Examination Matters – webinar series in the medical field

Post-published evidence – a risky game!

Katell Le Flao
Examiner, Cancer Immunology
22 November 2018
Presenting today

Katell Le Flao

Examiner Search/Examination/Opposition

Sector HBC – Cancer immunology
† Therapeutic use antibodies

Engineer, M.Sc., EQE
Post-published evidence – a risky game!

The Angel of the West

Structure of an immunoglobulin. Therapeutic antibodies
Post-published evidence – a risky game!

Objectives

β Share my personal experience based upon real cases
  • Examination, Opposition
  • Impressive data and discoveries, but not on time

β Allow to understand the decision making process

β Experience the situation of a member of an Examining Division or Opposition Division
Post-published evidence : PPE

Agenda

- Legal provisions (1/2)
  - Legal framework allowing to take into account Post-Published Evidence when assessing inventive step

- Indication on the link between A83-A56? Trap?
  - Legal framework and real cases

- Let's practise ... real cases
  - Presentation of real cases for which Post-Published Evidence (PPE) had been filed
Legal provisions (1/2)

PPE : legal provisions

- **EPC**, Article 56 EPC
- **G01/03**, point 2.5.2
- **Guidelines** G-VII, Inventive step
  5. Problem-Solution Approach
  11. Arguments and evidence submitted by the applicant
- **Guidelines** H-V, Allowability of Amendments
  2. Description
- **Case Law**, 8th edition 2016
  I.D.4, Technical Problem
Legal provisions (1/2)

PPE : legal provision

European Patent Convention

Article 56 EPC :
"An invention shall be considered as involving an inventive step if, having regard to the state of the art, it is not obvious to a person skilled in the art."
Legal provisions (1/2)

<table>
<thead>
<tr>
<th>PPE : legal provision</th>
</tr>
</thead>
<tbody>
<tr>
<td>§ Enlarged Board of Appeal G01/03, point 2.5.2</td>
</tr>
<tr>
<td>§ &quot;If ... there is lack of reproducibility of the claimed invention, this may become relevant under the requirements of inventive step or sufficiency of disclosure.</td>
</tr>
<tr>
<td>§ If an effect is expressed in a claim, there is lack of sufficient disclosure. Otherwise, if the effect is not expressed in a claim but is part of the problem to be solved, there is a problem of inventive step (T 939/92, OJ EPO 1996, 309)&quot;</td>
</tr>
</tbody>
</table>
Guidelines, G-VII, 5.2
Formulation of the objective technical problem

"The extent to which such reformulation of the technical problem is possible has to be assessed on the merits of each particular case. As a matter of principle any effect provided by the invention may be used as a basis for the reformulation of the technical problem, as long as said effect is derivable from the application as filed."
Legal provisions (1/2)

PPE : legal provision

Guidelines, G-VII, 11
Arguments and evidence submitted by the applicant

"The relevant arguments and evidence to be considered by the examiner for assessing inventive step may either be taken from the originally-filed patent application or submitted by the applicant during the subsequent proceedings."
Legal provisions (1/2)

Guidelines, G-VII, 11
Arguments and evidence submitted by the applicant

"Care must be taken, however, whenever new effects in support of inventive step are referred to. Such new effects can only be taken into account if they are implied by or at least related to the technical problem initially suggested in the originally filed application."
Legal provisions (1/2)

PPE : legal provision

Guidelines, G-VII, 11

Arguments and evidence submitted by the applicant

Example of a new effect:

- The Invention: pharmaceutical composition whose activity seems obvious having regard to the relevant prior art
- PPE shows unexpected low toxicity
- Reformulating the technical problem is possible
- Reason: pharmaceutical activity and toxicity are related in the sense that the skilled person would always contemplate the two aspects together
Legal provisions (1/2)

QUESTION Guidelines, G-VII, 11

Formulation of the technical problem as the provision of

An alternative pharmaceutical composition?
Legal provisions (1/2)

QUESTION Guidelines, G-VII, 11

Formulation of the technical problem as the provision of

β An improved pharmaceutical composition?
Formulation of the technical problem as the provision of
- an alternative pharmaceutical composition
- an improved pharmaceutical composition
Legal provisions (1/2)

PPE : legal provision

Guidelines, G-VII, 11
Arguments and evidence submitted by the applicant

"In the above example of a pharmaceutical composition, neither the reformulated problem nor the information on toxicity could be introduced into the description without infringing Art. 123(2)."

