

# Life Sciences seminar & Bird & Bird

Monoclonal Antibodies:  
Dawn of a New Era

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# Welcome

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# MAbs: How to protect them using patents and SPCs

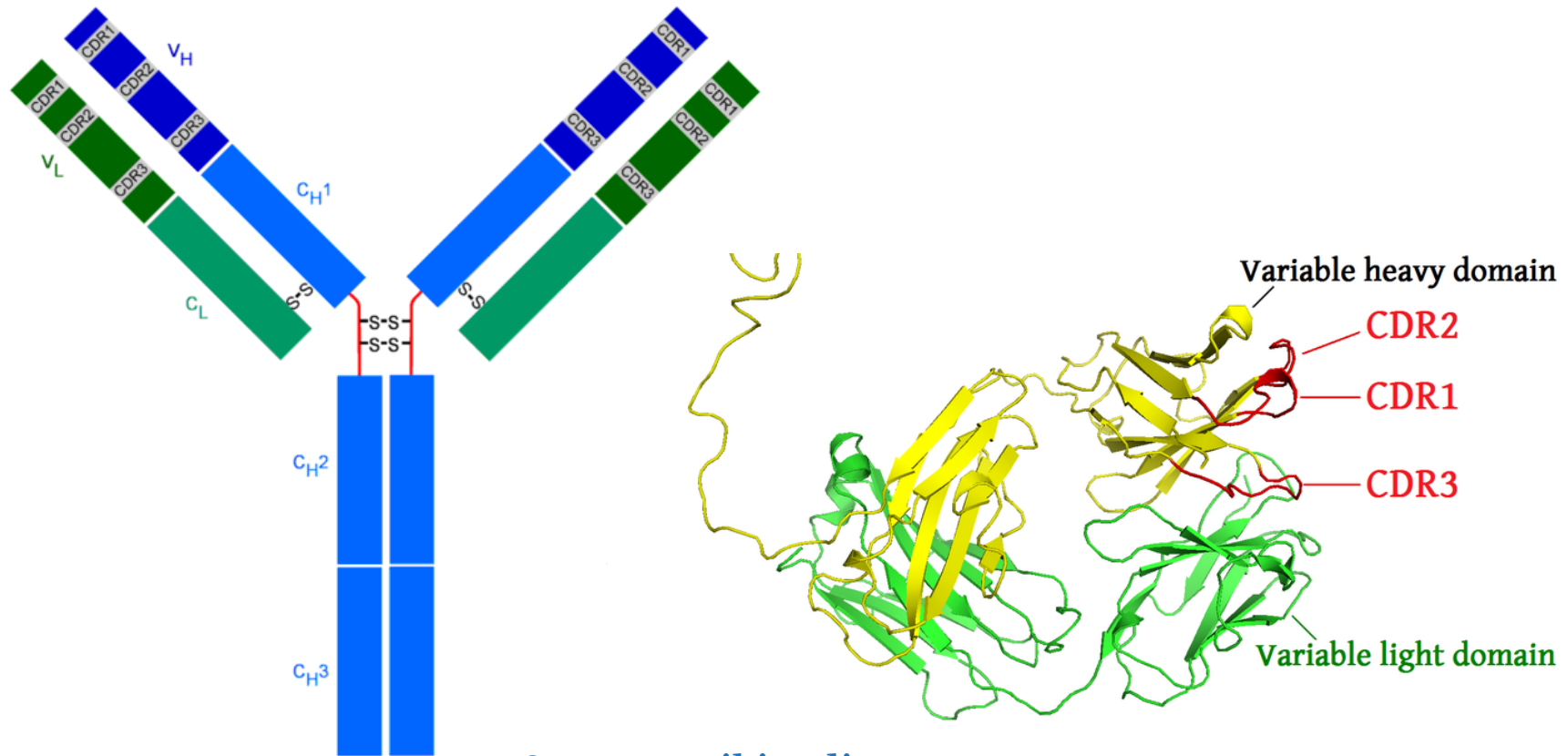
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# Background...

# MAbs – Technical background: Structure

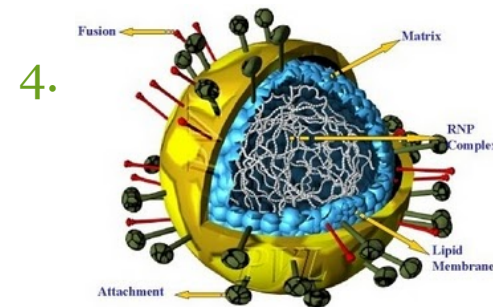
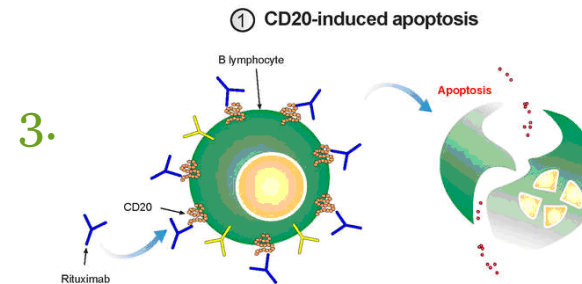
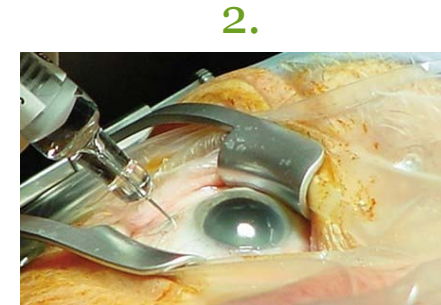
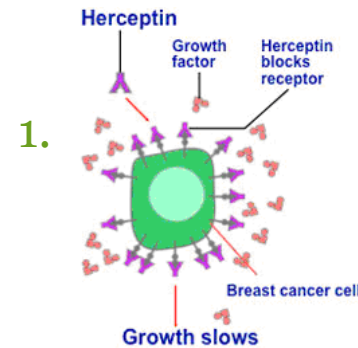


Source: Wikipedia

# mAbs – Technical background: Function

## Examples for modes of action

1. Binding to growth factor-receptors (Trastuzumab – Herceptin)
2. Binding to growth factors (Ranibizumab – Lucentis)
3. Binding to cancer cell – antibody-dependant cell-mediated cytotoxicity (Rituximab – MabThera)
4. Binding to viral protein (Palivizumab – Synagis)



# mAbs – Technical background: Function

## Examples for therapeutic indications

- Cancer treatment
  - Rituxan (Rituximab): 4.9 B USD\*
  - Herceptin (Trastuzumab): 4.3 B USD\*
- Autoimmune diseases
  - Remicade (Infliximab): 5.0 B USD\*
- Alzheimer's disease
  - Lucentis (Ranibizumab): 1.2 B USD\*
- Macula degeneration
  - Synagis (Palivizumab ): 1.1 B USD\*
- Virus infections
- Sepsis

# Patent protection...



# mAbs – What to protect?

## Examples for patentable inventions in the area of antibodies

1. Methods for obtaining / producing antibodies
2. Antibody, defined structurally
3. Antibody, defined functionally
4. Antibody, defined by a combination of functional and structural features
5. Pharmaceutical use of an antibody
6. Administration form of an antibody (e.g. dosage, patient group)

# mAbs - Patents: General issues

- Art. 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. (...)
- Art. 83 EPC
  - The European patent application shall disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

# Patent protection: method claims...

# mAbs - Patents: Method claims

- Method claims can have a broad scope of protection.
- Some process patents are basic patents for several SPCs.
- Of particular relevance if antibody is produced in a country in which patent protection exists.
- Protection conferred by a process claim also extends to the products directly obtained by such processes.

## Limitations

- Of limited value if claim refers to an early step in antibody production or if alternative processes are available; sometimes narrow scope of protection

# mAbs - Patents: Method claims

## Examples

- Methods for obtaining a certain category of antibodies such as monoclonal antibody, chimeric antibody, humanised antibody
5. A method for producing a filamentous bacteriophage particle displaying at its surface a binding molecule specific for a particular target epitope or antigen, which method comprises the steps of:

producing a population of filamentous bacteriophage particles displaying at their surface a population of binding molecules having a range of binding specificities, wherein the binding molecules are Fab antibody molecules able to bind target epitope or antigen, and wherein each filamentous bacteriophage particle contains a phagemid genome comprising nucleic acid with a nucleotide sequence encoding the binding molecule expressed from the nucleic acid and displayed by the particle at its surface;

selecting for a filamentous bacteriophage particle displaying a binding molecule with a desired specificity by contacting the population of filamentous bacteriophage particles with a target epitope or antigen so that individual binding molecules displayed on filamentous bacteriophage particles with the desired specificity bind to said target epitope or antigen.

(human antibody: EP 774 511 B1  
by Cambridge Antibody  
Technology Limited)

# mAbs - Patents: Method claims

## Example

- Purification methods

“A method of preparing a purified, virally inactivated IgG preparation from a starting solution comprising IgG and contaminants, the method comprising the steps of: a) adjusting the pH of the starting solution to 3.8 to 4.5 to produce an intermediate solution; b) adding caprylate ions to the intermediate solution and adjusting the pH (...), c) (...), d) (...), e) (...).” (simplified from T 1653/07)

# Patent protection: product claims...

# mAbs - Patents: Product claims

- MAb patentable if directed against target X and if X is novel and inventive.
- If target X is known, not patentable, if standard method for production of antibody is used; very often only patentable if unexpected property.

Example for monoclonal antibodies: T 735/00, section 26:

*“In 1989, the priority year of the patent in suit (...), the preparation of monoclonal antibodies was a matter of routine experiment. Therefore, no inventive merit can be seen in the method as such to provide the monoclonal antibodies. Further, the search as such for monoclonal antibodies (...) is not inventive either because there is an incentive in this art to look for useful antibodies. (...) The case law in this field acknowledges inventive step if and when there is evidence that a claimed monoclonal antibody prepared by routine methods shows unexpected properties (...)”*

This requires narrow claims, so that all of the claimed antibodies have the unexpected property.



# mAbs - Patents: Product claims

- Example of product claim categories\*

<b>Epitope claim</b>	<b>mAb binding to amino acids xx to yy on target</b>
Cross-blocking claims	mAb inhibiting binding of claimed reference mAb to target
MoA claim	mAb inhibiting binding of ligand to target or mAb inhibiting (or stimulating) target-mediated signalling
Affinity-based claim	mAb binding to target X with an affinity of at least ...
Potency based claim	mAb against target X with a potency in a specified assay of at least ....
Sequence based claim	mAb having at least ... % sequence identity with a claimed mAb
CDR based claim	mAb having the following CDR's: ....

\*by courtesy of Frank Landolt, Ablynx

# mAbs - Patents: Product claims

- Example for an inventive antibody (for the treatment of Alzheimer's disease):

“A humanized antibody, or fragment thereof, comprising:

a. a light chain comprising three light chain complementarity determining regions (CDRs) having the following amino acid sequences:

light chain CDR1: (SEQ ID NO:1); or (SEQ ID NO:15)

light chain CDR2: (SEQ ID NO:2)

and, light chain CDR3: (SEQ ID NO:3)

and a light chain framework sequence from a humanized immunoglobulin light chain; and

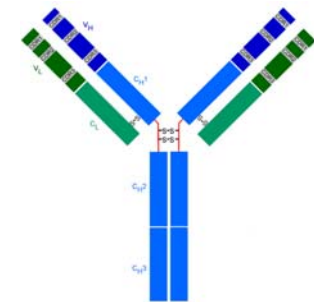
b. a heavy chain comprising three heavy chain CDRs having the following amino acid sequences:

heavy chain CDR1: (SEQ ID NO: 4)

heavy chain CDR2: (SEQ ID NO: 5); or (SEQ ID NO: 16)

and, heavy chain CDR3: (SEQ ID NO: 6)

and a heavy chain framework sequence from a humanized immunoglobulin heavy chain.”



