licensed to BMS for the US, which has a broad claim language that merely claims a method for tumor treatment by means of a monoclonal anti-PD-1 monoclonal antibody.

According to our *prima facie* analysis, it appears that pembrolizumab indeed falls under the scope of the US patent, as it merely claims a method for treatment of a tumor comprising administering to the patient an anti-PD-1 monoclonal antibody. The court trial has been scheduled for November 2016.

+ from our firm +

Article on Antibody Drug Conjugates accepted by mAbs

MH partner Dr. Ulrich Storz has authored an article on IP issues of Antibody drug Conjugates.

Antibody drug conjugates are highly complex entities, which combine an antibody, a linker and a toxin. This complexity makes them demanding both technically, as well as from a regulatory point of view, and also difficult to deal with under patent aspects. Ulrich's article discusses different issues of patent protection and freedom to operate with regard to this promising new class of drugs.

USPTO has published Update on Interim Guidance on Subject Matter Eligibility

The USPTO has produced an update pertaining to patent subject matter eligibility titled July 2015 Update: Subject Matter Eligibility in response to the public comment on the 2014 Interim Patent Eligibility Guidance. The July 2015 Update includes

meantime, the FDA had approved Sandoz' aBLA in early March.

The seriously fractured decision of the CAFC had to address two fundamental issues. The first related to the question of whether the BPCIA's patent information exchange procedure is mandatory or optional for the biosimilar (or "subsection (k)") applicant. Sandoz's approach was based on the latter. The relevant section 42 U.S.C. §262 (*l*)(2)(A) of the BPCIA provides:

> "Not later than 20 days after the Secretary notifies the subsection (k) applicant that the application has been accepted for review, the subsection (k) applicant *shall* provide to the reference product sponsor a copy of the application submitted to the Secretary under subsection (k), and such other information that describes the process or processes used to manufacture the biological product that is the subject of such application…"

The majority (Judges Lourie and Chen) concluded that it was *not* mandatory for the biosimilar applicant to disclose its aBLA and manufacturing information, and thus trigger the "patent dance", in spite of the use of "*shall*", because other sections of the BPCIA gave context that the disclosure was not mandatory. Section 42 U.S.C. §262 (*l*)(9)(C) considered the situation and consequences when the biosimilar applicant would *not* make the disclosure:

> "*If a subsection (k) applicant fails to provide the application and information* required under paragraph (2)(A), the reference product sponsor, but not the subsection (k) applicant, may bring an action under section 2201 of Title 28, for a declaration of infringement, validity, or enforceability of any patent that claims the biological product or a use of the biological product."

The majority of the panel of judges held that an interpretation of the law in the sense that the disclosure and "patent dance" were mandatory would render §262 (*l*)(9)(C) superfluous. Judge Newman dissented from this opinion, arguing the designated exchange of information was "fundamental to the BPCIA purposes of efficient resolution of patent issues".

The second crucial issue concerned the 180-day pre-launch notice set forth in 42 U.S.C. §262 (*l*)(8), which triggers a second, late-stage round of litigation:

> "The subsection (k) applicant *shall* provide notice to the reference product sponsor not later than 180 days before the date of the first commercial marketing of the biological product *licensed* under subsection (k)."

This time, the majority of the panel (Judges Lourie and Newman) held that "*shall*" in fact means "*shall*", i.e. that the notification is mandatory, as they did not identify any provision in the BPCIA that considers or specifies consequences of noncompliance with that paragraph. The obligation also applies if the biosimilar applicant chooses not to disclose its dossier and to avoid the "patent dance". In contrast to the District Court ruling before, the CAFC majority further concluded that the term "*licensed*" in the paragraph means that the product must have received regulatory approval, and not just that an application for

On July 7, 2015, BMS and Ono filed a second suit against Merck at the same court, this time based Ono's US patent US9073994 which is from the same family and was been granted the same day. The patent claims methods of treating metastatic melanoma using an anti-PD-1 antibody. The claimants alleged that Merck's pembrolizumab, infringes US9073994 patent, too.