- Inventive step is acknowledged based upon an effect not disclosed in the application.
- There is no requirement when formulating the problem-solution approach to comply with Art. 123(2).
Questions

now via chat to "All participants"
Legal provisions (1/2)

PPE: practise on real cases – 1st part

Facts concerning

- Claims
- Disclosure in the application
- Prior art
- Post-published evidence

Questions to be answered to

- Inventive step? YES – NO
## Legal provisions (1/2)

### PPE : case 1

<table>
<thead>
<tr>
<th>Claim</th>
<th>Disclosure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination of an antibody + a chemotherapeutic agent for use in treating a patient having cancer</td>
<td>Theoretical statement that combining an antibody with a chemotherapeutic agent results in an additive until synergistic killing effect on cancer cells</td>
</tr>
</tbody>
</table>
### Legal provisions (1/2)

**PPE : case 1**

<table>
<thead>
<tr>
<th>Closest prior art</th>
<th>An antibody has an effect on tumour sizes, the chemotherapeutic agent is used for treating cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-published evidence</td>
<td>The combination of an antibody with the chemotherapeutic agent has a synergistic effect.</td>
</tr>
</tbody>
</table>

**Inventive step?** YES or NO
Legal provisions (1/2)

PPE : case 1

<table>
<thead>
<tr>
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<tr>
<td>Post-published evidence</td>
<td>The combination of an antibody with the chemotherapeutic agent has a synergistic effect.</td>
</tr>
</tbody>
</table>

Inventive step?  YES or NO

T 1642/07
### Legal provisions (1/2)

<table>
<thead>
<tr>
<th><strong>PPE : case 1</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Claim</strong></td>
</tr>
<tr>
<td><strong>Disclosure</strong></td>
</tr>
<tr>
<td><strong>Reproducibility?</strong></td>
</tr>
<tr>
<td><strong>T 1642/07</strong></td>
</tr>
</tbody>
</table>
Post-published evidence : PPE

Agenda

- Legal provisions (2/2)
  - Legal framework allowing to take into account Post-Published Evidence when assessing inventive step

- Indication on the link between A83-A56? Trap?
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Legal provisions (2/2)

PPE : legal provision

Case Law, I.D.4, Solving a technical problem based on post-published documents

Assessment of inventive step is to be made at the effective date, on the basis of the patent and the common general knowledge.

Plausibility test: does the claimed subject-matter solve the problem it purports to solve? based upon the data in the application.

If not Problem is not solved, inventive step is denied,
or Reformulation of the problem is required
Legal provisions (2/2)

PPE : legal provision

Case Law, I.D.4, Reformulation of the technical problem

possible

- "if new effects submitted subsequently during the proceedings were implied by or related to the technical problem initially suggested."

required

- "in case where the only factor of importance in determining the problem objectively is the result actually achieved in relation to the closest state of the art (chemistry)."
Legal provisions (2/2)

PPE : legal provision

Case Law, I.D.4, Subsequently invoked technical effect

If additional advantages do not alter the character of the invention,

‡ Post-published evidence can be taken into account.

Without a technical relationship between the effect shown in the post-published evidence and the technical problem as originally defined,

‡ Post-published evidence cannot be taken into account.
Legal provisions (2/2)

PPE : legal provision

 Case Law, I.D.4, Solving a technical problem based on post-published documents

 Supplementary PPE may not serve as the sole basis to establish that the problem is solved.

 Common general knowledge at the priority date may be used to interpret the teaching in an application or a patent.