# mAbs - Patents: Product claims

- Example for an inventive antibody (high affinity antibody that binds human TNF $\alpha$ ):

1. An isolated human antibody, or antigen-binding portion thereof, with the following characteristics: a) dissociates from human TNF $\alpha$  with a  $K_{\text{off}}$  rate constant of  $1 \times 10^{-3} \text{ s}^{-1}$  or less, as determined by surface plasmon resonance; b) has a light chain CDR domain comprising the amino acid sequence of (SEQ ID NO:3), or modified from (SEQ ID NO:3) by a single alanin substitution at position 1, 4, 5, 7 or 8 or by 1-5 conservative amino acid substitutions at position 1, 3, 4, 6, 7, 8 and/or 9; c) has a heavy chain CDR domain comprising the amino acid sequence of (SEQ ID NO:4) or modified from (SEQ ID NO:4) by a single alanin substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 or by 1-5 conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12.

# mAbs - Patents: Product claims

- Example for patentable antibody (diagnosis of prion proteins):

1. An antibody binding exclusively to a Prp<sup>sc</sup> isoform of the prion protein and recognising the epitope having the three-dimensional confirmation provided by the protein sequence

Cys-Ile-Thr-Gln-Tyr-Glu-Arg-Glu-Ser-Gln-Ala-Tyr-Tyr

of the Prp<sup>sc</sup> isoform of the prion protein while not binding to the Prp<sup>c</sup> form, obtainable by a method comprising the step of ionising an animal with a peptide consisting of the amino acid sequence

Cys-Ile-Thr-Gln-Tyr-Glu-Arg-Glu-Ser-Gln-Ala-Tyr-Tyr

or

Cys-Ile-Thr-Gln-Tyr-Gln-Arg-Glu-Ser-Gln-Ala-Tyr-Tyr.

(upheld in T 0030/09)

# mAbs - Patents: Conclusion on product claims

- If target is known, monoclonal (chimeric, humanised, human...) antibodies against target are usually not inventive.
- Antibodies can be inventive if they have unexpected properties; scope of protection usually limited, otherwise not enabled or inventive in the whole area claimed.

# Patent protection: Pharmaceutical composition...

# mAbs – Patents: Pharmaceutical composition

- Claims on pharmaceutical compositions can be inventive if it was not expected that antibodies against a certain target might be useful in therapy.

- Example for an inventive claims:

“A **pharmaceutical** composition containing a human monoclonal antibody that binds to human tumour necrosis factor  $\alpha$  on human cell surfaces and is capable of inhibiting LPS-induced human tumour necrosis factor  $\alpha$  secretion by human monocyte cells.” (T 601/05)

# Patent protection: Administration of mAbs ...



# mAbs – Patents: Administration forms

- Other potential claim categories
  - Dosage regimens: G 2/08
  - Formulations
  - Definition of patient group
  - ...
- Potentially a very broad of protection

Example for a dosage regimen:

“Use of the anti-ErbB-antibody huMab 4D5-8 in the manufacture of a medicament for use in a method for treating a human patient diagnosed with breast cancer characterised 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.**”

(EP 1 210 115, revoked in first instance opposition proceedings)

# Patent protection: Post-filing evidence...

# mAbs – Post-filing evidence

- Art. 83 EPC

“The European patent application shall disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.”

- The invention has to be enabled and inventive within the whole area claimed (T409/91; T435/91).
- Consequence: If a group of compounds is claimed functionally (having the property xy), there must be enough information in the patent at issue and/or the prior art that enables the person skilled in the art to essentially arrive in all compounds claimed. Moreover, substantially all compounds claimed must have the advantageous properties.

# mAbs – Post-filing evidence

- Post-filing evidence might not be taken into account.
- T 601/05 (confirming T 609/02):
  - “As a consequence under Art. 83, unless this is already known to the skilled person at the priority date, the application must disclose the suitability of the product to be manufactured for the claimed therapeutic application.”
- Consequence: Relevant information should be in the patent application; clinical trials not required but are ideal in supporting the claim (attention: clinical trials can be novelty-destroying)

# Supplementary protection certificate

# mAbs – Supplementary protection certificate



SPC: Date of first market authorisation  
- Filing date of basic patent  
- 5 years

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Duration of SPC (max. 5 years)



# mAbs – Supplementary protection certificate

- Party A: Patent



Party A may ask for an SPC based on the market authorisation of party B.

Consequence:



Options for party B:

- Attacking patent of party A

OR

- Waiting for market authorisation until patent lapses

# mAbs – Supplementary protection certificate

- To obtain a valid SPC, the basic patent must specify the active ingredient in the wording of the claim

“1. Art. 3(a) of Regulation (EC) No. 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal products must be interpreted as precluding the competent industrial property office of a member state from granting a supplementary protection certificate relating to active ingredients which are not **specified in the wording of the claims of the basic patent** relied on in support of the application for such a certificate.”



# mAbs – Conclusions

## Checklist

- Selection of appropriate claim categories ✓
- Specify the most important embodiment in at least one claim ✓
- Evidence in the application as originally filed of improved properties /unexpected advantages; in particular for the most important embodiment ✓
- For broader claims enough evidence in the application as originally filed proving that substantially all compounds covered by the scope of protection have the advantages / unexpected property ✓

# Thank you

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# Infringement Issues Relating to MAbs

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# Some mAb patent disputes in the English Courts

- Synagis (INN Palivizumab)
  - *Celltech Chiroscience v Medimmune* (2003-2005)
    - EP 0 626 390 B (DE)
    - US patent corresponding to EP 0 626 390 B
      - Infringement
- Benlysta (INN Belimumab) (2008 on)
  - *Eli Lilly v Human Genome Sciences*
    - EP 0 939 804
      - Validity
- Lucentis (INN Ranibizumab) (2011 on)
  - *Medimmune v Novartis*
    - EP 0 774 511, EP 2 055 777
      - Infringement
      - Validity
      - Validity of SPC assuming infringement

# Synagis (INN Palivizumab)

- US Claim
  - “1. A CDR-grafted antibody heavy chain having a variable region domain comprising acceptor framework and donor antigen binding regions wherein the framework comprises donor residues at at least one of positions 6, 23 and/or 24, 48 and/or 49, 71 and/or 73, 75 and/or 76 and/or 78 and 88 and/or 91.”
- AA at 23 of Synagis not serine
- Application of US law on doctrine of equivalents and file wrapper estoppel

# Synagis (INN Palivizumab)

- EP Claim
  - “1. An antibody molecule having affinity for a predetermined antigen and comprising : CDR-grafted antibody heavy chain wherein,... residues 31 to 35, 50 to 65 and 95 to 102 are donor residues; and a complementary light chain, said CDR-grafted heavy chain having a variable domain comprising acceptor antibody heavy chain framework residues and donor antibody heavy chain antigen-binding residues, said donor antibody having affinity for said predetermined antigen, wherein, ... in said CDR grafted heavy chain, amino acid residues 23, 24, 26 to 30 and 49 at least are additionally donor residues, provided that ...”
- AA at 23 of Synagis not serine
- Application of DE law on equivalents

# Benlysta (INN Belizumumab)

- *Eli Lilly v Human Genome Sciences*
  - EP 0 939 804
    - High Court
      - Infringement not in issue
      - Invalid
        - Lack of industrial applicability
        - Lack of inventive step
        - Insufficient
    - Court of Appeal
      - Invalid for lack of industrial applicability
    - Supreme Court
      - Reversed Court of Appeal on industrial applicability
      - Remitted most other aspects of case

# Benlysta (INN Belizumumab)

- Antibody claims of EP 0 939 804 as proposed amended
  - 15. An isolated antibody or portion thereof that binds specifically to the Neutrokin- $\alpha$  portion of a Neutrokin- $\alpha$  polypeptide having the amino acid sequence encoded by the nucleic acid molecule of any one of claim 1 or the Neutrokin- $\alpha$  portion of a Neutrokin- $\alpha$  polypeptide of claim 11 or 12 .
  - 16. The antibody or portion thereof of claim 15 which is selected from the group consisting of: (a) a monoclonal antibody; (b) a polyclonal antibody; (c) a chimeric antibody; (d) a Fab fragment; and (e) an F(ab')<sub>2</sub> fragment.
  - 17. The antibody or portion thereof of any one of claims 15 to 16 which is labeled.
  - 18. The antibody or portion thereof of claim 17 which is labeled with a label selected from the group consisting of: (a) an enzyme label; (b) a radioisotope; (c) a fluorescent label; and (d) biotin.
  - 19. The antibody or portion thereof of claim 18 wherein the label is a radioisotope selected from the group consisting of ....
  - 20. A pharmaceutical composition comprising the nucleic acid molecule of any one of claims 1 to 4 , the polypeptide of any one of claims 11 to 14 , or the antibody or portion thereof of any one of claims 15 to 19 and optionally, a pharmaceutically acceptable carrier.



# Lucentis (INN Ranibizumab)

- *Medimmune v Novartis*
  - EP 0 774 511 B , EP 2 055 777 B
    - Infringement
      - On a direct product of infringing process theory
        - Process did not infringe
        - But Ranibizumab would have been a direct product if process had infringed
    - Invalid
      - Lack of inventive step
      - [Insufficiency and Added Matter attacks failed]
    - Validity of SPC assuming infringement?

# Lucentis (INN Ranibizumab)

- Claim 5 of EP 0 774 511 B to
  - “[1] A method for producing a filamentous bacteriophage particle displaying at its surface a binding molecule specific for a particular target epitope or antigen, which method comprises the steps of:
  - [2] producing a population of filamentous bacteriophage particles displaying at their surface a population of binding molecules having a range of binding specificities;
  - [3] wherein the binding molecules are Fab antibody molecules able to bind target epitope or antigen;
  - [4] and wherein each filamentous bacteriophage particle contains a phagemid genome comprising nucleic acid with a nucleotide sequence encoding the binding molecule expressed from the nucleic acid and displayed by the particle at its surface;
  - [5] selecting for a filamentous bacteriophage particle displaying a binding molecule with a desired specificity by contacting the population of filamentous bacteriophage particles with a target epitope or antigen;
  - [6] so that individual binding molecules displayed on filamentous bacteriophage particles with the desired specificity bind to said target epitope or antigen.”

# Lucentis (INN Ranibizumab)

- Claim 1 of EP 2 055 777 B to
  - “[1] A method for producing a binding molecule specific for a particular target epitope or antigen, which method comprises:
  - [2] producing a population of filamentous bacteriophage particles displaying at their surface a population of binding molecules having a range of binding properties,
  - [3] wherein the binding molecules comprise antibody antigen binding domains for complementary specific binding pair members,
  - [4] wherein the binding molecules are displayed at the surface of the filamentous bacteriophage particles by fusion with a gene III protein of the filamentous bacteriophage particles,
  - [5] and wherein each filamentous bacteriophage particle contains nucleic acid encoding the binding molecule expressed from the nucleic acid and displayed by the particle at its surface;
  - [6] selecting for a filamentous bacteriophage particle displaying a binding molecule with a desired binding property by contacting the population of filamentous bacteriophage particles with a particular target
  - ....

