Attributes of Pharma Biotech Patenting
- a European Perspective
Attributes of Pharma Biotech Patenting > Agenda

Agenda [Slide No.]:

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- Practical Difficulties with Biotech Patents [12 – 14]
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Defintion of Biotechnology

“Biotechnology is the integrated application of biochemistry, microbiology and process engineering with the aim of making technical use of the properties of micro-organisms, cell and tissue cultures and parts thereof.”

Source: European Federation of Biotechnology
Attraction of Biotechnology for the Pharmaceutical Industry

- **Big Ten Branded Blockbusters 2010**

### Sales 2010 (USD x 10^9)

<table>
<thead>
<tr>
<th>Product</th>
<th>Sales 2010 (USD x 10^9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipitor</td>
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<tr>
<td>Plavix</td>
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<tr>
<td>Enbrel</td>
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</tr>
<tr>
<td>Advair Diskus</td>
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<tr>
<td>Remicade</td>
<td>7.4</td>
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<tr>
<td>Avastin</td>
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<tr>
<td>Rituxan</td>
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<tr>
<td>Diovan</td>
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<tr>
<td>Crestor</td>
<td>5.8</td>
</tr>
<tr>
<td>Humira</td>
<td>5.4</td>
</tr>
</tbody>
</table>

Source: pharma.about.com
Attraction of Biotechnology for the Pharmaceutical Industry

- Top Ten Biologics Drugs July 2010 to June 2011

**Sales July 2010 - June 2011 (USD x 10^9)**

- Humira: 6.6
- Enbrel: 6.5
- Remicade: 6.4
- Avastin: 5.5
- RituJan: 5.4
- Lantus: 4.5
- Herceptin: 4.1
- Neulasta: 3.7
- Lovenox: 3.6
- Copaxone: 0.0

**Total World-wide Biologic Market:** $148.2 billion

*Source: IMS Health*
Attraction of Biotechnology for the Pharmaceutical Industry

- Drug Development Success (2006-2010)

Source: Genetic Engineering & Biotechnology News 2012
Biotech Patenting > Legal Background (EPC)

- Biotech-specific Regulation in the EPC:
  - Rule 26: Definitions
  - Rule 27: Patentability of Biotechnological Inventions
  - Art. 53: Exceptions from Patentability
  - Rule 28: (Ethical) Exceptions from Patentability
  - Rule 29: Human body

Notes (very basic):
- A technical solution is always required (Rule 27)
- Drug + medical use is patentable (Art. 53)
- Transgenic animals: Medical benefit required (Rule 28)
- Just a gene sequence is not patentable (Rule 29)
Important Definitions (Rule 26, EPC):

"Biotechnological inventions" are inventions which concern a product consisting of or containing biological material or a process by means of which biological material is produced, processed or used.

"Biological material" means any material containing genetic information and capable of reproducing itself or being reproduced in a biological system.

"Microbiological process" means any process involving or performed upon or resulting in microbiological material.
Biotech Patenting > Filing Strategies (Originators)

Patent filing along the development chain

- Cloning
- Expression
- Cell bank
- Process
- USP
- DSP
- Analytical
- methods
- Validation
- Non-clinical
- studies
- Pharmaceutical
- development
- GMP
- Validation
- Clinical
- studies
- (I-III)
- Dossier
- Approval

Multiple patent protection: Life cycle strategies
Filing Strategies > Patent Categories

- Two patent categories exist:

1. **Basic patents**
   - Define market entries for biosimilars
   - To be considered, may be opposed, circumvention not possible
   - Claims: Substance, DNA-sequence, AA-sequence, recombinant expression, biological function, key indication, dosing...
   - Basis for filing SPCs

2. **Secondary patents**
   - Circumvention possible, often opposed
   - May emerge late (during biosimilar development)
   - Claims: Process, improved quality, formulation, device, dosing regimen, follow on indication(s), combination therapy, ...
   - Moving targets for FTO assessments
Sequence of Patent Filings for Biopharmaceuticals:

- Sequence, cell clone, expression, function: basic patents → SPCs
- Fermentation conditions, purification methods: secondary patents
- Pharmaceutical composition, drug delivery: secondary patents
- Dosing, application, indication(s): basic/secondary patents

To maximize the patent protection period
Practical Difficulties with Biotech Patents

- **Total number of patents:** Very high for a given biotech product.

- **Scope of claims:** Often difficult to interpret. Claims may refer to sequences or even to deposited materials (cell clones).

