



Managing Patent Litigation and Intellectual Property

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Biosimilars – Gene Technology and Patent Questions

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gene technology

- ***gene technology is part of the field of biotechnology („bios“ („βίος“) = greek for „life“)***
- ***biotechnology***
 - ***wastewater treatment***
 - ***composting***
 - ***baking bread***
 - ***yoghurt production***
 - ***brewing beer (since 7000 B.C.)***



gene technology

➤ *gene technology*

➤ *„green“ gene technology: agriculture*

➤ *„red“ gene technology: medicine*

➤ *„white“ gene technology: industry and environmental technology*



gene technology

➤ *gene technology*

➤ *Collective term for methods for isolating, diagnosing, propagating („cloning“), manipulating, newly recombining genetic material or transferring such material to other organisms*

➤ *DNA (engl.) = deoxyribonucleic acid*



gene technology

- *gene technology ist possible,*
 - *because the „language“ or „lettering“ of the genetic material (DNA or the genes encoded by the DNA) is the same in all living beings and is therefore understood by all organisms (humans, animals, plants, fungi, bacteria, (viruses),)*



gene technology - basics

- *DNA is carrier of genetic information*
- *long and filamentous molecule in the cell nucleus of higher organisms*
- *central component of chromosomes*
- *DNA is composed of*
 - *„backbone“ of sugar (ribose) and phosphate*
 - *nucleic bases (4 different: Adenine, Thymine, Cytosine and Guanine)*



gene technology - basics

- *DNA is carrier of genetic information*
- *discovered and proven by Oswald Avery (US) in 1944*
- *1950: Erwin Chargaff (AT) discovers that A and T (and: C and G) is always equally present in a DNA-molecule („Chargaff’s Rule“)*



gene technology - basics

- *DNA is carrier of genetic information*
- *James Watson (US) and Francis Crick (GB) discover structure of the DNA-molecule 1953 (Nobel price 1962)*



gene technology - basics

- *structure of DNA-molecules*
- *nucleic bases (4 different: Adenine, Thymine, Cytosine and Guanine)*
- *„Couple generation“*
 - *Adenine and Thymine*
 - *Cytosine and Guanine*
- *$G \equiv C, A = T$ and $C \equiv G, T = A$*



gene technology - basics

- *Significant properties of the DNA-molecule:*
 - *Sequence of different bases = information memory*
 - *can replicate itself, thereby conserving the information contained*



gene technology - basics

- *sequence of the DNA-molecules can be found experimentally:*
- *„DNA-sequencing“*



gene technology - basics

➤ *DNA-sequencing: result:*

➤ *atggccctgt ggatgcgcct cctgcccctg ctggcgctgc
tggccctctg gggacctgac ccagccgcag cctttgtgaa
ccaacacctg tgcggctcac acctggtgga agctctctac
ctagtgtgcg gggaacgagg cttcttctac acaccaaga
cccgccggga ggcagaggac ctgcaggtgg ggcaggtgga
gctgggcggg ggccctggtg caggcagcct gcagcccttg
gccctggagg ggtccctgca gaagcgtggc attgtggaac
aatgctgtac cagcatctgc tccctctacc agctggagaa
ctactgcaac tag*

➤ *Walter Gilbert (US) and Frederick Sanger (GB): Nobel price 1980 for invention of DNA-sequencing-technology*



gene technology - basics

- *Significant properties of the DNA-molecule:*
 - *Sequence of different bases = information memory*
 - *can replicate itself, thereby conserving the information contained*



gene technology - basics

➤ *Specific properties of the DNA-molecule:*

➤ *DNA-sequencing*

➤ *DNA-replication*



gene technology - basics

➤ *DNA-sequencing: result:*

➤ atggccctgt ggatg'gcgcct cctgcccctg ctggcgcctgc
tggccctctg gggacctgac ccagccgcag cctttgtgaa
ccaacacctg tgcggctcac acctggtgga agctctctac
ctagtgtgcg gggaacgagg cttcttctac acaccaaga
cccgccggga ggcagaggac ctgcaggtgg ggcaggtgga
gctggg’cggg ggccctggtg caggcagcct gcagcccttg
gccctggagg ggtccctgca gaagcgtggc attgtggaac
aatgctgtac cagcatctgc tccctctacc agctggagaa
ctactgcaac tag