In June 2011, Merck had already filed an opposition against Ono's EP counterpart of US8728474, EP1537878. In its decision, the Opposition Division came to the conclusion that the claims were novel over WO0114557 assigned to Dana Farber. The corresponding US patent US6808710 is part of a PD-1 related portfolio Dana Farber nonexclusively out-licensed to different pharma companies, but claims immune downmodulation by administration of an anti-PD-1 antibody.

The Opposition Division found that WO0114557 did only disclose a relationship between anti-PD-1 antibodies and autoimmune diseases, but lacked a direct and unambiguous disclosure of a relationship between anti-PD-1 antibodies and cancer. Accordingly, the Opposition Division rejected the opposition in June 2014, and left the EP patent maintained in unamended form.

In February 2015, Merck filed an appeal against this decision, which is now pending.

Earlier, in April 2014, Merck had already filed an opposition against another European patent assigned to Ono, EP2161336, claim 1 of which claims ipilimumab by its CDR sequences, while claim 3 refers to monoclonal antibodies that cross-compete therewith, thus covering not only nivolumab, but also Merck's pembrolizumab. Ono's corresponding US patent US8779105 has claims of similar broadness. Co-opponents in that opposition are Novartis, 4-Antibody and Janssen.

In February 2015, Ono filed a new main request in which claim 3 and some dependent claims were deleted, thus no longer embracing pembrolizumab. Ono has pre-emptively deleted these claims, i.e., without waiting for the preliminary opinion by the Opposition Division. The Opponents had, *inter alia*, attacked these claims for added matter, lack of novelty and lack of inventive step.

In May 2014, Merck sued Ono in the UK for invalidity of the UK parts of EP1537878 and EP2161336. One month later, Ono and BMS countered by filing an action for a declaratory judgment that the EP1537878 patent would be infringed in the UK by the marketing of pembrolizumab. Merck replied by filing a request for declaration of non-infringement with respect to the EP2161336 patent. Because Ono had already amended the claims thereof in the co-pending EP opposition, they requested that the UK court only considers said

a new set of examples and discussion of various issues raised by the public comments, and is intended to assist examiners in applying the 2014 Interim Patent Eligibility Guidance during the patent examination process. The USPTO is now seeking public comment on the July 2015 Update.

We will analyze this update and discusss it in the next issue of the Rhineland Biopatent Gazette

Feedback please !

What do you think about this newsletter ? Let us have your comments here.

Archive

To obtain a neat overview of the quickly changing world of Biopatents, find prior issues of the Rhineland Biopatent Gazette here.

approval was pending, as Sandoz claimed. Now it was Judge Chen's part to dissent; he asserted that an extrastatutory further exclusivity period was created by that interpretation.

In case of survival at any higher instance, what are the strategic implications of the CAFC decision?

For biosimilar companies, the first part of the ruling saying that a subsection (k) applicant is not required to provide a copy of the application to the RPS opens up the chance to circumvent the patent dispute resolution procedure according to the BPCIA with all its current uncertainties in favor of traditional litigation via declaratory judgement (DJ) actions.

The second part of the ruling which provides that the 180-day pre-marketing notification to the RPS is obligatory after approval by the FDA might be less of an issue if the provision that the biosimilar approval "may not be made effective" (§262 (*k*)(7)(A)) before expiry of the 12-year marketing exclusivity is understood not to prevent the biosimilar applicant from filing the 180-day notice after successful completion of the regulatory approval process itself, well before the expiry of the 12-year period with approval becoming formally effective. Many second generation biosimilar projects currently in development might reach the end of the regulatory approval procedure well before the end of the 12-year market exclusivity period, so that the 180 days would not actually create a delay to the market, in contrast to the current situation with Sandoz's filgrastim biosimilar. However, even this does not seem to be fully clear at this point.

From the perspective of the RPS, the CAFC decision clips the chance of learning from the competitor's dossier before litigation starts and developing a streamlined, two-tier defense strategy with immediate and late-stage litigation. In addition, a relevant issue was pointed out in Judge Newman's dissenting opinion: if the biosimilar applicant chooses not to provide its application to the RPS, §262(l)(9) does not appear to authorize DJ actions for infringement of *process* patents. These, however, can be of particular relevance for biologic products, and here could lie a key advantage that biosimilar players might gain from the CAFC's construction of the law.