 PPE can only be used to back up the teaching derivable from the application.
Legal provisions (2/2)

PPE : legal provision

}* Article 56 EPC · Guidelines · Case Law

PPE are taken into account for assessing inventive step

if

✧ Technical relation exists between the new effects and the problem as initially defined,

✧ It is derivable from the application that the problem is solved
Legal provisions (2/2)

PPE : practise on real cases – 2\textsuperscript{nd} part

\begin{itemize}
  \item Facts concerning
  \begin{itemize}
    \item Claims
    \item Disclosure in the application
    \item Prior art
    \item Post-published evidence
  \end{itemize}
  \item Questions to be answered to
  \begin{itemize}
    \item \textbf{Inventive step?} \quad \textbf{YES – NO}
  \end{itemize}
\end{itemize}
## Legal provisions (2/2)

### PPE: case 2

<table>
<thead>
<tr>
<th><strong>Claim</strong></th>
<th>An antibody that binds Blys (= BAFF), wherein said antibody comprises amino acid residues 1-125 and 140-250 of SEQ ID NO: 124.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disclosure</strong></td>
<td>Hundreds of sequences of antibodies binding Blys, including SEQ ID NO: 124. The therapeutic interest of Blys was discussed. None of the antibodies was shown to have both high affinity and high neutralizing effect.</td>
</tr>
</tbody>
</table>
**Legal provisions (2/2)**

<table>
<thead>
<tr>
<th>Closest prior art</th>
<th>An anti Blys antibody.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-published evidence</td>
<td>The claimed antibody of SEQ ID NO: 124 has a good neutralizing effect combined with a high affinity. It is in clinical trials for treating different diseases.</td>
</tr>
</tbody>
</table>

**Inventive step?**  YES or NO
Legal provisions (2/2)

PPE : case 2

<table>
<thead>
<tr>
<th>Closest prior art</th>
<th>An anti protein X antibody.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-published evidence</td>
<td>The claimed antibody of SEQ ID NO: 124 has a good neutralizing effect combined with a high affinity. It is in clinical trials for treating different diseases.</td>
</tr>
</tbody>
</table>

Inventive step?  YES or NO

EP01946365 maintained during opposition, no appeal
Post-published evidence: PPE

**Agenda**

- Legal provisions
  - Legal framework allowing to take into account Post-Published Evidence when assessing inventive step

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Indication on the link between A83-A56? Trap?

骅 Link or Trap between A56 and A83?

骅 A lack of reproducibility can be objected against under either A83 EPC or A56 EPC

骅 Filing post-published evidence might emphasizes that the invention was not made at the filing date.

• Compliance with Art. 83?
Indication on the link between A83-A56? Trap?

PPE : legal provision

Link or Trap between A56 and A83?

Criteria set in G 01/03, point 2.5.2:

• If an effect is expressed in a claim, there is lack of sufficient disclosure objection according to Art. 83 EPC

• Otherwise, if the effect is not expressed in a claim but is part of the problem to be solved, there is a problem of inventive step objection according to Art. 56 EPC
Indication on the link between A83-A56? Trap?

PPE : Criteria
Indication on the link between A83-A56? Trap?

PPE: legal provision

Link or Trap between A56 and A83?
3 criteria

1. Product claim versus use claim
2. Specific embodiment versus generic disclosure
3. Consistent facts versus contradicting evidence

1. Product claim versus use claim
   † PPE filed to support the inventive step of a product claim are less susceptible to lead to a new objection under Art. 83.
Indication on the link between A83-A56? Trap?

PPE: legal provision

Link or Trap between A56 and A83? 3 criteria

2. Specific embodiment versus Generic disclosure

- one specific example disclosing the therapeutic use of a compound, e.g. the administration regimen, and the expected effect. The use of this specific compound is claimed for treating one specific disease: PPE is a mere confirmation ‡ requirements of Art. 56 are met

- From one specific examples the treatment of several diseases is claimed ‡ objections under A83 for the diseases not mentioned in the ex.
Indication on the link between A83-A56? Trap?

PPE : legal provision

Link or Trap between A56 and A83? 3 criteria

3. If contradicting facts are published before and after the filing of the application, the confirmation that the effect (treatment) is achieved is necessary in the application.

• PPE cannot be the sole evidence establishing the plausibility of a claimed effect (treatment).

† objection according to Art. 83.

