The Rhineland Biopatent Gazette

brought to you by Michalski Huettermann & Partner Patent Attorneys - Issue 3/2017

Duesseldorf/Munich, **09 May 2017** 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, we give an update on the outcome of the PD-1 patent dispute between Merck&Co and BMS, and discuss specific FTO issues related to Antibody Drug Conjugates.

New Developments in the BMS/Merck PD-1 dispute

Settlement seemingly favorable for Merck&Co

In an article recently published in mAbs[1], we have discussed the then ongoing litigation campaign between Bristol Myers Squibb and Merck & Co regarding anti PD-1 antibodies.

BMS, who has developed and now sells nivolumab (Opdivo) had sued Merck in the US (BMS & Ono v. Merck & Co 1:14-cv-01131) for infringement of US Patent US8728474, namely through the marketing of pembrolizumab (Keytruda). It appears that the latter indeed falls under the scope of said patent, which broadly claims a "method for treatment of a tumor comprising administering to the patient an anti-PD-1 monoclonal antibody". Note that the claim language is merely functional, with no structural limitation.

The court trial had been scheduled for November 2016. Soon thereafter, BMS added a second suit, based on US patent US9073994, which claims "methods of treating metastatic melanoma using an anti-PD-1 antibody".

In the two trials, BMS further alleged that in a corresponding opposition against their EP counterpart patent, EP1537878, Merck's representative had admitted that Merck was aware of the corresponding US patent, and thus knew that pembrolizumab would fall under said patent.

In fact, Merck's EP representative had justified late introduction of a prior art document with the fact that Ono had already disclosed the same document in the prosecution of one of the two corresponding US patents, hence

[1] Storz U, Intellectual property issues of immune checkpoint inhibitors. MAbs. 2016;8(1):10-26

Specific FTO problems related to ADCs

Prodrug situation can cause problems with regard to SPCs and Roche Bolar exemption

Technically speaking, Antibody Drug Conjugates (ADC) are prodrugs, comprising, *inter alia*, a target seeking antibody and a toxin payload that is delivered to the target.

However, prodrugs are not simple to deal with in Freedom to Operate studies.

Consider US Patent US6884869 (Seattle Genetics) which covers the auristatin toxin MMAE, which is often used in ADCs, like, e.g., the anti-CD30 ADC Brentuximab. The claim language covers the naked MMAE toxin only, although, in the specification, the use thereof in an ADC is still disclosed:

„In one aspect, the present invention provides compounds of the general structure "drug-linker-targeting agent", where the drug is a pentapeptide as disclosed herein and the targeting agent is a monoclonal antibody (mAb). Such compounds have the following structure, and may also be referred to herein as prodrugs."

However, the scope of a patent is defined by its claims, hence, the respective part of the specification can not be used to construe a claim scope which goes beyond the actual language thereof.

In an ADC, a toxin is chemically modified, and may hence no longer be identical to the original toxin as claimed in a patent. In such scenario, the question arises whether said modification caused by the conjugation avoids an infringement of such narrow patent ?

In chemical stricture claims, German courts apply a very narrow concept of equivalence. Hence, it may be that at least a German judge would consider said modification enough to avoid patent infringement. Unfortunately, there is no pertinent case law available so far.

Yet, if the toxin that is eventually released at the target is again identical to the original toxin claimed in the patent, then the risk of indirect/contributory infringement exists. This is yet a typical prodrug

+ from our firm +

We have moved (from floors 2 and 3 to 14) !

We have moved within our office Building in the Duesseldorf Media Harbour.

While we keep floor 1, with the reception and our conference rooms, our attorneys have moved from floors 2 and 3 to 14.

Floor 14 is bigger than 2 and 3, so our attorneys are now all on the same floor.

This increases efficiency and exchange, plus we have a fantastic view over river Rhine, Duesseldorf and the Media Harbour.

Come and see us for a coffee, to enjoy that fantastic view !

We have increased our seminar activity

The 10th **Rhineland Biopatent Forum** will take place June 8, 2016, in our premises in Duesseldorf. We have announced the programme in an earlier issue of this Gazette already.

acknowledging that Merck was positively aware of that patent.

The claimants have used this argument to establish that Merck wilfully infringed their US patents, which, under certain circumstances, might have qualified 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, 12–1184 (2014) 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 did not request an injunction, which they would theoretically be eligible for under 35 U.S.C. § 283, provided the court confirmed a patent infringement. Generally speaking, obtaining an injunction may be difficult before a US court in case public interest is affected, which is oftentimes assumed when healthcare issues are concerned.

Taking the predicted annual sales figures of pembrolizumab of 5 bn USD in 2020, as predicted by business intelligence provider EvaluatePharma, multiplied by royalties of 10 % (which appears the upper ceiling to calculate damages in pharma patents), and further considering tripling thereof because of alleged willfulness, the damages Merck would have to pay in case they were found liable for infringement could become quite substantial.