- **Difficult search:** Due to inconsistent nomenclature of the molecules and often meaningless titles and abstracts. Class-specific search or structural search is insufficient.

- **Indirect substance protection:** In most cases recombinant proteins receive no direct substance protection, since the corresponding natural occurring proteins are prior art. Hence, the patent protection is often related to specific production methods or biological targets (e.g. antibodies).

- **Multiple originators:** Regularly there are no monopolies for biotech products, several companies developed in parallel comparable (me-too) products.
Systematic Keyword Search in 2002

- First Wave of Biosimilar Candidates

<table>
<thead>
<tr>
<th>Protein</th>
<th>No. of Hits</th>
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<tr>
<td>Insulin</td>
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<td>IFNα</td>
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<tr>
<td>G-CSF</td>
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<td>hGH</td>
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<tr>
<td>IFNβ</td>
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<tr>
<td>FVIII</td>
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Databases: WPIX, HCAPlus, BiotechABS
### Practical Difficulties with Biotech Patents > Multiple Originators

<table>
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<tr>
<th>Rec. Therapeutic Protein</th>
<th>Originator</th>
<th>Product (EU-Launch)</th>
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<tbody>
<tr>
<td>Human Insulin</td>
<td>Eli Lilly</td>
<td>Huminsulin (1982)</td>
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<tr>
<td></td>
<td>Novo Nordisk</td>
<td>Insulin Actrapid (1991)</td>
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<td></td>
<td>Aventis</td>
<td>Insuman (1999)</td>
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<tr>
<td>Human Growth Hormone (hGH)</td>
<td>Eli Lilly</td>
<td>Humatrope (1988)</td>
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<td>Genentech</td>
<td>Genotropin (1988)</td>
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<td>Novo Nordisk</td>
<td>Norditropin (1988)</td>
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<td>Serono</td>
<td>Saizen (1989)</td>
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<td>Ferring</td>
<td>Zomacton (1994)</td>
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<td>Interferon alpha (IFNα)</td>
<td>Schering-Plough</td>
<td>Intron A (1986)</td>
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<td>Roche</td>
<td>Roferon A (1989)</td>
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<td>Amgen</td>
<td>Infergen (1999)</td>
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<td>Avonex (1997)</td>
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<td>Kirin-Amgen</td>
<td>Erypo, Eprex (1988)</td>
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<td>Roche (BMA, GI)</td>
<td>Neorecormon (1992)</td>
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<td>Granulocyte-Colony-Stimulating Factor (G-CSF)</td>
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<td>Immunex (Schering AG)</td>
<td>Leukine (1991?)</td>
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<td>Schering-Plough, Novartis</td>
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<td>Follicle Stimulating Hormone (FSH)</td>
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<td>Hepatitis B Vaccine (HBsAg)</td>
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<td>PEG-Interferon alpha (PEGIFNo)</td>
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<td>Roche</td>
<td>Pegasys (2002)</td>
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Examples of Biotech Products with Multiple SPC Applicants

- **Enbrel** (Amgen)
  - Immunex
  - Genentech
  - Abbott
  - AHP Manufacturing
  - Sanofi-Aventis & General Hospital

- **Humira** (Abott)
  - Abbott
  - Yeda Research
  - Peptech

- **Leucomax** (Schering-Plough)
  - Schering Biotech Corp
  - Novartis
  - Research Corporation

- **Herceptin** (Roche)
  - Genentech
  - Chiron
  - PDL Biopharma

- **Xolair** (Novartis)
  - Genentech
  - Tanox
  - PDL Biopharma

**Proprietor of Product**

**Licensor, Licensee or Codeveloper**

Szeged May 11, 2012

Walter Hinderer
Multiple SPCs > EC Regulation


**Article 3 / Conditions for obtaining a certificate**
A certificate shall be granted if, in the Member State in which the application referred to in Article 7 is submitted and at the date of that application:

a)...  
b)....  
c) the product has not already been the subject of a certificate;  
d)....

