HOFFMANN EITLE

Antibody patents in Europe
What is new or special?

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May 2019, Madrid, OEPM

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Therapeutic Antibodies – A General Overview

Half of the world‘s best-selling drugs are monoclonal antibody drug products.

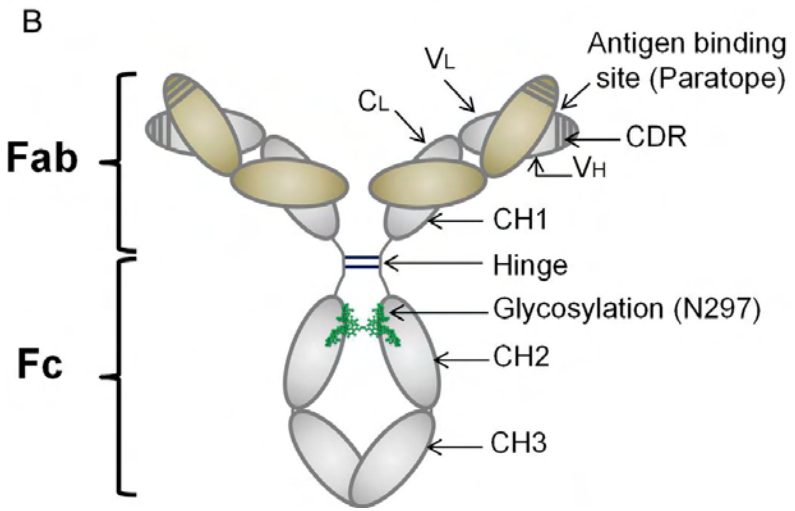
Best-seller Humira accounts for 2.2% of the entire market share of prescription medicine alone

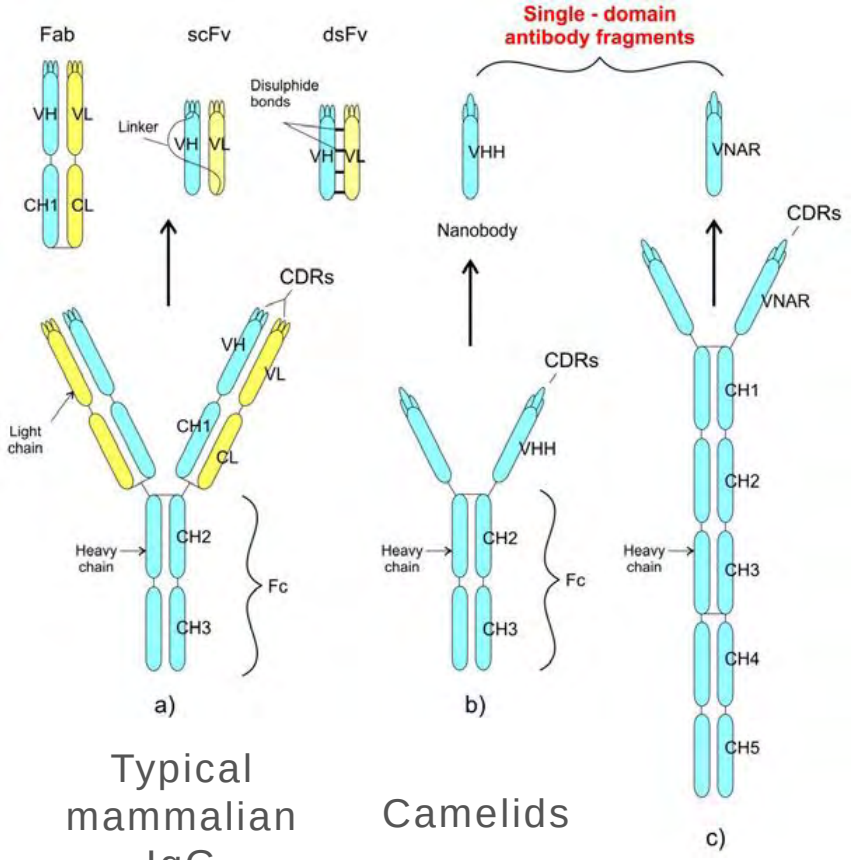
Global top 10 best-selling drugs in 2017