➤ *DNA-replication: result:*

➤ *From a single DNA-molecule two identical DNA-molecules are produced (important when cells divide: genetic information is conserved in both cells)*



gene technology - basics

- *Genetic Code: the DNA-molecule contains the genetic information (the genes) and its gespeichert and its operating instructions (gene regulation)*
- *Gene code for proteins (proteins are the most important structural elements in organisms and fulfil „specific tasks“*
 - *enzymes (anabolism, growth, energy generation, metabolism, etc.), collagen (skin, hair), albumin (blood), regulation (erythropoietin (EPO), tissue-plasminogen activator (t-PA), insulin, etc), ...*



gene technology - basics

- *Genetic Code: gene code for proteins*
- *Proteins are comprised of a sequence of 20 different amino acids (underlined: essential amino acids (cannot be made by the human body)):*
 - *Glycine (G), Valine (V), Alanine (A), Leucine (L), Isoleucine (I), Proline (P), Serine (S), Threonine (T), Cysteine (C), Methionine (M), Asparagine (N), Aspartic Acid (D), Glutamine (Q), Glutamic Acid (E), Tryptophan (W), Lysine (K), Arginine (R), Histidine (H), Tyrosine (Y), Phenylalanine (F)*



gene technology - basics

- *Genetic Code: genes code for proteins*
- *Proteins are comprised of a sequence of 20 different amino acids:*
 - *e.g. Glycine-Tyrosine-Methionine-Alanine-Leucine-Tryptophan-Methionine-Arginine-Leucine-Leucine-Proline-Leucine-Leucine-Alanine-Leucine-Leucine-...*
 - *MALWMRLLPLLALL...*



gene technology - basics

- *Genetic Code: genes code for proteins*
- *Each three nucleic acids („base-triplett“) on the DNA define one amino acid residue in the protein:*
- *atggccctgtggatgcgccctcctgcccctg*
- *M A L W M R L L P L*



gene technology - basics

- *Each three nucleic acids („base-triplett“) on the DNA define one amino acid residue in the protein:*

atg gcc ctg tgg atg cgc ctc ctg ccc ctg

➤ *M A L W M R L L P L*



gene technology - basics

- *Genetic Code: Each three nucleic acids („base-triplett“) on the DNA define one amino acid residue in the protein:*



gene technology - basics

- *DNA (gene, information) → proteins (function)*
- *DNA (gene, information, „data carrier“)*
 - ➔ *RNA (ribonucleic acid, „data vehicle“)*
 - ➔ *protein (function)*



gene technology - basics

- *Genes code for proteins*
- *Example: Insulin*
- *Insulin is an essential hormone which is produced in the pancreas (in the „Langerhand Islands“, → „Insulin“)*



gene technology - Insulin

- *Insulin regulates concentration of glucose (sugar) in blood (lowers sugar-concentration)*
- *Blood sugar concentration is the most important signal for liver and muscle cells, whether energy should be taken up or be produced („fuel injector“ in the „engine of life“)*
- *if no or too less insulin is present: diabetes occurs*



gene technology - Insulin

- *Insulin was extracted by Frederick Banting (CA) and Charles Best (CA) 1921 from dog and pig pancreas and successfully administered to diabetes patients → for the first time therapeutic success*
- *Nobel price 1923*



gene technology - Insulin

- ***structure analysis: amino acid sequence, three dimensional form: by Frederick Sanger (GB, Nobel price 1958) and Hans Tuppy (AT)***
- ***chemical synthesis: 1963 (Helmut Zahn)***



gene technology - Insulin

➤ *structure analysis: amino acid sequence:*

➤ MALWMRLLPL LALLALWGPD PAAAFVNQHL
CGSHLVEALY LVCGEFTRGF FYTPKTRREA
EDLQVGQVEL GGGPGAGSLQ PLALEGSLQK
RGIVEQCCTS ICSLYQFTLE NYCN



gene technology - Insulin

- *Problem: Production from animal pancreas is very costly and it is only possible to provide small amounts of insulin; yield from pig pancreas is very low → by far not enough insulin can be provided*
- *less patients receive necessary therapy*
- *1970-1980 shortage in insulin increases*



