Diagnostic Method Patents – risks of infringement for the service and research sector

Dr. Esther Pfaff, LL.M.
Counsel | Attorney at Law | WIPO Mediator
Diagnostic Method Patents – risks of infringement for the service and research sector

I. Diagnostics – the Future of Health Care

II. Dematerialization of Patent Law

III. „Rezeptortyrosinkynase II“ – process-product protection

IV. Bolar/Research Exemption in the context of diagnostic services

V. Legal Safeguards
### Diagnostic Method Patents – risks of infringement for the service and research sector

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.</td>
<td>Diagnostics – the Future of Health Care</td>
</tr>
<tr>
<td>II.</td>
<td>Dematerialization of Patent Law</td>
</tr>
<tr>
<td>III.</td>
<td>„Rezeptortyrosinkynase II“ – process-product protection?</td>
</tr>
<tr>
<td>IV.</td>
<td>Bolar/Research Exemption in the context of diagnostic services</td>
</tr>
<tr>
<td>V.</td>
<td>Legal Safeguards</td>
</tr>
</tbody>
</table>
I. Diagnostics – the Future of Health Care

Personalized Medicine

„It’s far more important to know what person the disease than what disease the person has“

Hippocrates

medical model using characterisation of individuals’ phenotypes and genotypes (e.g. molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention.
Personalised medicine relates to the broader concept of patient-centred care

- More effective patient monitoring – e.g. for diabetes patients
- Regenerative medicine – stem cell research allows for replacement, regeneration of missing or damaged tissue
- Advances in computational skills and medical imaging allow for personalized medical devices such as implants
- Pharmacogenomics – the study of DNA and RNA characteristics as related to drug response
- Genomics – the study of genetic disposition for disease outcome/tumor progression
Figure 2. Percentage of Patients for whom drugs are ineffective

Diagnostics rise up the value chain

Diagnostics gain more and more value in healthcare:
• Research – Identification of biomarkers
• Development - Clinical trials
• Treatment – Patient profiling before drug administration

**Companion Drugs** - New molecular drugs are authorized together with a diagnostic-kit

Co-Development required – often in cooperation with other entities, each with their own commercial interests- and patents!
<table>
<thead>
<tr>
<th>PGx biomarker</th>
<th>Active substance</th>
</tr>
</thead>
</table>
| HLA-B*5701    | Abacavir (Ziagen)  
|               | Abacavir/lamivudine (Kivexa)  
|               | Abacavir/lamivudine/zidovudine (Trizivir)  |
| CD30          | Brentuximab vedotin (Adcetris) |
| HER2          | Everolimus (Afinitor)  
|               | Trastuzumab (Herceptin)  
|               | Lapatinib (Tyverb)  
|               | Pertuzumab (Perjeta)  
|               | Trastuzumab emtansine (Kadcyla)  |
| RAS           | Panitumumab (Vectibix)  
|               | Cetuximab (Erbitux) |
| EGFR          | Cetuximab (Erbitux)  
|               | Gefitinib (Iressa)  
|               | Erlotinib (Tarceva)  
|               | Afatinib (Giotrif)  |
| ALK           | Crizotinib (Xalkori) |
| BRAF V600     | Vemurafenib (Zelboraf)  
|               | Dabrafenib (Tafinlar) |
| BCR-ABL       | Imatinib (Glivec)  
|               | Dasatinib (Sprycel)  
|               | Nilotinib (Tasigna)  
|               | Bosutinib (Bosulif)  
|               | Imatinib (actavis, accord, medac, teva)  
|               | Ponatinib (Iclusig) |
| Kit CD117     | Imatinib (Glivec) |
| CFTR G551D    | Ivacaftor (Kalydeco) |
| FIP1L1-PDGFR  | Imatinib (Glivec) |
| T315I         | Ponatinib (Iclusig) |
| RET mutation  | Vandetanib (Caprelsa) |
| PML/RAR-α     | Arsenic Trioxide (Trisenox) |
Diagnostics – the Future of Health Care

Development of a Companion Drug

Pre-Clinical → Phase I → Phase II → Phase III → Clinical Use

Research Services
- Study Design
- Custom Assay Design
- Biomarker Discovery
- Data Analysis

Clinical Services
- Assay Development
- Assay Validation
- Processing of Clinical Samples
- Rapid Response