Rank	Drug	Primary indication	Marketer	Sales ($m)	Growth (%)
1 (1)	Humira	Arthritis	AbbVie	18,427	14.6%
2 (2)	Enbrel	Arthritis	Amgen/PFE	8,225	-10.7%
3 (5)	Revlimid	Multiple myeloma	Celgene	8,187	17.4%
4 (4)	Rituxan/MabThera	Non-Hodgkins lymphoma	Roche	7,508	1.3%
5 (8)	Herceptin	Cancer	Roche	7,128	3.5%
6 (7)	Avastin	Cancer	Roche	6,797	-1.3%
7 (6)	Remicade	Arthritis	JNJ	6,315	-9.3%
8 (10)	Prevnar	Pneumococcal vaccine	Pfizer	5,601	-2.0%
9 (9)	Lantus	Diabetes I	Sanofi	5,211	-17.6%
10 (11)	Lyrica	Alzheimer’s disease	Pfizer	5,064	2.0%

Source: Hardman & Co Life Sciences Research

Therapeutic Antibodies – A General Overview



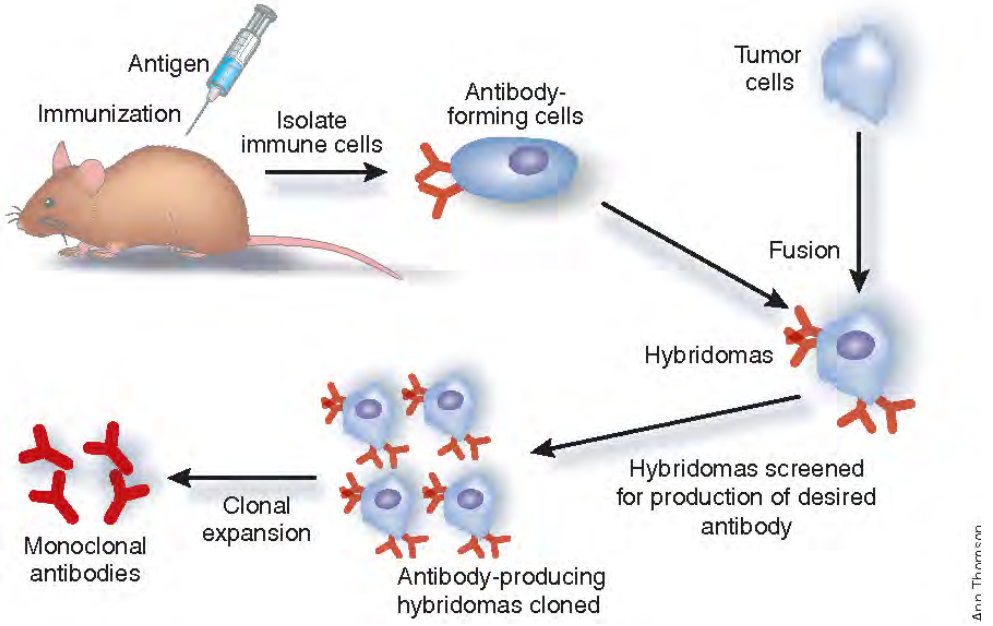


*Source:

Irani et al., Molecular Immunology 67 (2015) 171–182

Eyer and Hruska, Vet. Med. 57, 2012 (9): 439–513

1975: Development of hybridoma technology – generation of monoclonal antibodies

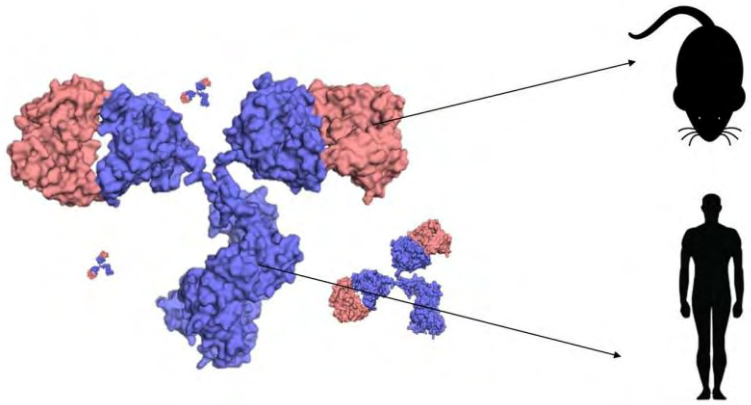


(Köhler and Milstein, Nobel Prize 1984)