Whether brooding over alternatives as Hamlet or not – experts in the field can rest assured that this decision will be far from the end of the story of putting the BPCIA into practice. In view of the vigorous panel split on both key issues, the case might well make it to an *en banc* rehearing by the full CAFC or even to the US Supreme Court. The only aspect the judges were apparently unanimous about appears to be the limited clarity of the BPCIA statute's wording. In a footnote of the decision's opening, the judges comment: "In these opinions, we do our best to unravel the riddle, solve the mystery, and comprehend the enigma" of this statute

amended set of claims. This motion is likely to dissolve any infringement issues relating to EP2161336, while issues relating to EP1537878 are still on the agenda. The UK court trial will address issues of both validity and infringement, and of both patents. Further, Merck sued Ono in Australia for revocation of AU2011203119, which is the Australian counterpart to the EP2161336 patent.

In the two US trials at the Delaware court, BMS and Ono further stated that Merck's representative in the opposition against EP1537878 had admitted that Merck were aware of the corresponding US patent, and thus knew that pembrolizumab would fall under said patent. The claimants have used this argument to establish that Merck willfully infringed their US-patent, which, under certain circumstances, may qualify them to demand tripled damages for past and future infringements. The claimants further asked for a reimbursement of their attorneys fees and other expenses under 35 U.S.C. § 285, i.e., on the grounds that this be an "exceptional case", which, according to a US Supreme Court ruling (Octane v. Icon, case no 12–1184) requires that it "stands out from others with respect to the substantive strength of a party's litigating position or the unreasonable manner in which the case was litigated".

Interestingly, BMS and Ono did not seek for an injunction so far, which they would be eligible for under 35 U.S.C § 283, provided the court confirmed a patent infringement. Taking the predicted annual sales figures of pembrolizumab of 3.5 bn USD, multiplied by royalties of 10 % (which is usually the upper ceiling to calculate damages in pharma patents) which could further be tripled because of willfulness, the damages Merck would have to pay in case they were found liable for infringement could become quite substantial.

In their SEC Form 10-K of February 27, 2015, Merck however emphasized that they maintain to believe that both the two US patents as well as the two EP patents are invalid.

Because this is a multi-faceted dispute, it remains exciting to see how the different cases evolve, not only because the outcome of this dispute will direct cash flow between the two parties. Further, because both nivolumab and pembrolizumab are still in the starting phase, the outcome of this dispute will be significantly contribute to the future market positions of both drugs, even for the time after expiry of the Ono patent and its family members.

Michalski · Huettermann & Partner are getting personal... Today: Dr. Patrick Liptau

Patrick Liptau was born in 1973 in Singpapore. After reserve officer training he studied chemistry at the University of Bonn. Having undertaken research in Münster and Zaragoza, he obtained his doctoral degree from the University of Münster in 2003 with a thesis in the field of organometallic chemistry and catalysis.

Patrick Liptau is co-author of several scientific publications relating to homogenous catalysis, C-H-activation and polymer chemistry.

Patrick Liptau started his training in intellectual property law in 2004. He is a chartered German Patent Attorney since 2007 and a European Patent Attorney since 2008. In the same year he has also passed the United States Patent and Trademark Office Registration Examination for Patent Attorneys and Patent Agents. Additionally, he has been admitted to practice as a European Trademark and Design Attorney at the Office for the Harmonization in the Internal Market in Alicante.

Patrick Liptau furthermore holds a teaching position with the Neuss University for International Business. He speaks German, English and Spanish.

MICHALSKI · HÜTTERMANN & PARTNER

Imprint: Michalski · Hüttermann & Partner Patent Attorneys, c/o: Dr. Ulrich Storz - email: st@mhpatent.de

Hafenspitze - Speditionstrasse 21 - 40221 Düsseldorf - Tel.: +49 (0)211 159 249 0 - Fax: +49 (0)211 159 249 20
Nymphenburger Strasse 4 - 80335 München - Tel.: +49 (0)89 208 027 274 - Fax: +49 (0)89 208 027 275