‡ Objection under A83/A56 may be overcome by arguments
Post-published evidence : PPE

Agenda

- Legal provisions
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Let's practise ... real cases
  - Presentation of real cases for which Post-Published Evidence (PPE) had been filed
Let's practise ... real cases

PPE : practise on real cases – 1st part

Facts concerning

• Claims
• Disclosure in the application
• Prior art
• Post-published evidence

Questions to be answered to

• Reproducibility? YES – NO
• Inventive step? YES – NO
Let's practise ... real cases

PPE : Criteria

- Category of the claim
- Post-Published Evidence
- Consistent or contradicting evidence
- Generic or specific
Let's practise ... real cases

**PPE : case 3**

<table>
<thead>
<tr>
<th><strong>Claim</strong></th>
<th>An antibody or antigen binding fragment thereof which specifically binds to a breast carcinoma protein encoded by SEQ ID NO:1 for use in treating a patient having breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disclosure</strong></td>
<td>Microarray disclosing the overexpression of some genes in breast cancer, including the gene of SEQ ID NO:1. No antibody, no overexpression at the protein level.</td>
</tr>
</tbody>
</table>
**Let's practise ... real cases**

**PPE : case 3**

<table>
<thead>
<tr>
<th>Closest prior art</th>
<th>Treatment of breast cancer with a chemotherapeutic agent.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-published evidence</td>
<td>A specific <strong>antibody</strong> binding the protein encoded by SEQ ID NO: 1 is shown to have inhibitory effect on cancer cell proliferation in vitro.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reproducibility?</th>
<th>YES or NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inventive step?</td>
<td>YES or NO</td>
</tr>
</tbody>
</table>
## Let's practise ... real cases

### PPE : case 3

<table>
<thead>
<tr>
<th>Closest prior art</th>
<th>Treatment of breast cancer with a chemotherapeutic agent.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-published evidence</td>
<td>A specific antibody binding the protein encoded by SEQ ID NO: 1 is shown to have inhibitory effect on cancer cell proliferation in vitro.</td>
</tr>
<tr>
<td>Reproducibility?</td>
<td><strong>YES or NO</strong></td>
</tr>
</tbody>
</table>

EP99966445 revoked in opposition, no appeal
**Let's practise ... real cases**

**PPE : case 4**

<table>
<thead>
<tr>
<th>Claim</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of <strong>Campath-1H</strong> for the production of a medicament for reducing the risk of relapse in a patient having a relapsing form of <strong>multiple sclerosis (MS)</strong> who has received prior therapy for MS, the treatment comprising a first treatment cycle of Campath-1 H followed by at least one further treatment cycle of Campath-1 H, in which each treatment cycle comprises 1-5 daily doses which are applied on consecutive days, wherein the daily dose is &gt; 0 and ≤12 mg, and wherein each treatment cycle is separated from the next treatment cycle by at least 1-24 months.</td>
</tr>
</tbody>
</table>
Let's practise ... real cases

| Disclosure | No result with the claimed dosage. |
| Closest prior art | Use of Campath-1H for treating multiple sclerosis (MS), daily dose of 20 mg. |
| Post-published evidence | Successful phase III results, daily dose 12 mg |
| Reproducibility? | YES or NO |
| Inventive step? | YES or NO |
**Let's practise ... real cases**

<table>
<thead>
<tr>
<th>PPE : case 4</th>
<th>Disclosure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Closest prior art</strong></td>
<td>No result with the claimed dosage.</td>
</tr>
<tr>
<td><strong>Post-published evidence</strong></td>
<td>Use of Campath-1H for treating multiple sclerosis (MS).</td>
</tr>
<tr>
<td><strong>Reproducibility?</strong></td>
<td>YES or NO</td>
</tr>
<tr>
<td><strong>T 0707/18, EP07802348</strong></td>
<td>revoked in opposition, under appeal</td>
</tr>
</tbody>
</table>

T 1592/12, point 20
Let's practise ... real cases

PPE : case 5

Claim

An anti-ErbB2 antibody for use in a method for the treatment of a human patient with a cancer characterized by overexpression of ErbB2 receptor, the method comprising administering an effective amount of a combination of an anti-ErbB2 antibody and a chemotherapeutic agent other than an anthracycline derivative, in the absence of an anthracyline derivative, to the patient, wherein the chemotherapeutic agent is a hormonal agent that acts to regulate or inhibit hormone action on tumours.
Let's practise ... real cases

**PPE : case 5**

**Disclosure**

- Treatment of breast cancer with a combination of an anti-ErbB2 antibody + anthracycline, cyclophosphamide or taxol.