Therapeutic Antibodies – A General Overview

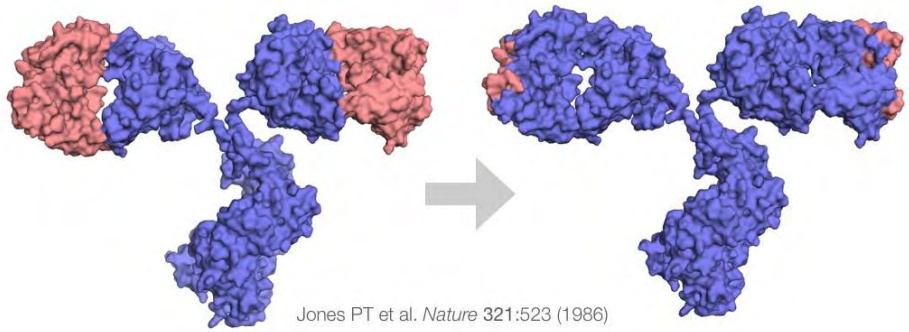
1986:

Chimeric antibodies – murine variable domains, human constant regions



Denoted by „xi“, e.g. infliximab

Humanized antibodies – human antibody with murine/rat CDRs („CDR grafting“)

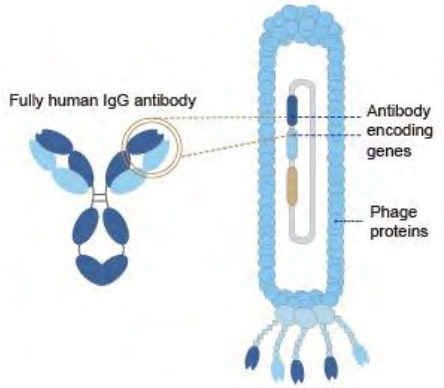


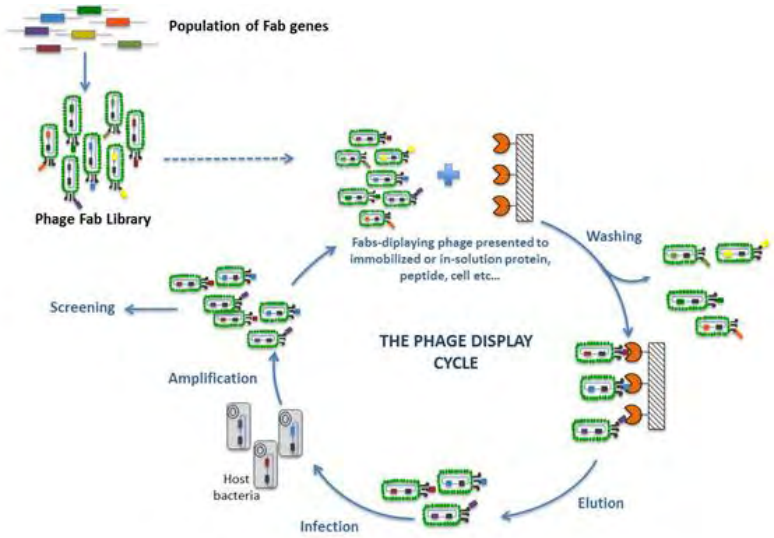
Denoted by „zu“, e.g. trastuzumab

Therapeutic Antibodies – A General Overview

1990:

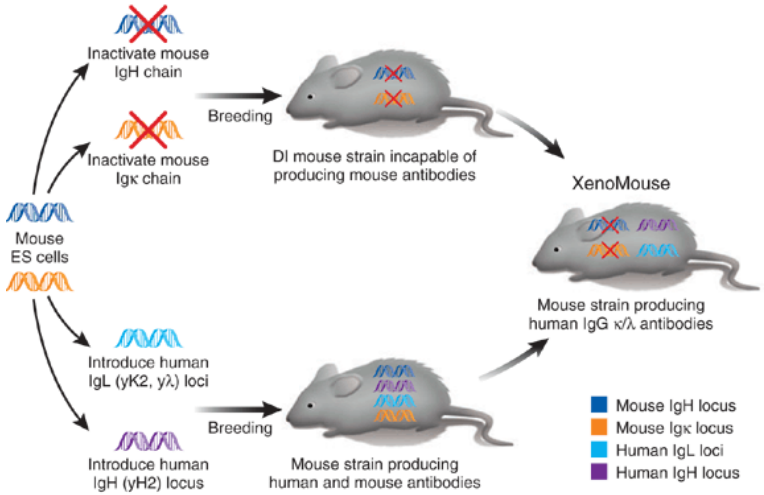
Development of phage display for antibody selection, enabling screening and expression of fully human antibodies in E. coli – „emulation“ of clonal selection in bacteria