# Lucentis (INN Ranibizumab)

- Claim 1 of EP 2 055 777 B to
  - .....
  - [7] so that individual binding molecules displayed on filamentous bacteriophage particles with the desired binding property bind to said target;
  - [8] separating bound filamentous bacteriophage particles from the target;
  - [9] recovering separated filamentous bacteriophage particles displaying a binding molecule with the desired binding property;
  - [10] isolating nucleic acid encoding the binding molecule from separated filamentous bacteriophage particles;
  - [11] inserting nucleic acid encoding the binding molecule, or a fragment or derivative thereof with binding specificity for the target, in a recombinant system; and
  - [12] producing in the recombinant system separate from filamentous bacteriophage particles a molecule with binding specificity for the target,
  - [13] wherein the molecule is said binding molecule or a fragment or derivative thereof with binding specificity for the target.”

# Lucentis (INN Ranibizumab)

- The SPC issue - applying C-322/10 *Medeva* and C-422/10 *Georgetown*
- Arnold J in *Novartis v Medimmune* [2012] EWHC 181 (10 February 2012)
  - "(53) In my view, counsel for MedImmune is also correct to say that the test laid down by the Court of Justice in *Medeva* and its progeny is unclear save in its rejection of the infringement test in combination cases. In particular, it is unclear precisely what is meant by "specified (or identified) in the wording of the claims". Does this mean that it is sufficient for the product to fall within the scope of the claim on its true construction, or is something more required and if so what? For example, is it sufficient, say, for the claim to incorporate a Markush formula which covers a large number of compounds one of which is the product in respect of which an SPC is sought? Is it sufficient for the product to be defined in functional terms? Even in combination cases, it is not clear to me how the test enunciated by the Court should be applied in a case like *Gilead*. Regrettably, therefore, it is inevitable that there will have to be further references to the CJEU to obtain clarification of the test."
- But no such reference in this case
  - Quite clear that Ranibizumab is not "specified (or identified)" in the claims, even had it infringed

# Closing thoughts

- High variability as to the nature of the claims that can protect mAbs
  - More easy generally to establish infringement of functionally defined claims
- However, given that earliest patents protecting mAbs will often have expired by the end of RDP protection for the reference mAb
  - Many real life controversies as to biosimilar MAbs will instead concern traditionally drawn patents to second etc medical uses
- SPC issues
  - Many patents that a mAb infringes will not constitute valid basic patent for an SPC on such mAb
  - Is a biosimilar mAb the same "product" as the reference mAb?
    - If not how can a biosimilar mAb infringe an SPC on the reference mAb?

# Thank you

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# New US biosimilar guidelines: Compared to the EU

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# Overview

- Chemicals vs. Biologics-bioequivalence and comparability
- Fastest growing sector in Pharma
- Biosimilars authorised to date
- Biosimilars in Europe-
  - Legal basis for authorisation
  - Draft Guideline for Biosimilars of Monoclonal Antibodies
  - Guideline on Quality-Draft of Revision released 24/5/12
- Biosimilars in US-Biologics Price Competition and Innovation Act of 2009 (BPCIA) and Draft Guidelines 2/2012
- Summary

# Generics: Chemicals vs Biologics

- Chemical products are created by mixing together well-defined chemicals under controlled circumstances. The resultant product can be analysed in a laboratory to determine that it is identical to that of an originator/innovator. Therefore easy to compare to reference product for bioequivalence.
- Biological products are alive (e.g., vaccines, mAbs, recombinant proteins). They are created by engineering living cells to produce the desired protein or antibody. As the living cells are unique, the products so produced can never be absolutely identical to that of an originator/innovator.
- “Biological medicinal products can be defined therefore largely by reference to their method of manufacture.”

# Biopharmaceuticals: Biogenerics, Biosimilars and Follow-on Biologics

- Biological pharmaceuticals manufactured by biotechnology methods, i.e., involving the use of living organisms (cells, bacteria, yeast)
- Biopharmaceuticals are defined by their manufacturing processes. If they originate in different cell lines, they are distinct, i.e. **not bioequivalent**. As such, there is ***technically no such thing*** as a biogeneric, though the term is still sometimes used.
- It is however, possible (and required) to demonstrate comparability to the originator's product, the term "biosimilar" is used in Europe, while the terms "biosimilar" and "follow-on biologic" have been used by the FDA, but notably all the draft guidelines in February adopted EU term 'Biosimilar'

# Relevance of this lack of “identity”

- Immunogenicity-significant danger to patients
- Very difficult to develop products from a different cell line-only very well-funded and sophisticated companies can manufacture and support biotech development.
- Very minor changes in the manufacturing process (or primary packaging) can result in profound differences in safety and efficacy of the product (e.g., Eprex)
- Extensive post-marketing surveillance is required, and effects “Interchangeability” by physicians and pharmacists (US).
- Perhaps particularly relevant in case of mAbs-due to multi-determined (and sometimes poorly understood) modes of action

# Why is this important?

- Biologics are the fastest-growing class of medicines
- In 2009 approximately \$60B spent on biologics in U.S.
- According to *Global Industry Analysts*, global biologics market projected to be worth \$150B by 2015
- According to *Datamonitor*, global biosimilar market projected to be worth \$3.7B by 2015

# Biosimilars to date

## EU approvals

- Abseamed-epoietin alfa
- Binocrit-epoietin alfa
- Biograstim-filgrastim
- Epoietin Alfa Hexal-epoietin alfa
- Filgrastim Hexal-filgrastim
- Filgrastim Ratiopharm-filgrastim
- Nivestim-filgrastim
- Omnitrop-somatropin
- Ratiograstim-filgrastim
- Retacrit-epoietin zeta
- Silapro-Stada-epoietin zeta
- Tevagrastim-filgrastim
- Valtropin-somatropin
- Zarzio-filgrastim

# Regulatory Development

- EU
  - Monoclonal Guideline
  - Guideline on Similar Biological Medicinal Products containing biotechnology-derived proteins as active ingredient: Quality issues (revision 1) (EMA/CHMP/BWP/247713/2012) released for comment until November 2012, on 24 May), which will replace EMEA/CPMP/BWP/49348/2005)
- US
  - Biologics Price Competition and Innovation Act (BPCIA)-3/2010
  - Draft Guidelines issued in February 2012:
    - Scientific Considerations in Demonstrating Biosimilarity to a Reference Product
    - Quality Considerations in Demonstrating Biosimilarity to a Reference Product
    - Biosimilars: Questions and Answers regarding Implementation of the BPCIA of 2009

# Eporex and PRCA

- J & J (Ortho Biotech/Janssen-Cilag) altered its manufacturing process (and presentation) of erythropoietin marketed in the EU, Eprex.
- On the market for 10 years, and in 2002, PRCA (pure red cell aplasia) was identified in patients with CRF and/or CRI that had received Eprex SC. MA in that indication suspended in EU for nearly 4 years.
- There were over 65 variations in the EU to the original Eprex registration.
- Significance is that problems of the RMP effect profoundly effect subsequent developments and regulatory strategies (specific exception made for Binocrit from the EPO development guideline in this case-Eprex was not used as a comparator in SC studies in renal anaemia patients and therefore no second randomised, parallel group clinical trial could be conducted).
- Regulatory authorities far more strict on safety issues and also in imposing post-marketing obligations-specifically addressed in BWP Draft Revision of general Biosimilar Guideline issued 5/12.



# Biosimilars in the EU

# Biosimilar MA Route-EU Legal Basis

- Amendments to Annex I of Directive 2001/83 (2003/63/EC)
- CPMP Guidance Notes (2003)
- Amendments to text of Directive 2001/83 (2004/27/EC)
- Various CHMP Guidelines in 2005-2007, particularly:
- "Guideline on similar biological medicinal products containing biotechnology –derived proteins as active substance: non-clinical and clinical issues (EMEA/CPMP/42832/05).
- Various Product-specific CHMP Guidelines (G-CSF, Somatropin, human soluble insulin, Erythropoietins, alpha interferon and LMW heparins (draft))
- Guideline on Biosimilars of Monoclonal Antibodies (discussed below)

# Amendment to Directive 2001/83 (2003/27/EC)

## Article 10.4

“Where a biological medicinal product which is similar to a reference biological product does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided. The type and quantity of supplementary data to be provided must comply with the relevant criteria stated in Annex I and the related detailed guidelines. The results of other tests and trials from the reference medicinal product’s dossier shall not be provided.”

In force as from 30 October 2005.

# Draft Guideline on biosimilar medicines containing monoclonal antibodies

- Released for Consultation 26 November 2010 until 31 May 2010
- Addresses Non-clinical, Clinical and Post-marketing issues (both PV and post-marketing clinical requirements)
- Quality issues are **not** addressed-rather the reader is referred to existing Guidances EC/CHMP/49348/05 (which is soon to be revised by EMA/CHMP/BWP 247713/2012) and CHMP/BWP/15753/07
- To be read in conjunction with the general guidelines set forth in the "Guideline on similar biological medicinal products containing biotechnology –derived proteins as active substance: Non-clinical and clinical issues (EMA/CPMP/42832/05)

# Non-clinical development for biosimilar mAbs

- Scientific Advice strongly recommended
- Risk-based approach to be evaluated on a case-by-case basis in the choice and extent of *in vitro* and *in vivo* studies
- Determination as to whether *in vivo* studies are required will depend on the availability of a relevant animal model-large comparative tox studies in non-human primates are not recommended, though, due to the specificity of mAbs, the relevant species for tox studies will in most cases be a non-human primate.
- If the conduct of the *in vitro* studies raises no specific safety concerns, it is possible that no *in vivo* animal studies will be required.

# Clinical development of biosimilar mAbs

- Again, close collaboration with EMEA through scientific advice is strongly recommended.
- A comparative PK study in a sufficiently sensitive and homogeneous population forms an integral part of biosimilar mAb development, usually in a parallel-group design due to the long half-life of mAbs and potential interference of immunogenicity.
- PK data can be used to extrapolate on both safety and efficacy to other indications-generally indication most sensitive to immunogenicity must be studied.
- Dose-concentration-response studies will always be required
- Specific considerations for extrapolation to additional oncological indications.
- Focus of exercise is to demonstrate similar efficacy and safety relative to the reference product, not to patient benefit, *per se*.

# Biosimilar monoclonals in development\*

\*as of September 10, 2011 from Citeline's Pipeline database

Company	Location	# Biosimilar Mabs	Highest Development Status
BioXpress	Switzerland	16	Preclinical
Gene Techno Science	Japan	6	Preclinical
Zydus Cadilla	India	5	Preclinical
PlantForm	Canada	3	Preclinical
BioCad	Russia	3	Preclinical
Celltrion	South Korea	2	Phase 3
LG Life Sciences	South Korea	2	Preclinical
Gedeon Richter	Hungary	2	Preclinical
Cerbios-Pharma	Switzerland	1	Preclinical
Hanwha Chemical	South Korea	1	Preclinical
PharmaPraxis	Brazil	1	Preclinical
Probiomed	Mexico	1	Phase 3
Samsung BioLogics	South Korea	1	Preclinical
Novartis	Switzerland	1	Phase 2
Teva	Israel	1	Phase 2
Zenotech	India	1	Phase 3
Spectrum	US	1	Preclinical
Biocon/Mylan	India/US	1	Preclinical

And the US....