Diagnostic Development Services
- Design Control
- Kit Manufacture
- Clinical Validation
- Regulatory Approval
- Test Distribution
- Sales and Marketing
- Reimbursement

Life Science IP Seminar 2017
Example of typical claims for diagnostic method patents

Method for diagnosing in a subject a tumor, comprising:

1. Subjecting a specific genetic sequence of a test sample to a gene amplification reaction
2. Detecting in the test sample one or more mutations at the DNA level in a marker gene of a specific sequence and determining the amount
3. Wherein the presence of any of the mutations is indicative for a tumor/disease x (diagnostic step)
4. Wherein an elevated amount is indicative of tumor progression (diagnostic step)
„If you want to build a ship, don‘t drum up people to collect wood, rather teach them to long for the endless immensity of the sea.“

Antoine de Saint-Exupery
Diagnostics – the Future of Health Care

Dematerialization of Patent Law

„Rezeptortyrosinkynase II“ – process-product protection?

Bolar/Research Exemption in the context of diagnostic services

Legal Safeguards
Consequence: Dematerialization of patent law

Common place: Information has become a viable commodity

- The „product“ according to Sec. 9 S. 2 Nr. 1 German Patent Act (e.g. the patentability of software)

- The „direct result“ of a process (process-product protection) Sec. 9 S. 2 Nr. 1 German Patent Act (FCJ – MPEG Videosignal, encoded data as product of a process)

- The „means“ in the context of indirect infringement, Sec. 10 par. 1 German Patent Act
Process-Product Protection for Information?

**MPEG- Videosignalcodierung, FCJ August 21, 2012, X ZR 33/10**

The FCJ held in its judgment „MPEG-Videosignalcodierung“ that a non-physical data-sequence, which represents data for transmission via the internet is eligible for IP protection despite its lack of a physical manifestation. 

"Father" disc → "Mother" disc → "Son" disc → Compact disc → Claimed process
MPEG Videosignal - Main Findings

• Process-product protection is justified if:

  • Product is the immediate outcome of the protected method

  • Further steps can be ignored if the product retains the characteristics of the process – different storage mediums do not impact product characteristics (final compact disc still a direct result of the protected process)

  • Result of process must be a tradeable asset – just like a physical product
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.</td>
<td>Diagnostics – the Future of Health Care</td>
</tr>
<tr>
<td>II.</td>
<td>Dematerialization of Patent Law</td>
</tr>
<tr>
<td>III.</td>
<td>„Rezeptortyrosinkynase II“ – process-product protection</td>
</tr>
<tr>
<td>IV.</td>
<td>Bolar/Research Exemption in the context of diagnostic services</td>
</tr>
<tr>
<td>V.</td>
<td>Legal Safeguards</td>
</tr>
</tbody>
</table>
Continuation of MPEG-Videosignalcodierung (and Blood/Brain Barrier (HRC Düsseldorf, InstGE 12, 258)) – when does the result of a patented process deserve protection as a product? When is it considered a product in the sense of the law?

Sparked a discussion on the value of diagnostic method patents/ the necessity of the promotion of their value for the industry
The patent in suit

- Patent in Suit refers to a method to detect FLT3 gene mutation including 2 steps:

  (a) *subjecting a nucleic acid sample from a human to a gene amplification reaction, wherein a nucleic acid fragment comprising exon 11 or exons 11 to 12 of the FMS-like tyrosine kinase 3 (FLT3) gene and having a tandem duplication mutation in the juxtamembrane is amplified, which can be found in FLT3 gene;*

  (b) *detecting the presence of the tandem duplication mutation in the nucleic acid fragment of step (a)*
The patent in suit

- FLT3 is a gene coding a receptor for a relevant growth factor which was found responsible for the progression of leukemia

- Serves the detection of a malign form of Leukemia

- No diagnostic step in the claim
The defendant's business model

- Defendants 1 and 3 offered diagnostics for gene defects on their website, they were based in a private clinic in Germany.

- The patient samples were then sent to a business partner, a laboratory in the CZ Republic. The defendants sent employees each week to drive to the partners in CZ, were the FLT3 analysis was conducted, in some cases, technical support was provided.