1994:

Generation of transgenic mice carrying human antibody gene segments – allowing generation of fully human antibodies via conventional hybridoma technology

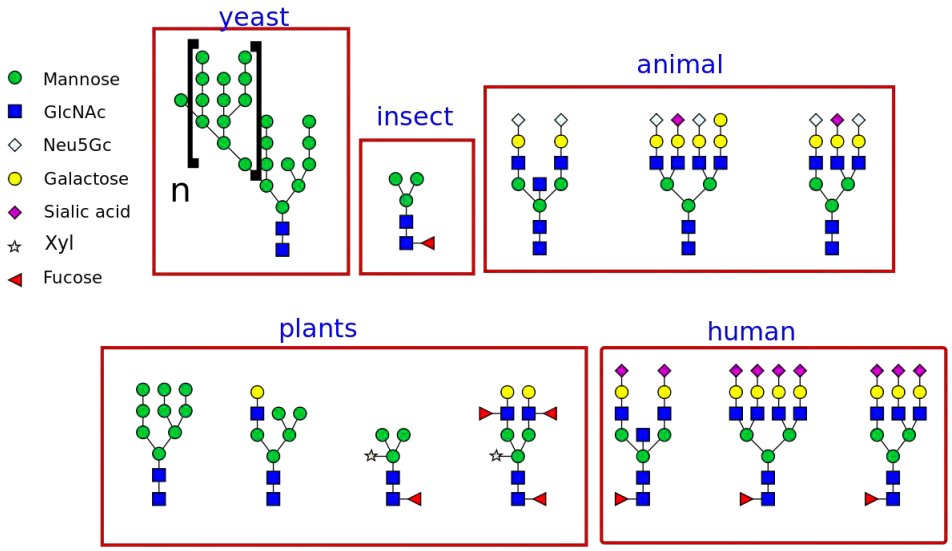


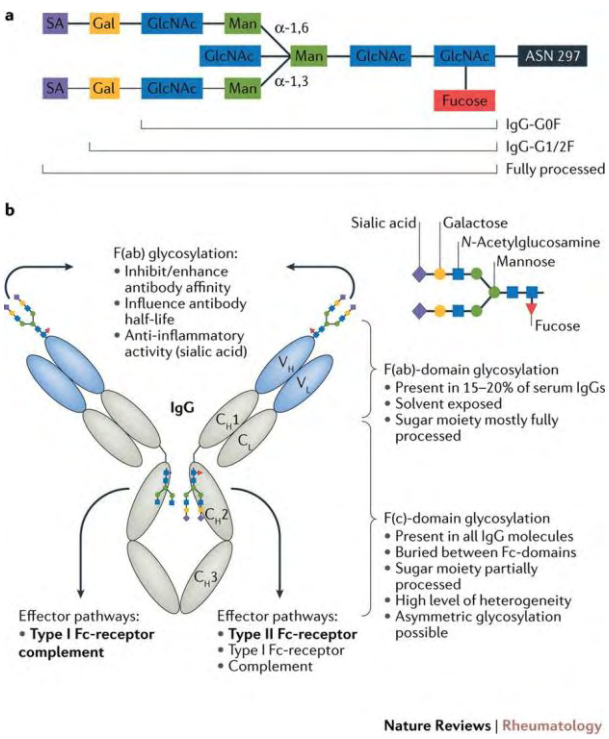
Fully human antibodies are denoted by „u“, e.g. adalimumab

Therapeutic Antibodies – A General Overview

Advent of next-generation sequencing, gene synthesis, advanced expression systems

Fine-tuning of antibodies‘ properties such as post-translational modifications, affecting effector functions (e.g. ADCC), pharmacokinetics, -dynamics





Functional definition of molecules

Functional features are permissible

- if the invention either can only be defined in such terms or cannot otherwise be defined more precisely without unduly restricting the scope of the claims, and
- if the result is one which can be directly and positively verified by tests or procedures adequately specified in the description or known to the person skilled in the art and which do not require undue experimentation (see T 68/85).

- *Small molecules: Functional definition of compounds by means of its binding to a receptor lacks a sufficient disclosure if identification of further compounds requires undue experimentation.*
- *Antibodies: Identification of antibodies does not require undue experimentation (T877/03)*

What about humanization?