gene technology - Insulin

- *Since all organisms use the same genetic code:*
- *Provide gene for human insulin and produce protein*
- *Problem: Where is the gene?*
 - *human DNA is 3,7 billion nucleic bases long*
 - *(Insulin-molecule is about 120 amino acids long → is encoded by about 360 nucleic bases)*



gene technology - Insulin

- *Problem: Where is the gene ?*
- *How can I get the gene out of the chromosomes ?*
 - *specific recognition and excision*
- *How can the protein be produced from the gene ?*
 - *efficient cultivation of microorganisms*



gene technology - Insulin

- *Since all organisms use the same genetic code :*
- *Gene for human insulin is provided (is excised by molecular „gene-scissors“ out of the chromosomes)*



gene technology - Insulin

- *Since all organisms use the same genetic code:*
- *Gene for human insulin is provided (is excised by molecular „gene-scissors“ out of the chromosomes)*
- *Gene is brought into fast growing bacteria by a „gene shuttle“*



gene technology - Insulin

- ***Bacteria produce human insulin***
- ***Can be programmed to over-express foreign gene and produce extreme amounts of human insulin and export the insulin into the growth medium***



gene technology - Insulin

- ***high (sufficient) amounts of human insulin can be produced***
- ***all diabetes patients can be treated (insulin sales of more than 20 billion US-\$ per year)***



gene technology - Insulin

- *1982: „recombinant“ (i.e. produced with re-combined) insulin is the first drug on the market which was produced by gene technology*
- *Gene technology has enabled to provide sufficient amounts of human insulin*



gene technology – other drugs

- ***Erythropoietin – EPO***
- ***increases production of red blood cells:
essential for survival of dialysis and tumour
patients***



gene technology – other protein drugs

- ***vaccines, hormones, antibodies, tumour medicaments, blood products (factor VIII)***
- ***Produktion in bakteria, yeasts***
- ***Produktion in cell cultures***
- ***Produktion in plants***
- ***Produktion in animals***



Biotech's „Billion Dollar Babies“

<i>Product name</i>	<i>turnover 2004 (M)</i>	<i>turnover 2005 (M)</i>
<i>Enbrel</i>	<i>\$2,580</i>	<i>\$3,657</i>
<i>Remicade</i>	<i>\$2,891</i>	<i>\$3,477</i>
<i>Procrit</i>	<i>\$3,589</i>	<i>\$3,324</i>
<i>Aranesp</i>	<i>\$2,500</i>	<i>\$3,273</i>
<i>Rituxan</i>	<i>\$2,963</i>	<i>\$3,154</i>
<i>Epogen</i>	<i>\$2,600</i>	<i>\$2,455</i>
<i>Neulasta</i>	<i>\$1,700</i>	<i>\$2,288</i>
<i>Gleevec</i>	<i>\$1,634</i>	<i>\$2,170</i>
<i>Epogin/NeoRecormon</i>	<i>\$1,826</i>	<i>\$1,710</i>
<i>Herceptin</i>	<i>\$1,259</i>	<i>\$1,629</i>





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recombinant proteins

- *The production of recombinant proteins is very complex*
 - *it often leads to heterogeneous mixtures of similar (but not identical) proteins*
 - *Each protein entity in the mixture is characterized by specific physical, chemical and biological properties*
 - *high standards for establishment of clinical safety and efficacy to guarantee a successful treatment*



recombinant proteins

- *The production of recombinant proteins is very complex*
 - *high standards for establishment of clinical safety and efficacy to guarantee a successful treatment*
 - *even subtle, apparently trivial manufacturing changes may lead to alterations of product characteristics and thus to substantial differences in the clinical properties of a product.*



recombinant proteins – t-PA as an example

- ***Tissue plasminogen activator (abbreviated PLAT or t-PA) is a secreted serine protease which converts the proenzyme plasminogen to plasmin, a fibrinolytic enzyme. Plasminogen is synthesized as a single chain which is cleaved by PLAT into the two chain disulfide linked plasmin***
- ***sold under “Ateplase”***



recombinant proteins – t-PA as an example

➤ *recombinant production of t-PA can lead to heterogeneous expression products („microheterogeneity“):*