- By country, the following steps were conducted:
The defendant's business model

- Offer on the website
- Preparation of the nucleic acids of the samples as generally required for DNA analysis, no specific preparation for FLT3 analysis
- Samples sent to CZ
- Saving of CZ test results in IT system

- FLT3 analysis of patient sample according to patent in suit, detecting mutation and the amount of mutation
- Results sent directly to the customer and a copy to the partner in Germany
Infringing acts as raised by Claimant

• Offer of the protected diagnostic method on the website, Sec. 9 sentence 2 Nr. 2 GPA

• Use/sale of the data/test report generated in CZ in Germany as the data is subject to process-product protection, Sec. 9 sentence 2 Nr. 3 GPA

• Joint tortfeasorship, respective attribution of acts of the businesspartners

• Preparation of the samples in Germany as an indirect infringement by German partners, Sec. 10 par. 1 GPA
„Rezeptortyrosinkinase II“ travelling all instances

RC Munich (7 O 13161/14) : Manufacturing process but no product
No Infringement

HRC Munich (6 U 4891/14) : Work process
No Infringement

FCJ (X ZR 124/15) : Work process
No Infringement
Process-product protection

- Process-product protection, Sec. 9 sentence 2 Nr. 3 GPA:

  *A third party not having the consent of the patentee shall be prohibited*

  [...]  

  3. *from offering, putting on the market or using, or importing or possessing for such purposes, the product produced directly by a process which is the subject matter of the patent.*

- Rationale: Introduced in 1891 when there was no substance protection for chemical compounds
Process-product protection

Reasoning of FCJ on process-product protection:

- The process cannot be considered a manufacturing process – First instance: the information was previously not available and therefore „manufactured“ – the Appeal Court had differed from the 1st instance by designating the method as a work process, FCJ confirmed this view.

- The test report/data is not considered a product in the sense of Sec. 9 sentence 2 Nr. 3 GPA
Process-product protection

• The FCJ noted that «non-physical» data has in some cases („MPEG-Videosignalcodierung) been eligible for process-product protections (derivativer Erzeugnisschutz).

• However: The protection does not extend to information that represent merely
  • an intellectual insight,
  • which can be stored by the human brain,
  • be communicated verbally
  • and where the economic value is exhausted after a single transfer

• Situation not comparable to lack of protection for chemical compounds
Requirements for a product of a manufacturing process to qualify for process-product protection:

- Non-physical items if they can be used and re-used (in connection with a storage medium etc.) in the same way as a physical asset
- The market value should not be exhausted after a single transfer
- The non-physical product should show technical features which can be traced back to the protected method (such technical „imprint“ by the protected method was not explicitly required in MPEG-Videosignalcodierung)
Process-product protection

• In the specific case:
  • „Imprint“ of production process
    • Information does not show specific features due to the process by which it was manufactured
    • Counterargument claimant: The patented process is the only process to measure the specific mutation

• A „product“ as a tradeable asset
  • Other than the encoded information in MPEG-Videosignalcodierung, the information cannot be traded as an asset on the market, its value is exhausted after a single use
  • Counterargument claimant: Data can be traded, e.g. to pharmaceutical companies; several aftermarkets not a criteria founded in patent law
FCJ distinguishes between:

- The physical product, e.g. obtained via a method to manufacture a data carrier (manufacturing process + product)

- The packaging of information, e.g. obtained via a method to encrypt/encode information (manufacturing process + product)

- The information/intellectual insight itself, e.g. obtained via a method to obtain a certain information by means of analysis (work process + no product)
No liability for offering the protected method

- Liability for offering a method is only possible under narrow circumstances, the offerer must offer to conduct a method or enable a third party, the use by the third party must constitute an infringement.

- In any case, offering a method only constitutes an infringement under the GPA if it is offered for use/application in Germany.

- The use in this case occurred solely in CZ.

- The method was not listed specifically on the website.
No liability for joint tortfeasorship

• Liability under Sec. 9 GPA does not require a person to commit any infringing act herself/himself (FCJ – MP3 Player Import)

• No common design required according to German Patent Law for joint tortfeasorship (FCJ – Radio Clock)

• But: The defendant must have committed a domestic act which has essentially caused or led to the infringement, (FCJ – Prepaid Telephonecard)
  • At least one step of the protected method must have been conducted in Germany
  • Economic effect on the German market
No liability for joint tortfeasorship

• No steps of the protected method were conducted within Germany

• General preparation of DNA samples is not part of the patented steps

• Not considered to be implied in step 1 of the protected method

• Therefore: the fact that the order might have been taken in Germany for a German customer (effect on the market) is not taken into account
The Diagnostic Step