What is a routine method at the filing date?

General definition via:

Structure: amino acid sequences

Production process: hybridoma cell line

Function…

General definition via:

General Functional Features

- Therapeutic mechanism: Agonistic/antagonistic, inhibitory/activating, etc.
- Physiological parameters: Tissue penetration, half-life, immunogenicity
- Cross-reactivity (species, isoforms, related proteins, etc.)
- Therapeutic efficacy: Reduction of symptoms, increase in survival, etc.

Monoclonal antibodies – Relevant features

General definition via:

Functional Features via Antigen

Claims

1. Use of an anti-PD-1 antibody which inhibits the immunosuppressive signal of PD-1 for the manufacture of a medicament for cancer treatment.

EP 1 537 828 B1 (Honjo et al., anti-PD1)

Commercially highly relevant:

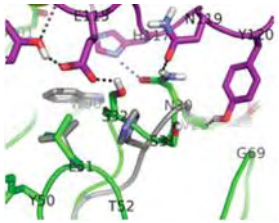
- Claim covers e.g. Merck‘s later-developed anti-PD1-mAb Keytruda (Pembrolizumab) Merck pays US **$625 million** + **6.5%** on global Keytruda sales until 2023 / 2.5% until Dec. 2026 to Ono/BMS
- Other anti-PD1 (and anti-PD-L1) antibodies under development

General definition via:

Functional Features via Epitope

Linear epitope: at least 5 amino acids, preferably more

Conformational (discontinuous) epitopes



Indirect epitope definition by reference to another antibody

Example of linear epitope claim: EP 2 293 819 B1 (Arribas et al.)

1. An antibody or a fragment thereof that recognises an epitope of a HER2 receptor truncated form defined by SEQ ID NO: 1, said epitope being defined by a sequence included in SEQ ID NO: 2, wherein the antibody or fragment thereof is suitable to distinguish the protein of SEQ ID NO: 1 from the HER2 receptor.

Definition by linear epitope usually considered clear and reproducible

If the epitope was not known (i.e. new) and an unexpected effect* is shown (i.e. inventive), then the claim is patentable.

*Note that determination of an linear epitope may be considered to be a result of routine screening (epitope mapping).

Example of conformational epitope claim: Decision T 735/00

Claim: Antibody against CRP (C-reactive protein), epitope defined as „side face of a disk-like subunit of a C-reactive protein (CRP)”

Prior art: Antibodies against CRP

EPO BoA: Epitope not clear – no definition of the described structure disclosed. Burden of proof reversed: on the Patentee. **Not novel**.

Guidelines for Examination G VI. 6.

It may happen that in the relevant prior art a different parameter, or no parameter at all, is mentioned. If the known and the claimed products are identical in all other respects (which is to be expected if, for example, the starting products and the manufacturing processes are identical), then in the first place an objection of lack of novelty arises. The burden of proof for an alleged distinguishing feature lies with the applicant. No benefit of doubt can be accorded if the applicant does not provide evidence in support of the allegations (see **T 1764/06**). If, on the other hand, the applicant is able to show, e.g. by appropriate comparison tests, that differences do exist with respect to the parameters, it is questionable whether the application discloses all the features essential to manufacture products having the parameters specified in the claims (**Art. 83**).

Example of „indirect“ epitope claim: Decision T1859/08

Use of an anti-ErbB2 antibody in the preparation of a medicament to provide clinical benefit by measured increased time to disease progression of malignant breast cancer characterized by overexpression of ErbB2 in a human patient, wherein said antibody binds to epitope 4D5 within the ErbB2 extracellular domain sequence as determined by a cross-linking assay using said antibody and antibody 4D5 obtainable from deposit ATCC CRL 10463…

- „binds to the same epitope as…“ usually acceptable
- Definition by competition with other antibody: expect clarity and sufficiency of disclosure objection in examination

General definition via:

Structural Features

Antibody Structure

- Amino acid sequence / nucleotide sequence
  - Entire antibody sequence (incl. framework sequences)
  - Variable domains sequences (heavy/light chain variable domains, VHH fragment sequences)
  - CDRs
- Type of antibody
  - Framework type (species)
  - Antibody type (e.g. scFv)
  - Antibody class (e.g. IgG3)

Decision T 511/14 (2018)

Claim: Antibody against DKK-1 defined by 3 CDRs of a light chain variable domain sequence and **one or more** CDR of the a heavy chain variable domain sequence.