Multiple SPCs (per country) are in conflict with Art. 3(c) of the EC Regulation 469/2009. Later granted SPCs should be invalid. [“1 Product → 1 SPC”]

Szeged May 11, 2012  
Walter Hinderer
Case Study: Multiple Indications: Humira

- Approved indications in the EU of Humira (adalimumab)

- Sequential approval of **seven** distinct indications
- Different dosing regimens
- Specific medical use patent applications filed
- Claims mirror regulatory variations (labeling)

<table>
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<th>Year</th>
<th>RA</th>
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<th>CD</th>
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</tbody>
</table>

1) RA = Rheumatoid Arthritis
2) PsA = Psoriatic Arthritis
3) AS = Ankylosing Spondilitis
4) CD = Crohn’s Disease
5) Ps = Psoriasis
6) JIA = Juvenile Idiopathic Arthritis
7) UC = Ulcerative Colitis

Walter Hinderer
Decisions on Patentability of Dosage Regimens at the EPO

**T1020/03 (IGF-1) [Genentech]**
- A pure dosage regimen is patentable

**T1319/04 (nicotinic acid) [Abbott]**
- Referral to Enlarged Board of Appeal (→G2/08)

**G2/08 (19.02.2010)**
- Art 54(5) EPC does not exclude patentability of a different treatment with a known medicament in a known indication
- A new dosage of a known medicament in a known indication is patentable
- Swiss-type claims may no longer be used in such cases
**EP1210115B1 (Genentech): New Dosage Regimen**

Claim 1 as granted (emphasis added):
Use of the anti-ErbB2 antibody huMab 4D5-8 in the manufacture of a medicament for use in a method for treating a human patient diagnosed with a breast cancer characterized by overexpression of ErbB2, said method comprising the steps of administering to the patient an initial dose of 8 mg/kg of the anti-ErbB2 antibody; and administering to the patient a plurality of subsequent doses of the antibody in an amount that is 6 mg/kg, wherein the doses are separated in time from each other by three weeks.

Posology in Breast Cancer/SmPC/EMA (emphasis added):
The recommended initial loading dose is 8 mg/kg body weight. The recommended maintenance dose at three-weekly intervals is 6 mg/kg body weight, beginning three weeks after the loading dose.
Case Study > Medical use claims > Mabthera

- **EP1210115B1 (Genentech):** Revoked after Opposition

- A dosing patent on a new 3-weekly dosage (swiss-type claims)
- Claims mirror product labeling (adapted during prosecution)
- 1st line treatment in breast cancer overexpressing ErbB2
- For this dosage regimen there were no clinical data disclosed
- A clear derivation of the 3-weekly scheme 8mg/6mg is missing
- The patent was revoked by the Opposition Division on basis of Art. 83 EPC (insufficient disclosure)

**Comment:**
Too early filing of new dosage regimens without any data is at risk to violate Art. 83 EPC especially in view of the “raising the bar“ philosophy at the EPO.
**EP1613350B1 (Genentech): Selection of Patient Groups**

**Claim 1 as granted (emphasis added):**

Use of an antibody which binds to CD20 and which upon binding to CD20 destroys or depletes B cells in a mammal in the manufacture of a medicament for treating rheumatoid arthritis by administration of two doses of antibody of 1000mg to a mammal who experiences an inadequate response to a TNFα-inhibitor, wherein the first dose is administered on day 1 of treatment and the second dose on day 15.

**Product Labeling /SmPC/EMA (emphasis added):**

MabThera in combination with methotrexate is indicated for the treatment of adult patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs (DMARD) including one or more tumour necrosis factor (TNF) inhibitor therapies.
Case Study > Medical use claims > Mabthera

- **EP1613350B1 (Genentech):** Revoked after Opposition
  - A dosing patent for the 3rd indication RA (swiss-type claims)
  - The claims mirror product labeling (adapted during prosecution)
  - 2nd line treatment (after TNFα inhibitor)
  - The dosage regimen was prior art (Genentech Press Release)
  - The definition of a patient group “inadequate response to a TNFα-inhibitor” should render the claim novel over prior art
  - This patient group was not accepted by the Opposition Division

Basis for the revocation: T233/96 and T1399/04:
“The selection of a patient group should provide a particular technical effect and be based on pathological and/or physiological criteria”
Raising the Bar > Intermediate Experience

- The effect of “Raising the Bar” (Examination and Opposition)

- Art. 56 – Inventive Step: ↑↑↑
- Art. 115 – Third Party Observations: ↑↑↑
- Art. 83 – Disclosure/Sufficiency: ↑↑
- Art. 94(3) – Examination: ↑↑
- Art. 123(2)/(3) – Added Subject Matter: ↑↑
- Art. 82 – Unity: ↑
- Art. 84 – Clarity/Claims: ↑
- Art. 92 – European Search: ↑
- Art. 54 – Novelty: →
- Art. 57 – Industrial Application: →

Thank You

Köszönöm