- Using an anti-ErbB2 antibody together with anthracycline should be avoided due to side effect.

- Chemotherapeutic agents are listed as known to treat cancer. Anastrazole is not individualised.
Let's practise ... real cases

PPE : case 5

Closest prior art
Treatment of breast cancer with an anti-ErbB2 Ab + anthracycline and cyclophosphamide or taxol in an animal model. Treatment of breast cancer with anthracycline, cyclophosphamide or taxol.

Post-published evidence
An anti-ErbB2 Ab + Anastrazole, is effective to treat breast cancer

Reproducibility? YES or NO
Inventive step? YES or NO
Let's practise ... real cases

PPE : case 5

Closest prior art

Treatment of breast cancer with an anti-ErbB2 Ab + anthracycline and cyclophosphamide or taxol in an animal model.

Post-published evidence

An anti-ErbB2 Ab + Anastrazole, is effective to treat breast cancer

Reproducibility? YES or NO
Let's practise ... real cases

PPE : case 5

<table>
<thead>
<tr>
<th>Closest prior art</th>
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</thead>
<tbody>
<tr>
<td>Post-published evidence</td>
<td>An anti-ErbB2 Ab + Anastrazole, is effective to treat breast cancer</td>
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Reproducibility?  YES or NO
Inventive step?   YES or NO
Let's practise ... real cases

PPE : case 5

<table>
<thead>
<tr>
<th>Closest prior art</th>
<th>Treatment of breast cancer with an anti-ErbB2 Ab + anthracycline and cyclophosphamide or taxol in an animal model.</th>
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**Reproducibility?** | **YES or NO**
**Inventive step?** | **YES or NO**

T 1559/13, EP10177992

refused in examination, appealed, withdrawn
Let's practise ... real cases

<table>
<thead>
<tr>
<th>PPE : case 6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Claim</strong></td>
</tr>
<tr>
<td>limited to one single individual compound, <strong>dasatinib</strong>, from a broad Markush formula initially claimed, related to <strong>thiazole</strong>.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disclosure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wide range of compounds allegedly useful as protein tyrosine kinase (PTK) inhibitors</td>
</tr>
<tr>
<td>Different PTK exists</td>
</tr>
<tr>
<td>No experimental results in any assay</td>
</tr>
<tr>
<td>No threshold level for activity has been given</td>
</tr>
</tbody>
</table>
## Let's practise ... real cases

### PPE : case 6

<table>
<thead>
<tr>
<th>Closest prior art</th>
<th>Thiazole derivatives for the same use.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-published evidence</td>
<td>Dasatinib is an active PTK inhibitor and inhibits Src or Abl kinas, PTKs associated with cancer, thereby being suitable for treating cancer</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reproducibility?</th>
<th>YES or NO</th>
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<tr>
<td>Inventive step?</td>
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Let's practise ... real cases

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<td>Reproducibility?</td>
<td>YES or NO</td>
</tr>
<tr>
<td>T 0488/16, EP00922102</td>
<td>revoked in opposition, confirmed in appeal</td>
</tr>
</tbody>
</table>
PPE : a risky game?

Conclusion

- The nature of the objection can be anticipated based upon the criteria set up in **G 01/03** but it also depends on the structure of the compound.

- To comply with A83, the description has to make plausible the effect shown later in Post-Published-Evidence.

- Filing post-published evidence may/will overcome a lack of inventive step objection.
<table>
<thead>
<tr>
<th>now</th>
<th>via chat to &quot;All participants&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>later</td>
<td>via mail <a href="mailto:academy@epo.org">academy@epo.org</a></td>
</tr>
</tbody>
</table>
Post-Published Evidence: a risky game?

**PPE: decisions**

**Landmark decisions:**
- T 609/02, T 1329/04, T158/96, T 1397/08, T 184/82,
- T 1306/04, T 1396/06, T 0861/08, T 415/11, T 488/16

**Decisions in Biotechnology:**
- T 0775/08, T 1642/07, T 578/06, T 294/07, T 716/08,
- T 2233/08, T 2134/10, T1592/12

**Other decisions:**
- T 1336/04, T 433/05, T 1422/12
Thank your for your attention