Surprisingly, Merck has not instituted an Inter Partes Review (IPR) against the respective patents. According to 35 U.S.C. § 315 (b), the term to do so expired one year after the date on which Merck was served with Ono's complaint, i.e., Sept 4, 2015. We have interpreted this passive conduct as a first sign that the parties may want to settle.

While, on the patent side, BMS seemed to have an advantage, it appears that in the clinic, Merck's pembrolizumab is ahead of BMS's nivolumab, which recently disappointed in a non-small cell lung cancer (NSCLC) trial, while Merck's pembrolizumab succeeded.

Interestingly, in their trial, Merck enrolled patients who expressed PD-L1 in at least 50% of their cells (which is the case in about 50% of all NSCLC patients), while BMS applied a lower cutoff for PD-L1 expression

The dispute had a counterpart in Europe, where Merck had already filed an opposition, inter alia, against one of BMS's European PD-1 patents, EP2161336. Claim 1 claims nivolumab

scenario.

Consider also EP0590058B1 (Genentech, which is expired already), which claims trastuzumab by its VL/VH sequences, plus qualifies it as "a humanized antibody"

Would an ADC comprising trastuzumab – like Genentech's Kadcyla – still qualify as a „humanized antibody", and hence fall under the scope of said claim ? If not, could it be considered to be a prodrug for said antibody, or is the antibody a mere shuttle, and the toxin is the actual drug ? (note that it has been reported that in Kadcyla, trastuzumab retains its maintains its anti-Her2 activity).[2]

ADCs raise also problems when it comes to research issues. Art 10 of EU Directive 2001/83/EC on medicinal products for human use stipulates that "clincial trials of a drug that falls under the scope of a 3rd party patent do not consitute infringement thereof in case they are made to achieve regulatory approval" – the so-called „Roche Bolar Exemption".

The Language of Art 10 is not restricted to generic/biosimilars trials While many EU member states have qualified innovator trials as falling under the exemption, situation in other member states is slightly unclear.

However, provided the exemption would also apply to innovative ADC trials, it is still questionable what happens if only one component of the tested ADC is still under patent protection ?

Consider the clinical trial refers to an ADC which, as a whole, is not subject of 3rd party patent, but (i) the antibody or (ii) the linker is still protected.

Is the ADC that is used in the clinical trials „the drug that falls under the scope of the 3rd party patent" protecting the antibody or the linker, in the meaning of Art 10 of the directive ?

While the antibody component would probably qualify as a drug, the linker component would probably not. Still, the ADC having such antibody or linker would still be „a drug".

Therefore, it appears that clinical trials of an ADC comprising a component (be it an active ingredient or a linker) that is still patent protected could be privileged by the Roche Bolar exemption. Again, we need to realize that no caselaw is available yet which adresses this situation.

Another FTO problem related to the Roche Bolar Exemption is caused by the lengthy supply chain that usually coincides with ADC development.

Decision I-2 U 68/12 (OLG Duesseldorf) set forth that the supply of a patent protected substance to a generic company for obtaining marketing authorization is only privileged under Roche Bolar under very restrictive conditions, namely that the supplier needs to be co-organiser of the tests carried out by its customer under the Roche Bolar exemption

This is of particular importance for ADC manufacturers, who typically buy one or more of the components (e.g., a toxin) from a supplier, then produce the conjugate (or have it produced by a CMO) and, eventually, use the latter for clinical trials.

[2]Junttila et al., Trastuzumab DM1 retains all the mechanisms of action of trastuzumab and efficiently inhibits growth of lapatinib insensitive breast cancer. Breast Cancer Res. Treat. 128, 347–356 (2011).

We also have a **general patent seminar** which will take in the Industrieclub in Düsseldorf on May 11, 2017.

Speakers include Birgid Wichmann, Lanxess AG, Robert Furr, Invista (USA) and Jakob Kellenberger, Procter & Gamble, plus attorneys from our firm.

Further, on May 19, 2017, we will organize a **lunch seminar** tited „Most effective Chinese and U.S. patent prosecution".

Speakers include Stephen Yang, managing partner of Chofn IP law firm China, and Andrew Schwaab of Knobbe Martens.

Please send an email to Mrs Felsner if you want to take part, or need a full programme of any of the three seminars.

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.

by it's CDR sequences, while claim 3 refers to monoclonal antibodies that cross-compete therewith, thus covering not only nivolumab, but also Merck's pembrolizumab. Co-opponents in the opposition are Novartis, 4-Antibody and Janssen.

The latter claim rose quite a controversy about the legitimacy of such claim types, because they encompass antibodies that the applicant never has made, make it difficult for competitors to determine the actual scope of protection, and are likely to lack novelty. The Opponents had, *inter alia*, attacked these claims for lack of novelty, in view of the earlier patent application WO2004056875 assigned to Wyeth.

During the proceedings, the patentee filed a new main request in which claim 3 and some dependent claims were deleted, thus no longer embracing pembrolizumab.