Application: Exemplary antibody shown to exhibit exceptional in vivo performance.

Prior art: Different antibody against DKK-1, not shown to exhibit similar in vivo performance

EPO BoA: Distinguishing feature: Structure of the claimed antibodies. Technical effect: None over the whole scope of the claim. Objective technical problem: Provision of alternative anti-DKK-1 antibodies. Solution obvious and arbitrary. **Not inventive.**

→ Although a claimed exemplary antibodies is demonstrated to represent an improvement over the prior art, technical effect is not acknowledged as plausible for antibodies not having all 6 CDRs.

Note: A single amino acid change in the CDR may affect the binding to the target (Rudikoff et al., PNAS 1982, Vol. 79, 1979-1983)

Is the only way out a definition by the complete sequence or at least the exact sequence of the 6 CDRs?

Often beneficial: Combination of both

Structural Features & Functional Features

Definition via sequence + sequence identity percentage – generally requires:

a) Features for keeping relevant sequences (e.g. CDRs) constant (requires adequate basis in the application)

b) Functional limitation: Technical effect in the claim → Problem plausibly solved over the whole scope

Decision T 418 /07 (2011)

Claim: Human antibody against TNF-alpha defined by CDR3 sequences of the light and heavy chain variable domain sequence, allowing for specific mutations, and **a functional feature defining the Koff rate**.

Application: Exemplary antibody shown to neutralize TNF-alpha with therapeutically relevant efficacy.

Prior art: Mouse anti-TNF-alpha antibodies with similar Koff rates, human anti-TNF-alpha antibodies with worse Koff rates.

EPO BoA: Closest prior art: Mouse anti-TNF-alpha antibodies with similar Koff rates. Distinguishing feature: Antibody is human. Objective technical problem: Provision of anti-TNF-alpha antibodies with slow dissociation. Solution not obvious, because of no reasonable expectation of success (all prior art human antibodies did not achieve the claimed Koff rate). **Inventive.**

→ Although not all CDRs are recited in the claim, the functional feature limits the claim to inventive embodiments.

Decision T 617 /07 (2009)

Claim: Monoclonal antibody against TrkA, characterized by at least one CDR and by the function of preventing the functional activation of NGF by TrkA.

Opponent: Determination of function represents undue burden.

Board: Provision of functional equivalent is a complex task. Prior art explains how variants can be made on the basis of the structure of a known structure of a specific antibody (e.g. by 3D modelling). Provision of functional equivalents does not require undue burden.

Summary

- Broad protection of antibodies available by definition via antigen or epitope
- Possibly shift of burden of proof in case of functional definition (conformational epitope; other parameters)
- Novelty usually straight-forward to establish via structural features (e.g. CDR or variable region sequences)
- Functional features may be helpful to establish inventive step and/or sufficiency of disclosure

Biosimilars

- *A biological medicinal product is a medicinal product whose active substance is made by or derived from a living organism.* EMA. Glossary (terms and abbreviations)

- Biologicals or biotechnological products are distinguishable from their chemically synthesised counterparts with respect to their manufacturing process and its impact on the drug product quality and safety.*

- Minor changes in the process can affect the quality of the drug product.*

-

- *EMA: Guideline CPMP/BWO/328/99 (Development Pharmaceutics for Biotechnological and Biological Products)

This has implications…

1) On regulatory approval

- Biosimilar must be similar, in molecular and biological terms, to the active substance of the reference medicinal product (e.g.the amino acid sequence is expected to be the same).
- Intended changes to improve efficacy (e.g. glycooptimisation) are not compatible with the biosimilarity approach. However, differences that could have an advantage as regards safety (for instance lower levels of impurities or lower immunogenicity) should be addressed, but may not preclude biosimilarity.

➢ Clinical trials necessary to prove safety and efficacy (Phase I and III)

2) On patent protection for biologics

Biosimilars

- According to the US Biologics Price Competition and Innovation Act (BPCIA), Applicant and the Reference Product Sponsor (“RPS”) engage in a formal information exchange, sometimes called the “patent dance”
- In the course of this “patent dance”, RPS identifies relevant patents.
- At the conclusion of the patent dance, the RPS can bring an action for patent infringement.
- Of the 26 BPCIA litigations thus far:
  - In 15 litigations, there are 5 or fewer patents asserted
  - In 5 litigations, there are more than 25 patents asserted

Biosimilars: Secondary patents

Types of Patents Asserted in BPCIA Litigation*

Of 119 asserted patents:

- 22 patents are composition or product patents
- 97 are process patents
  - 36 patents are method of treatment
  - 19 patents are method of making

What are the other 42 process patents?