➤ *Modifications which have been experimentally observed and described:*

- *single/two chain ratio:* *2 possible variants*
- *N-terminal sequence* *1 possible variants*
- *N-glycosylation at Asn117* *7 possible variants (6 different oligosaccharides + unglycosylated)*



recombinant proteins – t-PA as an example

- *recombinant production of t-PA can lead to heterogeneous expression products („microheterogeneity“):*
- *Modifications which have been experimentally observed and described:*
- *Total possible variants: $1,09 \times 10^9 =$
1 billion variants*



recombinant proteins – EPO as an example

- ***the „EPO patent wars“:***
- ***Amgen vs. Genetics Institute***
- ***EP 0 148 605 B1 vs. EP 0 205 564 B1***
- ***US 4,703,008 vs. US 4,677,195***



the EPO patent wars

- *Amgen vs. Genetics Institute*
- *Amgen vs. Hoechst Marion Roussel*
- *Amgen vs. Chugai*
- *Amgen vs. Roche*
- *Amgen vs. TKT*



the EPO patent wars

- *Amgen vs. Genetics Institute*
- *Amgen (Kirin, Johnson & Johnson, Ortho, Janssen Cilag)*
- *Genetics Institute (Chugai, Roche (after Boehringer Mannheim))*
- *TKT (Aventis (after HMR))*



the EPO patent wars

- *Amgen's US 4,703,008 (against EPO drug producers)*
- *“7. A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding a polypeptide having an amino acid sequence sufficiently duplicative of that of erythropoietin to allow possession of the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells, and to increase hemoglobin synthesis or iron uptake”*



the EPO patent wars

- *Amgen's US 5,955,422 (against EPO drug sellers)*
- *1. A pharmaceutical composition comprising a therapeutically effective amount of human erythropoietin and a pharmaceutically acceptable diluent, adjuvant or carrier, wherein said erythropoietin is purified from mammalian cells grown in culture*



the EPO patent wars

- *Amgen's US 5,756,349 (against TKT)*
- *1. Vertebrate cells which can be propagated in vitro and which are capable upon growth in culture of producing erythropoietin in the medium of their growth in excess of 100 U of erythropoietin per 10^6 cells in 48 hours as determined by radioimmunoassay, said cells comprising non-human DNA sequences which control transcription of DNA encoding human erythropoietin*



the EPO patent wars

- *Amgen's EP 0 148 605 A (as filed)*
- *“1. A purified and isolated polypeptide having part or all of the primary structural conformation and one or more of the biological properties of naturally occurring erythropoietin and characterized by being the product of procaryotic or eucaryotic expression of an exogenous DNA sequence”*



the EPO patent wars

- ***Amgen's EP 0 148 605 B1 (as granted)***
- ***"19. A recombinant polypeptide having part or all of the primary structural conformation of human or monkey erythropoietin as set forth in table VI or table V or an allelic variant or derivative thereof possessing the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells and to increase hemoglobin synthesis or iron uptake and characterized by being the product of eukaryotic expression of an exogenous DNA sequence and which has higher molecular weight by SDS-PAGE than erythropoietin isolated from urinary sources"***



the EPO patent wars

- *Amgen's EP 0 148 605 B1 (as granted)*
- *EPO: Discovery (unpatentable) or Invention (patentable) ?*
- *Novelty:*
 - *over the gene and gene product present in any human body*
 - *over u-EPO from urine of patients*



the EPO patent wars

- *Novelty over u-EPO from urine of patients:*
 - *u-EPO was not successful in a (small) clinical trial*
 - *partial sequence (first 26 amino acids) contains errors (2 residues)*



the EPO patent wars

- *Amgen's EP 0 148 605 B1 (as granted)*
- *disclosure sufficient („any allelic variant or derivative thereof“)?*
- *deposit necessary?*
- *Clarity („being the product of eukaryotic expression....“)?*



the EPO patent wars

- *Amgen's US 4,703,008*
- *Novelty, non-obviousness, enablement, written description, etc.*
- *First inventor ?*



the EPO patent wars

- *Biosimilars for EPO (or t-PA):*
- *final claim scope not evident for a long time (even after grant; opposition, national infringement proceedings, interference proceedings)*
- *differs from country to country*
- *„designing around“ ?*
- *freedom to operate*



Biosimilars (for EPO or t-PA)

- ***Microheterogeneity***
 - ***„Biosimilar“ or „Biodifferent“ ?***
- ***Patentability of Biosimilars***
 - ***Novelty***
 - ***Inventive Step***
 - ***Dependence from Originals ?***





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