Said move came pre-emptively, i.e., without waiting for the preliminary opinion by the Opposition Division. As a consequence, the patent was maintained in amended form on March 2, 2017.

From an observer's perspective, and in the interest of legal certainty, said move is somewhat regrettable, because it would have been interesting to see how the respective Board of Appeal would have judged about this claim type, in view of the objections raised.

The appeal term hence ended May 2, 2017. Because the patent claims are now restricted to the nivolumab sequences, it could be that the opponents will abstain from appealing the decision.

And what about the US litigation ? An announcement in January 2017 that the parties have settled their dispute did therefore not come completely unexpected. In that agreement, Merck has undertaken to pay BMS $625 million, plus royalties of 6.5% on pembrolizumab sales until 2023, and 2.5% until 2026. BMS will relay ¼ of the respective revenues to Ono, who developed nivolumab and owns the patents.

While these figures seem to be more or less within the ordinary, it still appears modest when the wilful infringement issue that came up is considered. Further, the two US patents will expire 2023, hence the lifetime of the agreement until 2016 is surprising.

Still, newer estimates suggest even better sales figures for pembrolizumab ($4.6 billion in 2017, increasing to more than $10 billion in 2022, according to Credit Suisse). Hence, it appears that BMS can actually count in a considerable *pretium doloris.*

In case one of the ADC components is still patent protected in some jurisdictions, ADC conjugation should take place in a patent free jurisdiction, and imported for the trials, to avoid running into the trap set by the above decision.

Still another issue that affects the FTO of ADCs is Supplementary Protection Certificates (SPCs). SPCs extend the exclusivity for a given drug that was protected by a patent, to account for lengthy regulatory approval procedures, which may have hindered the IP owner to enter the market place timely.

The underlying EU regulation, is, to put it mildly, not very well drafted, and has hence occupied the Court of Justice of the European Union (CJEU) several times. Most of the respective decisions are related vaccines, where there is often a delta between (i) the product that is subject of the patent (usually only one immunogen) and (ii) the product that is authorised (combo product of different immunogens).

However, other than in ADCs, the different immunogens in vaccines are usually not chemically conjugated.

For these reasons, the ´question arises whether an ADC falls under the scope of an SPC that protects only one of its components ?

Consider, e.g., an ADC comprises trastuzumab, which is off-patent, but still protected by an SPC. Would the ADC comprising trastuzumab still fall under the scope of the SPC protecting (naked) trastuzumab ?

Art 4 of the EU regulation 469/2009/EC concerning SPCs for medicinal product sets forth that the "protection conferred by an SPC shall only extend to the product covered by the marketing authorisation (MA)".

Now it appears quite clear that an ADC comprising trastuzumab would no longer be covered by the MA of trastuzumab – it is quite simply a different drug which needs its own MA.

There is yet one decision by the CJEU which broadened the strict concept dictated by Art 4. Decision C-392/97 (Farmitalia) held that "where an active ingredient in the form of a salt is referred to in the (…) MA (…) the certificate is capable of covering the active ingredient as such and also its various derived forms such as salts and esters (…) in so far as they are covered by the protection of the basic patent"

"Farmitalia" meant to cover routine pharmaceutical derivatives which for example hydrolyze, or are metabolized, to the same active compound that is subject of the MA (e.g., salts and esters), even if not subject of the MA.

However, as set forth above, ADCs comprising a given antibody are more than just routine pharmaceutical derivatives of a given antibody or toxin.

It is hence unlikely that the broadening of the concept of Art 4 would also apply for ADCs, in view of an SPC protecting either the naked toxin or antibody.

As a conclusion, ADCs raise quite a few questions when it comes to FTO issues. It is therefore highly recommended to have a qualified IP counsel at hand.

EURIPTA® EEIG is getting personal... Today: Wulf Höflich – MH Patent

Wulf Höflich, born in 1962, studied Aeronautical Engineering at the Technical University of Munich. He received his degree in 1990. Starting his career at aircraft engine manufacturer MTU as engineer and patent professional he passed the German Patent Bar Examination in 1995.

Subsequently he was in charge of intellectual property departments of companies in the aerospace and automotive sector: Knorr-Bremse, General Motors Europe / Adam Opel AG and Airbus Group. Together with colleagues from Knorr-Bremse he founded the law firm AKLaw in Munich. As Chief Intellectual Property Officer of Airbus Group Wulf Höflich chaired Airbus Group Intellectual Property organisation which is one of Europe's 1.000+ first filing companies. To leverage Airbus Groups' technology portfolio he established a Technology Licensing organisation which concluded transactions from which companies such as Maserati took advantage.

Wulf Höflich is speaker at international congresses, seminars and universities, e.g. he lectured at the University of Applied Sciences in Ingolstadt. At recent events he was invited to share his experience on subjects like Technology Licensing and IP rights in the context of 3D printing. He has contributed to various article in international and corporate magazines about the subject of intellectual property management and technology licensing.

Wulf Höflich is married and has three sons. He speaks German, English and French. He is a passionate private pilot and loves skiing.

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