# The Biologics Price Competition and Innovation Act of 2009 (“BPCIA”)

- The Public Health Service Act (PHSA), § 351 governs licensing biologics
- The BPCIA signed into law on March 23, 2010, amended
  - § 351 of the PHSA (42 U.S.C. § 262)
  - § 271(e) of the Patent Act
  - Created a statutory framework for FDA approval of follow-on-biologics (FOB) as biosimilar to or “interchangeable” with reference products

# Outline of the BPCIA

- Changes to PHSA § 351(i) (42 U.S.C. § 262(i))
  - Provides new and amended definitions
- New PHSA § 351(k) (42 U.S.C. § 262(k))
  - Provides regulatory pathway for biosimilar/interchangeable products.
  - Provides RP data exclusivity
- New PHSA § 351(l) (42 U.S.C. § 262(l))
  - Provides patent dispute resolution mechanism

# BPCIA Definition of “Biological Product”

- “...a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, ***protein (except any chemically synthesized polypeptide)***, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings...” (historically, some proteins have been approved as drugs under §505 of the FD & C Act)
- Clarified definitions in February draft guidelines:
  - Protein-any alpha amino polymer with a specific defined sequence greater than 40 amino acids in size
  - Chemically-synthesized polypeptide-any alpha amino acid polymer that is (1) made entirely by chemical synthesis; and (2) is less than 100 amino acids in size
- Transition provision-application for biological must be submitted under §351 of the PHS Act, except that until 23 March 2020, FD & C Act if reference approved under §505, unless there is another biological product approved under §351 of PHS Act that could have served as reference product.

# BPCIA Definition of Biosimilar

- “Biosimilar” means:

“(A) that the biological product is **highly similar** to the reference product notwithstanding minor differences in clinically inactive components; **and**

(B) there are **no clinically meaningful differences** between the biological product and the reference product in terms of the safety, purity, and potency of the product.”

# Determination of biosimilar status under BPCIA

- Establishing “biosimilarity” (42 U.S. § 262(k)(2)(A)(i)(I))
  - Analytical studies demonstrating highly similar to RP
  - Animal studies, including toxicity
  - Clinical study or studies, including immunogenicity, pharmacokinetics, pharmacodynamics, sufficient to demonstrate safety, purity, and potency in one or more approved conditions
  - RP and biosimilar use same mechanism of action to extent mechanism of action is known
  - RP and biosimilar directed to same conditions (biosimilar can be fewer)
  - RP and biosimilar have same route of administration, dosage form, and strength
  - FDA assessment of biological product manufacturing, processing, and packaging sites
- FDA can decide that analytical and/or clinical studies are unnecessary

# Interchangeability under BPCIA-a higher bar

- Biosimilar to RP

**and**

- Can be expected to produce the same clinical result as the RP in any given patient,

**and**

- For a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the RP is not greater than the risk of using the RP without such alteration or switch.

42 U.S.C. § 262 (k)(4)

# What's the benefit of “interchangeability”?

- The interchangeable product “may be substituted for the reference product **without** the intervention of the health care provider who prescribed the reference product.”
- A biosimilar product can only be switched for RP upon physician's instruction

# Exclusivity for Interchangeable Biosimilars

- Exclusivity for first approved “interchangeable” product (of a given RP)
  - No subsequent biosimilar can be found to be interchangeable until the **earliest** of the following:
    - 1 year after first commercial marketing of first interchangeable biosimilar
    - 18 months after final court decision or dismissal with or without prejudice on patents involved in suit against first interchangeable biosimilar
    - 42 months after approval of first interchangeable biosimilar, if patent litigation is still ongoing within the 42-month period or 18 months after such approval, if no patent suit was filed against first interchangeable biosimilar



# Practical Questions??

- What's the risk for “interchangeability”?
  - Are there ethical issues in conducting a “switching study”?
    - Will IRBs (Ethical Committees) approve such studies?
  - Many biosimilars are not dispensed at the pharmacy/and how likely is it that physicians will recommend a switch for a product that has been deemed biosimilar and not interchangeable?
  - Worth the time and money to become “interchangeable” with a 12-year-old product?

# Types of Exclusivity

“EFFECTIVE DATE OF BIOSIMILAR APPLICATION APPROVAL - Approval of an application under this subsection may not be made effective by the Secretary until the date that is 12 years after the date on which the reference product was first licensed under subsection (a)”

“FILING PERIOD – An application under this subsection may not be submitted to the Secretary until the date that is 4 years after the date on which the reference product was first licensed under subsection (a).”

42 U.S.C. § 262(k)(7)(A)-(B)

# Data vs Market Exclusivity-clarified in Draft Guideline

- Data exclusivity: Precludes reliance upon RP data, or, acceptance by FDA, of a BLA under §351 for 4 years from authorisation of RP, but also
- Market exclusivity: Precludes access to RP market, i.e., would permit FDA and biosimilar applicant to access RPS data after expiration of 4-year period but FDA could not approve biosimilar for another 8 years (4 years data + 8 years market exclusivity)

(Compare EU 8+2+1 system for all medicinal products, and US 5 years for other drug products)

# FDA likely to follow EMA lead and establish product-specific guidelines

- Though optional, FDA is likely to issue additional guidelines
  - FDA must allow for public comment period
  - Public would be entitled to provide “input regarding priorities for issuing guidance”
  - Opportunity for RPs to provide information to FDA regarding criteria for Biosimilar approval
    - Requires balance of maintaining any trade secret information with disclosure
    - Known structure of final product
    - Known production issues
    - Known impurities
    - Prior failed attempts

# Strategic Questions regarding BPCIA

- How much time and money is really saved?
- What is the opportunity cost of a biosimilar development relative to a stand-alone development?
- What is the cost in terms of proprietary information exchange required under BPCIA?
- The Reference Medicinal Product issue-clarified significantly by FDA in February (particularly Q and A Guidance) and by EMA in draft guideline 24 May 2012.
- What is the likelihood of obtaining “interchangeable” status?
- What is the benefit of obtaining interchangeability with a product that is already 12 years old?

# Comparisons between US and Europe

- EU Global Authorisation concept has been adopted in US-no “evergreening”
- Data and market exclusivity in EU is clear (8 +2+1 for all products), while politically volatile in US. (Though February draft guidelines clarify somewhat). Biologics and drugs have different data/market exclusivity periods in US.
- US patent-linkage system more difficult to maintain for biologics, which are defined by their method of manufacture
- Product-specific guidelines are laid down in EU (but hindrance has been in uptake at national level, leading to slow market access), but yet to be adopted in US
- EU Monoclonal antibody draft guideline is again setting the worldwide trend
- Reference Product issue substantially clarified: whether it is possible to conduct one set of trials that will satisfy FDA and EMA

# Thank you

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Bird & Bird

# An update on the regulatory framework for MAbs and ATMPs

Brussels

7 June 2012



# Table of contents

- Monoclonal antibodies (MAbs): a glance at the current status of the EU regulatory framework
- Advanced Therapy Medicinal Products
  - The use of cells and tissues
  - Regulation 1394/2007
  - Interaction with tissues and cells legislation
  - Practical considerations and issues
- Closing thoughts

# Monoclonal antibodies (MAbs): a glance at the current status of the EU regulatory framework

# Monoclonal antibodies in the EU pharmaceutical legislation (1)

## Annex I to Regulation 726/2004

- mandatory central procedure for MA applications
- Includes “*medicinal products developed by means of hybridoma and monoclonal antibody methods*”
  - Notice to Applicants (Eudralex vol. 2A, Chapter 4) specifies that this concerns any medicinal product for which a monoclonal antibody is used at any stage in the manufacturing process
- From a regulatory perspective : medicinal products in which MAbs are used have to be authorised through the centralised procedure
  - No significant evolution of the regulatory framework, though important work is in process as to scientific requirements (lots of guidance documents in the making in the EMA –see further)

# Monoclonal antibodies in the EU pharmaceutical legislation (2)

- MAbs are a class of highly innovative biotechnological products, derived from a **monoclonal cell line** and characterised by a **specific structure** (based on the immunoglobulin structure) and a **clearly defined functional activity** (primarily based on a specific binding characteristic to an antigen).
- Monoclonal antibodies may be generated by
  - recombinant DNA (rDNA) technology,
  - Hybridoma technology,
  - B lymphocyte immortalisation
  - other technologies (e.g. display technology, genetically engineered animals)
- The evolution of techniques has led to the development of more and more products based on/containing Mabs
  - However, regulatory work has long not kept pace with the new and innovative developments in the field (main guidance on the subject of MAbs for pharmaceutical use dated back to 1994)
  - Latest adopted guideline : Guideline on development, production, characterization and specifications for monoclonal antibodies and related products (in effect since 1 July 2009)

# Monoclonal antibodies in the EU pharmaceutical legislation (3)

## Adopted guidelines so far :

- Radiopharmaceuticals based on monoclonal antibodies (last revised in May 1991)
- Production and quality control of monoclonal antibodies (1994) replaced by Guideline on development, production, characterization and specifications for monoclonal antibodies and related products (in effect since 1 July 2009)

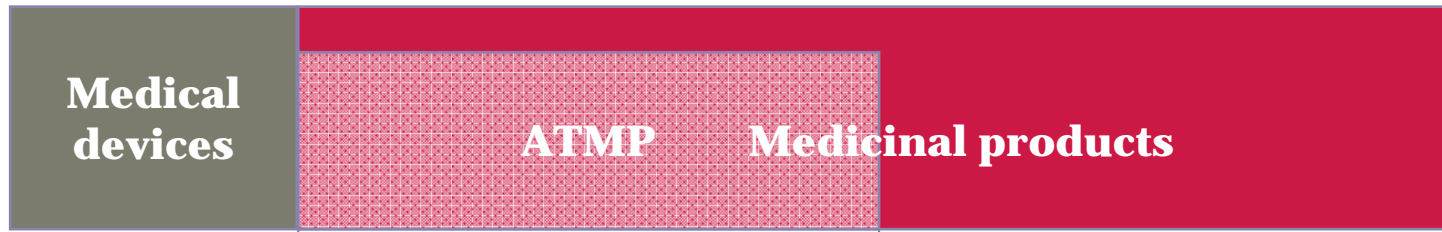
## 6 draft guidelines with consultation closed

- Draft guideline on production and quality control of monoclonal antibodies and related substances
- Concept paper on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use
- Concept paper on the revision of the guideline on radiopharmaceuticals based on monoclonal antibodies
- Concept paper on the development of a guideline on similar biological medicinal products containing monoclonal antibodies
- Draft guideline on similar biological medicinal products containing monoclonal antibodies
- Draft guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use

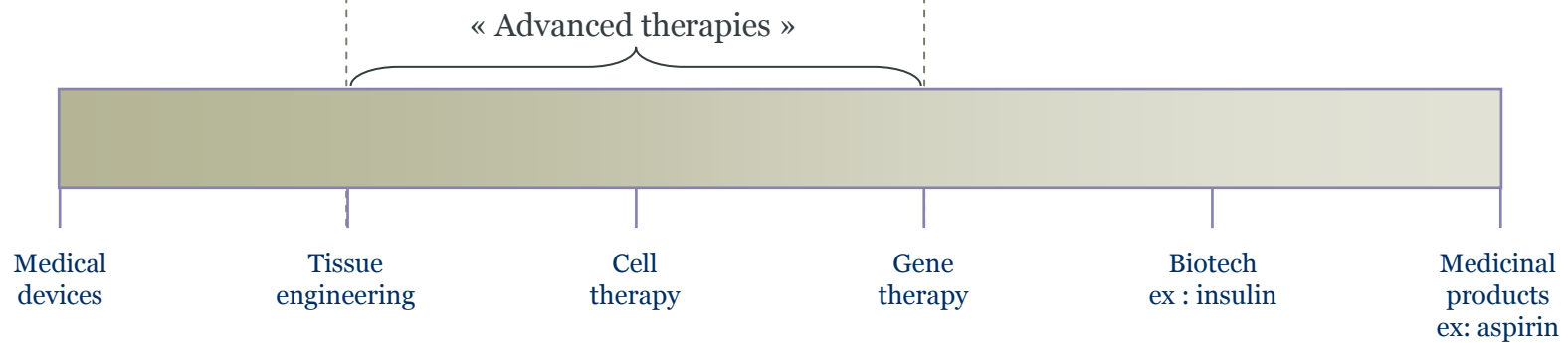
# Advanced Therapy Medicinal Products

# Advanced Therapies

## Regulatory framework



## Science



## EMA committee



Source : P. Selis, 1<sup>st</sup> EMEA Workshop on ATMP, 3/4/2009

# ATMP's and the use of cells and tissues



# Use of cells and tissues

## European Directives

**Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells**

### **Objectives**

- standards of quality and safety on EU scale
- Protection of donors as well as receivers