- Note for other cases: Diagnostic Step is also a relevant step when assessing infringement and not a mere indication of purpose (HRC Düsseldorf, I-2 U 36/15)

- The case might have been decided differently if patent in suit included a diagnostic step

- If a qualification of the results according to the diagnostic step is added in Germany and forwarded with the results, joint tortfeasorship could be argued
No liability for indirect infringement, according to Sec. 10 par. 1:

Section 10

(1) A patent shall have the further effect that any third party not having the consent of the patentee shall be prohibited from offering or supplying within the territory to which this Act applies to any other persons, other than such persons entitled to use the patented invention, means relating to an essential element of said invention for use of the invention within the territory to which this Act applies, if said third party knows or it is obvious from the circumstances that such means are suitable and intended for use of the invention.
Patient samples provided from Germany to CZ as means to an essential element of the invention?

FCJ: Samples are not delivered for use of the invention in Germany! The method was used only in CZ, no relevant step was conducted in Germany.

Note again: The assessment might have been different if the patent in suit would have included a „Diagnostic Step“
Criticisms of „Rezeptortyrosinkinase II“

• Contradiction to MPEG-Videosignal? Is a technical imprint of the manufacturing process on the final product required or not?

• Clear guidelines missing. What is an asset and what is merely an intellectual asset? When can information be traded „like a physical product“?

• Value of information not fully recognized, circumvention of patent protection possible
Diagnostic Method Patents – risks of infringement for the service and research sector

I. Diagnostics – the Future of Health Care

II. Dematerialization of Patent Law

III. „Rezeptortyrosinkynase II“ – process-product protection?

IV. Bolar/Research Exemption in the context of diagnostic services

V. Legal Safeguards
IV. Bolar/Research Exemption in the context of diagnostic services

On websites of diagnostic services you often find a disclaimer such as

„Services for research/privileged purposes only“

• General rule: The commercial offering/use of a patented method against a fee is not privileged

• Only in a few constellation, such disclaimer can prove effective ➔ careful analysis of individual case required
### Bolar/Research Exemption in the context of diagnostic services

<table>
<thead>
<tr>
<th>Services</th>
<th>Research Exemption</th>
<th>Bolar Exemption</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Research Services</strong></td>
<td>(-) if used as research tool,</td>
<td>(-)</td>
</tr>
<tr>
<td></td>
<td>(+) if research on diagnostic method itself, CRO possibly covered</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical/Development Services</strong></td>
<td>(-) if used as research tool,</td>
<td>(+) if MA is sought for biomarker (companion drug),</td>
</tr>
<tr>
<td></td>
<td>(+) if new information is obtained on biomarker itself, CRO possibly covered</td>
<td>arguably (+) if use of diagnostic method as a tool regulatory required</td>
</tr>
<tr>
<td><strong>Diagnostic Services for patient treatment</strong></td>
<td>(-)</td>
<td>(-) if used as a research tool and patent-free alternatives are available</td>
</tr>
</tbody>
</table>
Diagnostic Method Patents – risks of infringement for the service and research sector

I. Diagnostics – the Future of Health Care

II. Dematerialization of Patent Law

III. „Rezeptortyrosinkynase II“ – process-product protection?

IV. Bolar/Research Exemption in the context of diagnostic services

V. Legal Safeguards
V. Legal Safeguards

As ordering client:

• Consider FTO‘s for risk assessment – often commercially not feasible for the service provider

• No pool for diagnostic patents – obtaining licences covering all diagnostics is challenging

• If necessary consider a provider in another location for risk minimization

• Disclaimers usually don‘t work! Check the general terms and conditions carefully!
As service provider:

• Consider FTOs where possible

• Consider contractual safeguards, e.g. indemnification clauses

• Check structure of your business – avoid any step, including the „diagnostic step“ in a country with patent protection; Avoid exchanging information within a country with patent protection
Summary:

- The intellectual result of an analytical method does not qualify for process-product protection of Sec. 9 S. 2 No. 3 GPA!

- Liability for use of a protected method can occur even if only some of the required steps occur in the country where patent protection exists! The „Diagnostic Step“ counts as well!

- The rules for „contributory infringement“ are very broad under German patent law – check twice whether you risk being a „contributor“!
Thank you for your attention

Dr. Esther Pfaff, LL.M
Counsel | Attorney at Law | WIPO Mediator

EPfaff@HoffmannEitle.com