### **Implementing directives**

- **Directive 2006/17/EC**
  - Technical requirements for the donation, procurement and testing
  - Requirements concerning donors
  - Donation, procurement and reception procedures
- **Directive 2006/86/EC**
  - Technical requirements for tissue establishments and preparation processes
  - Notification of serious adverse reactions and events
  - Minimum donor/recipient data set to be kept
  - Information contained in the European Coding System

# Use of cells and tissues

## Scope of Directive 2004/23/EC

In **scope** : human tissues and cells **intended for human application**

- NOT in scope : tissues and cells used for purposes other than application to the human body (in vitro research or in animal models)
- Including **all types of stem cells**, a.o. haematopoietic peripheral blood, umbilical-cord (blood), bone-marrow stem cells, reproductive cells (eggs, sperm), foetal tissues and cells adult stem cells, embryonic stem cells.
  - Exclusion of human blood (except hematopoietic cells) and organs, and exclusion of animal tissues and cells insofar regulated by another European legislation

Exceptions

- where manufactured products are covered by other directives, the Directive applies only to donation, procurement and testing
- tissues and cells used as an autologous graft (tissues removed and transplanted back to the same individual), within the same surgical procedure and without being subjected to any banking process

# Directive 2004/23/EC

## Main principles

7 operations (Article 2 of Directive 2004/23) :

Donation

Procurement

Testing

Processing

Preservation

Storage

Distribution

The whole regulation is organised around those operations

Collection and application of the biological material are not ruled by the Directive (general medical law)

# Directive 2004/23/EC

## Main principles

**All operations must be performed in accredited tissue establishments or procurement organisations**

**The tissues and cells must comply with quality and safety standards**

Implies, a.o., traceability

**Main requirements as to protection of donors**

### **Donation**

- Voluntary
- Unpaid
- Compensation for the donors strictly limited to the expenses and inconveniences related to the donation.

### **Procurement**

- Should be carried out on a non-profit basis,
- By persons who have successfully completed a training programme,
- In a tissue establishment authorised for procurement

**Page 92** ● Or in a procurement organisation

# Directive 2004/23/EC

Tissue establishments and procurement organisations in national implementation measures

## Tissue establishments

Accreditation

The Directive does not indicate how Member States should rule tissue establishments

Differences possible between Member States

Examples : Belgium has provided for 4 types of establishments (see further) and France only has « Banques de Tissus » (Article L.1243-2 of the Public Health Code)

## Procurement organisations

health care establishment or a unit of a hospital or another body

task : procurement of human tissues and cells

that may not be accredited, designated, authorised or licensed as a tissue establishment

# Structures : example of implementation in Belgium

<b>Human biological material</b>	collection	procurement	testing	processing	preservation	storage	distribution	Importation and exportation	Human application	
Banks for human biological material										
Intermediary structures				*	*	*	*			
Production establishments		**		**	**	**	**	**		**
Biobanks						***				



Ruled by the provisions of the law and/or its implementing provisions



Must be performed in a hospital

\* :

in cooperation with a bank

\*\* :

only for the production of autologous ATMPs

\*\*\* :

also makes the material available. Only for scientific research without human application

# Directive 2004/23/EC

## Implementation issues

Directive : minimum requirements

- National implementing instruments may provide a broader scope

Restrictions

- National restrictions regarding any specific type of human cells may (continue to) apply : « ethical neutrality » : possibility for the Member States to put restrictions to the use of human cells and tissues intended for human use

Differences in regime applicable to « tissue establishments » between member states

Tension between directive 2004/23/EC and « data protection directive » as to informed consent for (second) use

# Advanced therapy medicinal products: Regulation 1394/2007



# Regulation 1394/2007

## Objectives and scope

ATMPs are medicinal products

- Gene therapy medicinal products
- Somatic cell therapy medicinal products
- Tissue engineered products

already ruled by Part IV of  
Annex I to Directive  
2001/83/EC (as modified  
by Directive 2003/63/EC)



Principles of existing legislation on medicines apply to advanced therapies:

- Centralised procedure for marketing authorisation
- demonstration of Quality, Safety & Efficacy
- post-authorisation vigilance

# Scope of Regulation 1394/2007

ATMPs may contain **human** or **animal** cells

ATMPs can be autologous or allogeneic

Not in scope : non « manufactured » products from the scope, i.e. non substantial manipulations so that the biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved

- Not substantial manipulations (Annex to Regulation 1394/2007) :
  - cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilization, irradiation, cell separation, concentration or purification, filtering, lyophilization, freezing, cryopreservation, vitrification.

The cells and tissues are not intended to be used for the same essential function or functions in the recipient and donor

# Examples of ATMPs

## Gene therapies

- **Gendicine** (Shenzhen SiBiono GeneTech - gene therapy against cancer) – only approved in China;
- Classified as gene therapy by CAT : non-integrative vector including a gene coding for an anti-HSV-1 Meganuclease for the ex-vivo transduction of human cornea intended for prevention of infectious diseases in cornea grafted patients.

## Somatic cell therapies

- **C-Cure** (Cardio3BioSciences) – not approved yet;
- **Provenge** (Dendreon Group) – FDA approved;
- Classified as somatic cell therapy by CAT : allogeneic human aortic endothelial cells cultured in a porcine gelatin matrix intended for treatment of vascular injury. CAT considered this as not being a combined ATMP.



## Tissue-engineered products

- **Chondrolect** (Tigenix) : first (and until now, only) ATMP approved in Europe under Regulation 1394/2007;
- **MACI** (Genzyme);
- Recently classified as tissue-engineered product by CAT : autologous bone marrow-derived progenitor cells intended for treatment of patients with failed left ventricular recovery despite successful reperfusion therapy post acute myocardial infarction, chronic ischemic heart disease, peripheral vascular diseases and Buerger's disease.

**Remark** : the classification of every product is assessed on a case-by-case basis within the CAT.

# Chondrocelect : MA procedure history

## Overview of the procedure

- Eligibility to centralised procedure : agreed upon by the EMEA/CHMP on 26 September 2006, MA application received by the EMEA 1 June 2007 and effective start of the procedure : 20 June 2007
- Procedure involved First Assessment report, a first list of questions, inspections on manufacturing site in Belgium (twice), written and oral explanations (three rounds)
- 24 June 2009 : positive draft opinion for granting a Marketing Authorisation to ChondroCelect from CAT
- 25 June 2009 : positive opinion for granting a MA to ChondroCelect from CHMP
- MA granted on 5/10/2009
- Note: a type II variation (change in AS manufacturing process) has been performed begin 2011

## Main study performed : TIG/ACT/01/2000

- Phase III, multicentre, randomized, controlled trial (comparison of ChondroCelect with « microfracture procedure »)
- 13 centres in 4 countries
- Duration of the study : 4 years
- 151 participants

# Advanced therapy medicinal products: interaction with tissues and cells legislation

# Interaction Directive 2004/23 and Regulation 1394/2007

Donation  
Procurement  
Testing

Always ruled by Directive 2004/23 insofar as the human tissues and cells are intended for human applications

Processing  
Preservation  
Storage  
Distribution

Ruled by Directive 2004/23 except in the case of manufactured products covered by other Community legislation (e.g. Regulation 1394/2007)

# Interaction Directive 2004/23 and Regulation 1394/2007

		donation	Procurement	Testing	Processing	Preservation	Storage	distribution
Tissues and cells intended for human application (without substantial manipulation)		<b>Directive 2004/23</b>						
Manufactured products derived from human tissues and cells and intended for human use		<b>Directive 2004/23</b>			<b>Regulation 1394/2007 and Directive 2001/83</b>			
Manufactured products derived from animal tissues and cells and intended for human use ruled by another European legislation		<b>Regulation 1394/2007 and Directive 2001/83</b>						
Tissues and cells intended for scientific research	With human application	<b>Directive 2004/23</b>						
	Without human application	<b>Other legislations</b>						

# Impact of the interaction in practice

- For the purpose of producing and marketing an ATMP in some MS, a company has to comply with
  - General pharma requirements such as GMP requirements
  - Directive 2004/23 implementing measures –i.e. be an accredited production establishment
- Example of difficulties specific to some MS: testing must take place in a hospital
- Interaction between both regimes can result in difficulties due to national legislation and burdensome obligations



# Practical considerations and issues

# EMA : regulatory and procedural guidance and scientific guidelines

The EMA has adopted several regulatory and procedural guidance documents, among which :

- Guideline on the minimum quality and non-clinical data for certification of advanced therapy medicinal products
- Guideline on safety and efficacy follow-up - risk management of advanced therapy medicinal products
- Procedural advice on the evaluation of combined advanced therapy medicinal products and the consultation of notified bodies in accordance with Article 9 of Regulation (EC) No. 1394/2007
- etc.

Some scientific guidelines have been adopted while many more are in the making:

- Gene therapies : 5 guidelines adopted – 10 more guidelines in the making
- Cell therapies and tissue engineering : 2 adopted guidelines, 6 more guidelines in the making

# ATMP classification and SEM certification : agenda of the upcoming deadlines

## ATMP classification requests deadlines :

Deadline for submission of request for ATMP classification	Start of procedure	Recommendation adopted by CAT pending receipt of comments from the European Commission (EC) *	Adoption in case of major comments received from EC
02/08/2012	17/08/2012	14/09/2012	12/10/2012
30/08/2012	14/09/2012	12/10/2012	09/11/2012
27/09/2012	12/10/2012	09/11/2012	07/12/2012
25/10/2012	09/11/2012	07/12/2012	11/01/2013
22/11/2012	07/12/2012	11/01/2013	15/02/2013

\*Expected dates for adoption if the CAT requires no additional information is required to conclude on the classification (no clock stop during the procedure).

## SME certification procedure (scientific evaluation by the CAT of quality and (where available) non-clinical data for ATMPs under development by SMEs (with issuance of a certificate by the EMA))

- A 90-day procedure has been developed for the evaluation and certification – Guidance documents : procedural advice (EMA/CAT/418458/2008/corr.) and minimum quality and non-clinical data
- for certification (EMA/CAT/486831/2008/corr)

Submission of draft application	Submission of final application	Start of procedure	Coordinator's evaluation report	Comments for CAT members and peer reviewer(s)	Consolidated evaluation report	Discussion at CAT (Day 60)	CAT adoption of opinion (provided that no need for written/oral explanation)
02/07/2012	10/08/2012	20/08/2012	24/09/2012	01/10/2012	05/10/2012	12/10/2012	09/11/2012
30/07/2012	07/09/2012	17/09/2012	22/10/2012	29/10/2012	05/11/2012	09/11/2012	07/12/2012
24/08/2012	05/10/2012	15/10/2012	19/11/2012	26/11/2012	30/11/2012	07/12/2012	11/01/2013
01/10/2012	09/11/2012	19/11/2012	03/01/2013	07/01/2013	09/01/2013	11/01/2013	15/02/2013
15/11/2012	21/12/2012	03/01/2013	28/01/2013	04/02/2013	08/02/2013	15/02/2013	15/03/2013
03/12/2012	11/01/2013	21/01/2013	25/02/2013	04/03/2013	08/03/2013	15/03/2013	19/04/2013
07/01/2013	15/02/2013	25/02/2013	02/04/2013	08/04/2013	12/04/2013	19/04/2013	24/05/2013
04/02/2013	15/03/2013	25/03/2013	06/05/2013	13/05/2013	17/05/2013	24/05/2013	21/06/2013
04/03/2013	12/04/2013	22/04/2013	03/06/2013	10/06/2013	14/06/2013	21/06/2013	19/07/2013
09/04/2013	17/05/2013	28/05/2013	01/07/2013	08/07/2013	12/07/2013	19/07/2013	16/08/2013

# Overview of the CAT activity since 2009

## Initial evaluation of MAA for ATMP :

Initial Evaluation of MAA for ATMP					
	2009	2010	2011	2012	Total
Submitted	3	1	2	1	7
Positive draft Opinion	1	0	1 <sup>i</sup>	0	2
Negative draft Opinion	1 <sup>*</sup>	0	1	0	2
Withdrawals	1	1	0	0	2

\* Application subsequently withdrawn

<sup>i</sup> Re-examination opinion (Glybera)

# « Hospital exemption »

## Principle (Article 3(7) of Directive 2001/83/EC)

### **Directive 2001/83/EC does NOT apply to ATMPs that are**

- prepared on a non-routine basis according to specific quality standards
- used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner
- in order to comply with an individual medical prescription for a custom-made product for an individual patient

### **Manufacturing authorisation** of these products are **granted by the competent authority of the Member State**

- traceability and pharmacovigilance requirements and specific quality standards have to be equivalent to those provided for at Community level in respect of ATMPs for which authorisation is required pursuant to Regulation (EC) No 726/2004

### **Directive 2004/23/EC applies in every case**

# « Hospital exemption »

## Remarks and consequences

### Issues

- Discrepancies between the Member States policies lead to different approaches
- Hospitals are not subject to the same requirements as the industry
- Need for harmonization ? Supervision by EMA ?

So few ATMPs reach the market through MAA procedure

- So far only 7 MA initial applications to the EMA
- So far only one ATMP covered by MA

Weakens biotech companies' R&D opportunities ?

Source : CAT May 2012 monthly report (22 May 2012 EMA/CAT/337185/2012)

# « Hospital exemption » Remarks and consequences

The screenshot shows the MHRA website interface. At the top, there is a navigation bar with links for 'Healthcare professionals', 'Patients and public', 'Pharmaceutical industry', and 'Devices industry'. Below this is a search bar with the text 'Google Recherche personnalisée' and a 'Rechercher' button. A secondary navigation bar includes 'About us', 'How we regulate', 'Safety information', 'Committees', 'Conferences and education', 'Publications and consultations', and 'Media Centre'. The main content area is titled 'How we regulate advanced therapy medicinal products' and contains a list of links: 'Guidance on the UK hospital exemption', 'Application form for the UK hospital exemption licence', 'Getting advice about ATMPs', 'What is an ATMP?', 'How are ATMPs regulated?', 'How are combination ATMPs regulated?', 'Who is responsible for providing advice about the regulatory arrangements that apply to products containing or derived from stem cells?', 'Background to the ATMP regulation', and 'Contacts at the MHRA'. A red box highlights the first link, 'Guidance on the UK hospital exemption'. An arrow points from this link to a larger, detailed view of the same link in a separate box on the right, which also contains the other links from the table of contents.

# Closing Thoughts



# Closing Thoughts

Diversity in the implementing measures adopted by the Member States regarding the use of cells and tissues

Complexity of interaction between Directive 2004/23/EC and ATMP provisions

Is the current legal framework adapted to reality?

- only one MA granted in three years
- Role of the hospital exemption

# Thank you

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# An industry perspective

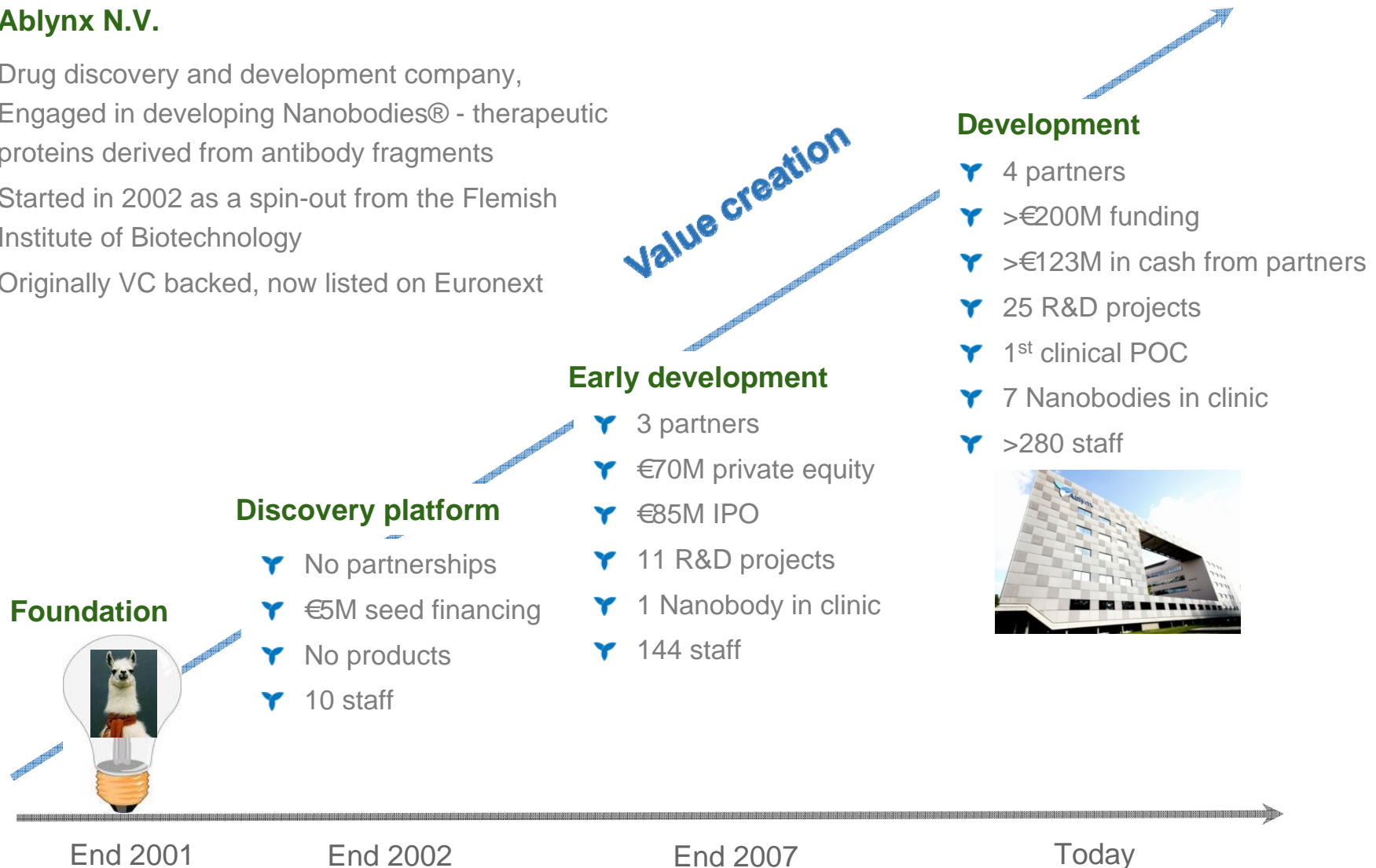
Frank Landolt

IP and Legal Counsel, Ablynx

# Evolution from platform to product based company

## Ablynx N.V.

Drug discovery and development company,  
 Engaged in developing Nanobodies® - therapeutic proteins derived from antibody fragments  
 Started in 2002 as a spin-out from the Flemish Institute of Biotechnology  
 Originally VC backed, now listed on Euronext



# What we are going to talk about

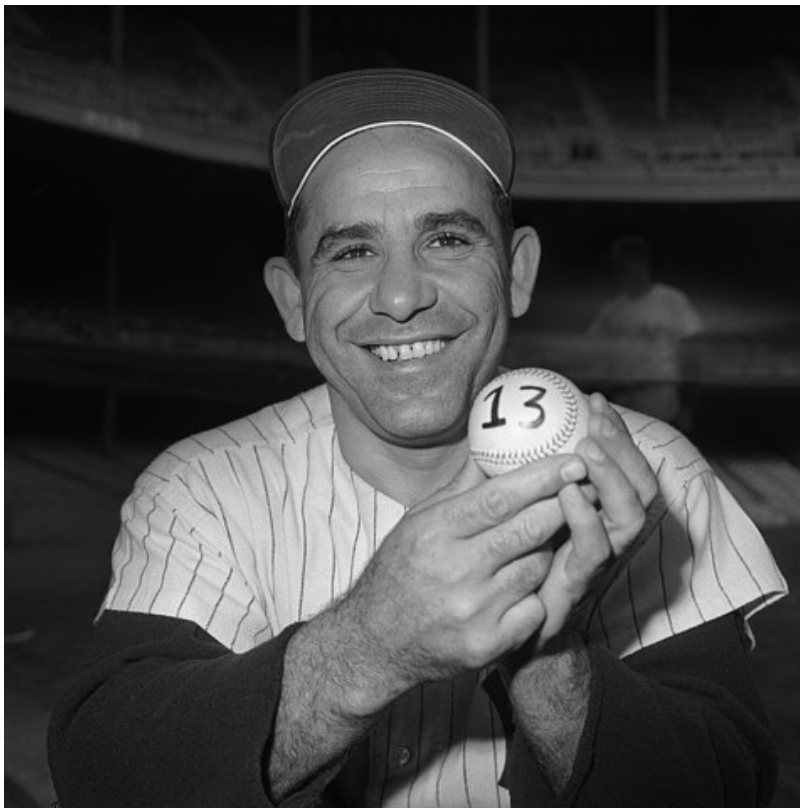
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## Biotech is (about) the future

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*"The future ain't what it used to be" – Yogi Berra*





# The players



## Biotech IP strategy

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Changes in IP rules can invalidate business models

“Genomics companies” and “reach through claims”;

Platform-based service providers under threat from “offshoring”

Recent developments in patentability of antibody claims (?)

It is (still) all about protecting the final product

Often difficult for platform technologies due to lack of “reach through” claims

And “reach-through licensing” is currently less accepted than 10-15 years ago

Important drivers behind evolution of platform companies into pipeline companies

“Reach-through claims” well-established for antibodies

Even when no antibodies were made (leading to patent thickets and FTO issues)

Relatively easy for “downstream” technologies (manufacture, formulation)

But there the expertise will usually be in the hands of big pharma

Generally, more licensing (required) in biotech

Although a lot of basic technologies from the 80’s/90’s are now coming off patent



## “Biotech IP” vs “big pharma IP”

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For biotech, *“IP is the product”*

The (main) test for “biotech IP” comes with financing and partnering  
Big pharma IP is (more) about protecting products - so less “platform filings”

Compared to big pharma IP, more people look at biotech IP, at an earlier stage, and with different expectations

Investors want to see broad claims that generally cover the platform

Business people want to go out and partner at an early stage

Big pharma wants to see strong claims around products

Biotech is generally more concerned about being “scooped” than big pharma

As a result, biotech generally files (much) earlier than big pharma, with less data

If biotech IP is not up to big pharma standards, deal terms may be affected

Big pharma has more downstream technology (production, formulation)

Which means more ability to generate strong “life cycle IP”

## What do the “clients” of biotech want ?

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Big pharma emphasizes the importance of in-licensing for filling pipelines

Get in early, or wait for later stage products with (more) clinical validation ?

License or acquire ?

Current M&A sweet spots: formulation platforms, single late stage product

Big pharma itself faces some choices

Focus on many specialty markets or a few big markets ?

Nearly all have moved into biologicals

Perception that patent cliffs are easier to manage with biologicals (at least for now)

Impact of possible entry of biosimilars (see further slides)

Many see growth markets outside Western countries

Where IP protection may be less established

And which in some cases is the home market of major generic companies

## Aim of the legislators

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Legislators try to balance innovation with (bio)generic competition

Use patent law to protect the innovators,

Use regulatory rules to encourage generic competition and so reduce drug prices

In doing so, they have to reconcile regulatory rules and patent law

Easier for small molecules (well-established technologies) than for biologicals (relatively new technologies)

More opportunities for life cycle management when it comes to biologicals

Result: increased integration of the patent and regulatory fields

2<sup>nd</sup> medical use and “dosage regimen” claims; SPC’s; data exclusivity; Bolar-type provisions, orphan drugs legislation; biosimilars

Optimal IP strategy takes account of patent law and regulatory protection

As both can create a barrier to entry for (generic) competition

Which again raises concerns with legislators and competition authorities (cf. the pharma sector inquiry)

And could lead to further changes in the rules if legislators feel that (economic) goals are not achieved

## Some facts (from the pharma sector inquiry report)

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Average costs of developing an NCE (EMEA-route) is \$800 m

Average time for obtaining marketing authorisation for an NCE (EMEA-route ):  
10 to 12 years

This means 10-12 years of effective patent life is lost (without SPC)

After generic competition enters the market, market share of originator product can drop by as much as 80%.

On average, two years after generic entry, generics have 45% market share and prices go down by an average of 40%

42 drugs (incl. some “blockbusters”) have gone off-patent in 2005-2009

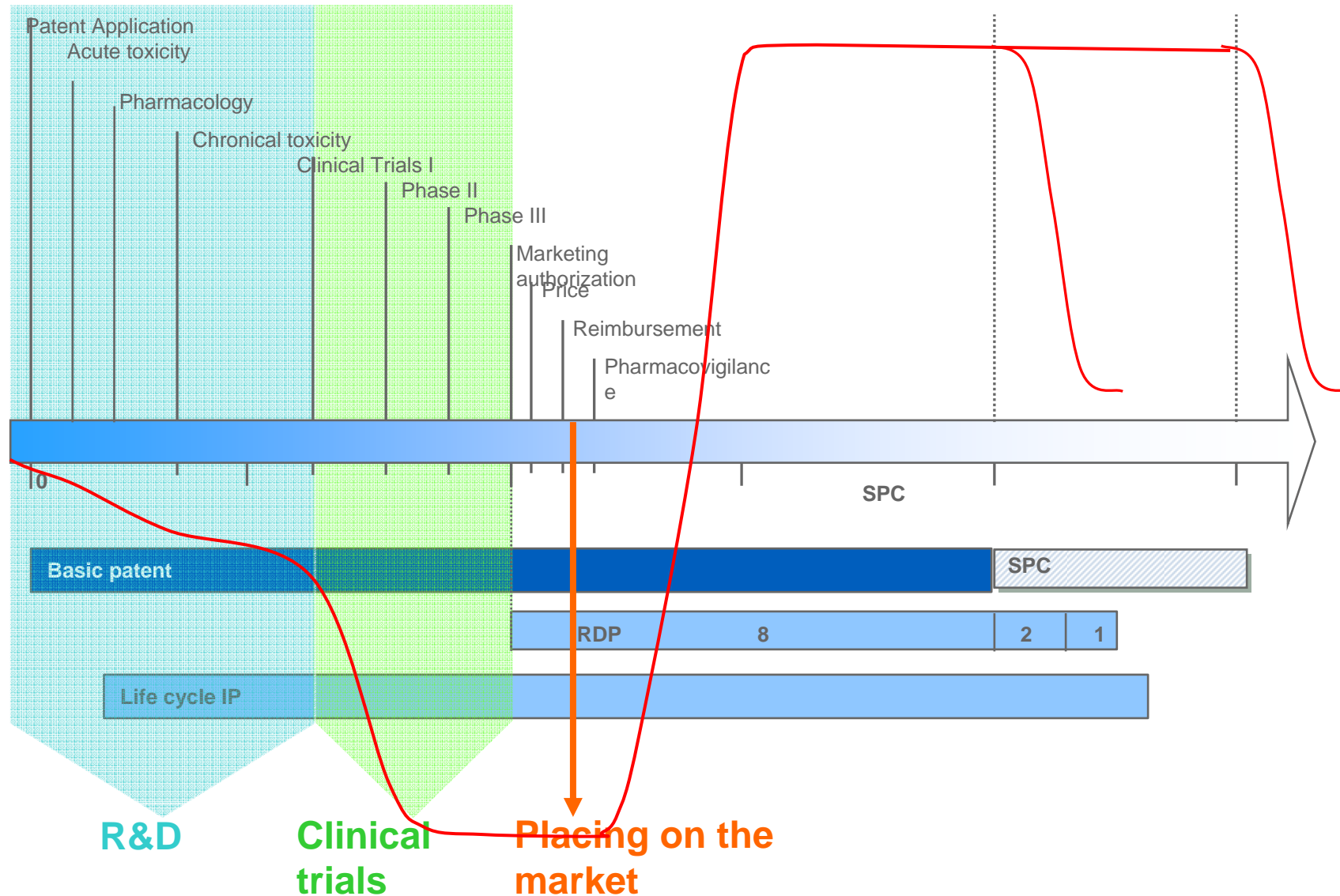
Biologicals are among best-selling/fastest growing drugs in the world

Epogen/Procrit®, Enbrel®, Humira®, Remicade®, Herceptin®, Avastin®

For some of these, the basic patents will expire in the coming years (but likely additional protection under SPC's and follow-on/manufacturing patents)

In some cases, multiple licenses were required to bring these products to market

# IP vs (return on) investment



## Small molecules vs. biologicals

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Life cycle management is more challenging for small molecules

Often orally administered drugs prescribed by a general practitioners

Opportunities for generic OTC's

Well-established formulation technologies available

Relatively easy for generics to achieve high margins

Issues are well understood by legislators and regulators

Biologics: “process is the product”

Administration via injection or infusion is often required

Which means the “market” is formed by healthcare specialists

Opportunities for new formulations and routes of administration

Generics must invest in process development and GMP manufacture

Issues are relatively new for legislators and regulators

# The EPO



## The EPO complains...

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*“[...] the system is being clogged up by applications that people know are not going anywhere. The fact is, they find it useful to submit applications for reasons that have nothing to do with the patentability of their invention. When we look at the global volumes, I’m not sure we should encourage this behaviour”*

*Alison Brimelow, former EPO President*

*“At the EPO we want to keep high patenting standards. More is not better!”*

*Alison Brimelow, former EPO President*



... and of course, this has nothing to do with them...

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*“After steady growth in the 1990’s, the number of biotechnology patents filed under the PCT started to decrease from more than 10 000 applications in 2000 to almost 7200 in 2005 (-7.5% on average over 2000-2005, compared to +20.2% on average between 1995 and 2000). [...]*

*On average, biotechnology patents represented 5.8% of countries’ patent portfolio over 2003-05, compared to 9.4% in the mid-1990’s.”*

*Source: OECD, 2008 Compendium of Patent Statistics*

By comparison, between 2000 and 2007, the number of pharma applications before the EPO doubled, and total number of applications increased by 30%

*Source: EU Pharma sector inquiry*

EPO patent statistics 2010: “Back to growth” !

Year	1993	1998	2003	2008	2009	2010
Biotech applications	2515	5686	5907	5583	5214	7435

## What the EPO “learned” in the 1990’s

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Starting with the genomics cases in the 1990’s, the EPO found two new ways to “influence” applicants: fees and non-unity

- Claims fees for > 20 claims

- New rules on non-searched subject matter

- 2 year time limit on filing of divisionals

Non-unity: routinely involves amounts > 100K, but in practice impossible to get an appealable decision

- Under the new rules, examiners can just sit on their hands for two years

- Right to be heard ? Human rights convention ?

The EPO has to act on backlogs and abuses of the system, but..

... all this hits cash-strapped biotech harder than big pharma, at a time when even big pharma acknowledges the role of biotech in innovation and the need for more inlicensing to fill big pharma pipelines

## Biotech applications ...

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In the 80's and '90's, biotech patenting drifted away from patenting in other fields of chemistry

Overly broad claims and prophetic patents following *Onco-mouse* and *Genentech*

EPC: No “written description” and art. 84 EPC not a ground for opposition

A lot of broad and prophetic patents were subsequently invalidated by the courts

Efforts by the Boards to redress the balance have resulted in even more “biotech-specific” case law

“AGREVO-type” inventive step objections

“*One way of performing the invention*” vs “*invention to be performed over the whole range claimed*”

“*reasonable expectation of success*” vs “*try and see*”

Some argue that the pendulum has now swung too far against applicants

## ... vs antibody applications

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Now, the antibody field is drifting away from the biotech field...

“Reach through”

Examples required

Prior art

Patentability of “alternatives”

Impact of structural differences on inventive step

Use of “arbitrary” parameters in patentability and setting claim scope

Case law also extended to other antibody-based technologies

But the principle should still be the same:

T 1063/06: *“As the applicant is entitled to claim patent protection only for his actual contribution to the art, it is therefore both reasonable and imperative to limit the claim's subject-matter accordingly. Patent protection under the EPC is not designed for the purpose of reserving an unexplored field of research for a particular applicant, as reach-through claims do, but to protect factual results of successful research as a reward for making concrete technical results available to the public”*

## “Method-based” and “try and see” approach - issues

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Making a successful antibody is not as easy as patent offices seem to think

As a result, it is also not easy to improve on commercially successful antibodies

*“Reasonable expectation of success” vs “well-ploughed field”*

Would the skilled person reasonably have expected that the prior art could be improved upon ?

As techniques for improving antibodies (humanization, affinity maturation) become generally accepted, will any antibody be patentable ?

*“[...] we are nearing the point when all antibodies will be considered obvious in light of a disclosure of any antibody that binds and blocks or agonises a target of interest.[...]”*

*Unless the EPO changes its approach, most antibodies discovered within the last several years will not be patentable.”*

*Stewart et al., EPI information 2/11, p.72-76*

# Biosimilars



## Some observations on biosimilars

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Investment case is different from small molecule generics

- GMP manufacturing and clinical trials required

- Makes biosimilars more like a “me-too” than a true generic

Market for biologicals is different from the small molecule market

- Used in hospitals rather than OTCs prescribed by GP’s and sold by pharmacies

- Established relationships with hospital specialists may be important (also for doing clinical trials)

The players in the field seem to be evolving

- Initial interest from “traditional” generic companies seems to have waned

- Upcoming players: CMO’s, big pharma with established capabilities in biologicals, alliances between big generics and CMO’s, companies from the BRICs

- Examples: Teva/Lonza alliance, Hanwa/Merck deal on biosimilar Enbrel, Merck/Parexel alliance

- Not sure if this is what the legislators intended

- In particular: does this mean investment is now flowing into biosimilars that otherwise would have gone into innovative medicines ?

## Some more observations

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Not yet clear when biosimilar “blockbusters” will reach the market

General guidelines for biosimilar monoclonals still in the early stages

And after that, we still need “product specific” guidelines

Generally more “life cycle IP” to deal with

**Not fully clear if SPC’s for originator products will also cover biosimilars**

Biosimilar Enbrel may be a test case - but few biological markets are as established as the anti-TNF market

Will biosimilars encounter competition from true “biogenerics” ?

With biosimilars expected to enter the market at some point, differentiation will become even more important for “innovative” biologicals

And companies developing new biologicals will need to consider issues of pricing and reimbursement at a much earlier stage of development



## Biologicals and SPC's

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SPC's are about products that have reached the market

SPC regulations are older than Biosimilar regulations

SPC regulations were intended as a **purely administrative** procedure

Capable of being applied by national patent offices in the European Union that had a registration procedure for patents rather than material examination

Instead, what has evolved is a material procedure for examination and grant of SPC's, with extensive jurisprudence (incl. multiple ECJ decisions)

No special regimen for biologicals under the SPC regulations

But there are examples of case law on SPC's in which a distinction is made between small molecules and biologicals (the *Yeda* case – see next slide)

And decisions on individual SPC applications take account of the special nature of biologicals ("Process is the product")

Biologicals: often multiple patents covering one product (rare for small molecules)

## Dutch Supreme Administrative court in *Yeda*

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Supreme Administrative Court of the Netherlands, 19-08-2009 (*adalidumab*, *Humira* ®) – the *Yeda* case

Background: Yeda tried to apply reasoning of the ECJ in *Farmitalia* (a case on SPCs for small molecules) to SPCs for biologicals

Dutch supreme administrative court said refused to do so:

*"[...] in medical science, it is generally accepted that chemical derivatives of an active ingredient, such as salts and esters, as a rule have the same medicinal action as the active ingredient itself. For this reason, in [art. 10 of the Medicines Directive 2001/83/EC] such derivatives of the active ingredient are in principle deemed to be the same active ingredient.*

*[...]*

*In medical science, it is not generally accepted that related biological drugs as a rule have the same medicinal action. For example, in the Biosimilars Guidelines, it is stated that the simplified procedure of art. 10 of the Medicines Directive is not suitable for biological drugs, because of the complex structure that such biological drugs have.*

## Definitions from SPC Regulation

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### Article 1 (b):

*"product" means the active ingredient or combination of active ingredients of a medicinal product*

### Article 3:

*A certificate shall be granted if [...]*

*(a) the product is protected by a basic patent in force*

*[...]*

"Basic patent" may be freely chosen:

Product/substance patent (including patent for combination of two compounds)

Method patent (e.g. for a basic technology or manufacturing process);

Formulation patent or "use" patent (also second medical use and dosage regimen)

With formulation and use patents, the invoked marketing authorisation will often not be the "first" MA as required by the SPC regulation (ECJ: C-202/05, *Yissum and C-431/04, MIT*)

**If a basic patent relates to a research technology or manufacturing process and does not explicitly disclose the compound, can an SPC be granted ?**

## Example: Dutch SPC's under the "Queen patent"

	Product	Other SPC's (year of filing of basic patent)
EP 0 451 216 (PDL, "Queen patent"), <b>1989</b>	Ranibizumab (Lucentis <sup>®</sup> , Genentech)	Genentech ( <b>1998</b> ) Medimmune/MRC ( <b>1991</b> )
<i>[idem]</i>	Palivizumab (Synagis <sup>®</sup> , Medimmune)	
<i>[idem]</i>	Trastuzumab (Herceptin <sup>®</sup> , Genentech)	<b>Chiron (1985)</b> Genentech (1992)
<i>[idem]</i>	Bevacizumab (Avastin <sup>®</sup> , Genentech)	Genentech (1998)
<i>[idem]</i>	Omalizumab (Xolair <sup>®</sup> , Genentech + Novartis)	Genentech (1992) Tanox (1988)
<i>[idem]</i>	Natalizumab (Tysabri <sup>®</sup> , Biogen + Elan)	Elan (1995) Hutchinson Res. Center (1990)
<i>[idem]</i>	Daclizumab (Zenapax <sup>®</sup> , Roche)	

## Observations from the previous slide

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A lot of the SPC's mentioned on the previous slide were **granted to companies that were not the holder of the marketing authorisation**

OK: C-181/96 (*Biogen*) and C-110/95 (*Yamanouchi*)

Not OK: Court of The Hague, 4-11-2009 (*Stallergene*) and ECJ in *Medeva* (although the latter may have been a mistake in the way the decision was written)

The invoked “basic patent” can be older than the first/later “product patent”

Where this happened, the later product patent was apparently novel and inventive over the older “basic patents”

In other words, “older” basic patents could not have disclosed the “product”, otherwise the later product patent would not have been patentable

So it would seem that a “basic patent” does not need to disclose the “product” in such way that this disclosure meets the “novelty test”

**So how much basis is required ? What does “protected” mean ?**

## So when is a “product” “protected” by a “basic patent” ?

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SPC regulation itself does not give definition, and does not say which law/rules/principles should be applied

ECJ in C-392/97 (*Farmitalia*, the “salts and esters” case):

*“As Community law now stands, the provisions concerning patents have not yet been made the subject of harmonization at Community level or of an approximation of laws.*

*Accordingly, [...], the extent of patent protection can be determined **only in the light of the non-Community rules which govern patents.**”*

Reasoning repeated in *Medeva* and *Georgetown*

So “protected” appears to be an issue of national law(s)...

## But who decides, who can decide, and on what basis ?

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Mr. Justice Kitchin in *Gilead*: (the “*infringement test*”)

*"This suggests the Court of Justice in Farmitalia **must have had** the infringement test, and, for the Contracting States to the EPC, **Article 69 in mind. Anything less would have required the Court to interpret the term "protected" in the context of the Regulation as having a particular and different meaning, and that was something it declined to do. [...].***

Appeals court of The Hague, 21-02-2008 (*Atorvastatine*):

***"The question of whether the SPC was validly granted [...] is essentially different from the question of whether the basic patent would have been infringed [...].***

*For determining infringement, the judge has to determine the scope of protection of the patent, in accordance with Article 69 EPC [...].*

*In doing so, the judge is not limited to answering the question of whether the [infringing product] falls under the literal text of the claim as read in the light of the specification [...], but the judge can also [apply the doctrine of equivalence]*

***SPC's are granted by national patent offices [...]. The Dutch patent office does make judgments on infringement. This is up to the civil courts to do"***

## “Protected” or not ? The two types of cases so far

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Does the basic patent “protect” the product where...

... the patent is for substance X, and "product" is a combination of active substances X and Y ?

... the “product” falls under the claims, but is not specifically mentioned in the specification or the claims ?

Several “tests” were proposed and applied by national courts/patent offices

*“Commercialisation test”, “infringement test”, “claimed test”, “subject matter test”, “clear pointer test”, “disclosure test”*

For combination products, the question now been answered by the ECJ in  
C-322/10 *Medeva* and C-422/10 *Georgetown*

But does this reasoning from these decisions extend to biologicals/biosimilars ?

And if so, how ?

For combination products, there is also an infringement case before the ECJ

C-442/11 *Novartis/Actavis* (referral by UK High Court of Justice)

Question referred: Is an SPC for compound X infringed by combination X+Y ?



## Medeva and Georgetown – the “combination” cases

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Fundamentally, the ECJ seems to opt for the so-called “**claimed test**”:

28. [...] Article 3(a) of Regulation No 469/2009 must be interpreted *as precluding the competent industrial property office of a Member State from granting a SPC relating to active ingredients which are not specified in the wording of the claims of the basic patent* relied on in support of the SPC application.

For combination products, this would mean very few granted/valid SPCs

But the ECJ then applies a **teleological interpretation** to the outcome

30. *First, it must be noted that the fundamental objective of Regulation No 469/2009 is to ensure sufficient protection to encourage pharmaceutical research [...]*

31. *”[...] the period of effective protection under the patent is insufficient to cover the investment put into pharmaceutical research and the regulation thus seeks to make up for that insufficiency by creating a SPC for medicinal products [...]”*

36. *It is clear that such an outcome cannot be compatible with the fundamental objectives pursued by Regulation No 469/2009 by the creation of a SPC for medicinal products.*

The ECJ then applies reasoning that is highly specific for combination products, and so finds a way around the strict outcome of the claimed test

## So what does this mean for biologicals and SPC's

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ECJ applies “**claimed test**”: SPC can not be granted for “**active ingredients which are not specified in the wording of the claims of the basic patent**”

ECJ does not explain what “specified” means

Does this mean some sort of “novelty test” ?

And that SPCs can only be granted on patents that claim the actual compound ?

If so, what does this mean for SPCs based on (earlier) patents for enabling technologies ?

Strict application of “claimed test” may be tempered by teleological considerations, allowing grant of an SPC where the “claimed test” would not

Reasoning in *Georgetown* and *Medeva* highly specific for combination products

Emphasis of the ECJ seems to be on having the opportunity to recoup investment

Will we see a lot of “teleological” exceptions made on a case-by-case basis ?

Will sufficient arguments be available where an SPC applicant did not make a major investment *in the product itself* (but for example in an enabling technology) ?

## SPC's - what is the “active ingredient” ?

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SPC's are granted for the "active ingredient or combination of active ingredients“

To determine what the “active ingredient” is, patent offices look at the marketing authorisation that is invoked by the SPC applicant

Some patent offices even consult national regulatory authorities

Usually, this authorisation mentions the INN name, and this is what (most) patent offices use as the basis for the description of the “product” in the SPC

If they deviate from this, it is usually to limit the description of the “product” in view of specific limitations in the claims of the invoked basic patent

The scope of protection for the SPC is limited to the description of the “product” in the SPC (within the scope of protection of the basic patent)

SPC's do not have a description

SPC regulation does not contain provisions on interpretation of scope (i.e. similar to art. 69 EPC) – so likely no interpretation of the “product description” to include equivalents

## SPC's for small molecules

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SPC's for small molecules mention the INN name (including salts and esters)

Position of patent offices:

same INN name = same "active substance" = same "product";

different INN name = different "active substance" = different "product"

"Generic" small molecules have the same INN name as the originator compound, and thus:

- contain the same "active substance" as the originator compound
- are the same "product" as the originator compound
- fall under the SPC for the originator compound

"Me-too's" have a different INN name, and thus should be a different "product" (even when they fall under the same basic patent)

Prodrugs have a different INN name and are considered a different "product"

So for small molecules, INN name appears decisive

## Biosimilars

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MA's granted for biosimilars refer to the INN name of the originator product (i.e. the "reference product")

Use of the same INN name would suggest that a biosimilar is the same "product" as the originator compound, and thus falls within the scope of protection of an SPC for the originator drug

But: case law like the Dutch *Yeda* decision suggests that SPC's for biologicals could be treated differently from SPC's for small molecules.

However, this case law relates to the requirements for grant of an SPC (in particular, what is "protected" by the basic patent)

Not certain if a similar distinction will (also) be made when it comes to the scope of protection of a granted SPC

Teleological interpretation would probably refer back to the desire for "15 years of effective patent life" for the originator compound

Also, if a biosimilar was deemed a different "active ingredient", it could be the subject of a new SPC application by the originator, based on the basic patent of the originator and the marketing authorisation for the biosimilar

## Thank you – any questions ?

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*”It is difficult to make predictions, especially about the future”*

Markus M. Ronner, but often attributed to Yogi Berra

*“All predictions true or your money back”*

Gregg Easterbrook, about his (free) predictions on TMZ

Any questions for the Panel?

# Thank you for joining us

Please feel free to contact us below for further information on the topics covered today or to be kept up to date generally through our newsletters and updates.

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