* As of Mar. 8, 2019

Biosimilars: Secondary patents

Examples….

- Method for removing viruses (EP 1 561 756 B1)
- Method for purifying an antibody (EP 1 308 456 B1)
- Method for reduction of glucose consumption (EP 1 342 780 B1)
- Method for the prevention of the reduction of a disulfide bond in a polypeptide (EP 2 188 302 B1)

Does the purpose restrict the claim scope, and if so, how?

Biosimilars: Secondary patents

Guidelines for Examination F IV. 4.13

In contrast to an apparatus or product claim, in the case of a method claim that defines a working method which, for example, commences with such words as "*Method for remelting galvanic layers*", the part "*for remelting* ..." is not to be understood as meaning that the process is merely suitable for remelting galvanic layers, but rather as a functional feature concerning the remelting of galvanic layers and, hence, defining one of the method steps of the claimed working method (see **T 848/93**).

…

For a claim that is directed to a method or process, the indication of an intended use of this method may at most be seen as limiting to the extent that the method has to be suitable for that use (see **T 304/08**). Such a claim would therefore be anticipated by a prior-art document describing a method having such suitability although not mentioning the specific use.

?

Biosimilars: Secondary patents

T 1931/14 of 21.2.2018 – Headnote

In the context of a method it is important to **differentiate** between **different types of stated purpose**, namely those that define the application or use of a method, and those that define an effect arising from the steps of the method.
Where the stated purpose defines the specific application of the method, in fact it requires certain additional steps which are not implicit in the remaining features, and without which the claimed process would not achieve the stated purpose.
On the other hand, where the purpose merely states a technical effect which inevitably arises when carrying out the other remaining steps of the claimed method and is thus inherent in those steps, such a technical effect has no limiting effect because it is not suitable for distinguishing the claimed method from a known one.

Biosimilars: Secondary patents

Therapeutic antibodies:

- Are very valuable
- Often used in combination with other drugs
- Patent stratification usually possible, leading to smaller patient cohorts in clinical trials

➢ For each therapeutic antibody, there are numerous clinical trials.

➢ Desired to protect result of clinical trial by patent.

Biosimilars: Secondary patents

XCALIBr trial (prior art):

Bevacizumab + capecitabine in the first line treatment of patients with metastatic breast cancer (MBC), previously untreated with chemotherapy except in (neo)adjuvant setting (interval > 6 months)

- Median time to progression (TTP) 5.7 months

Ribbon-1 (clinical trial in EP 2 752 189 B1):

Bevacizumab + capecitabine in the first line treatment of MBC patients, no neoadjuvant treatment for at least 12 months

- Progression Free Survival (PFS) 8.6 months compared to 5.7 months for capecitabine alone

Novel?

Biosimilars: Secondary patents

EP 2 752 189 B1

1. Bevacizumab for use in a method of treating locally recurrent or metastatic breast cancer in a human subject, the method comprising administering to the subject a treatment regimen comprising an effective amount of capecitabine and bevacizumab, wherein said subject has not received any chemotherapy for locally recurrent or metastatic breast cancer, and has not received prior adjuvant chemotherapy in recurrence less than or equal to 12 months since last dose; and wherein the treatment regimen effectively extends the progression free survival of the subject compared to treatment with capecitabine alone.

Biosimilars: Secondary patents

G2/08

In the past, a whole body of jurisprudence has developed concerning the question as to when a technical effect of a claimed therapeutic application not previously described in the state of the art can be recognized as conferring novelty on said application and this jurisprudence continues to be applicable to the assessment of the individual cases under consideration (see in particular T 290/86, OJ EPO 1992, 414; T 1020/03, OJ EPO 2007, 204; **T 836/01 of 7 October 2003**; T 1074/06 of 9 August 2007).

Biosimilars: Secondary patents

T 836/01;

… a hitherto unsuspected property of a known molecule/composition does not necessarily translate into a novel use (be it medical or otherwise) of that molecule/composition, but for an application to be construed as a further use or "further medical use"/"further therapeutic application", this new technical effect would have to lead to a truly new industrial/commercial application arising from e.g. the opening a new field of application, the healing of a different pathology/ clinical situation, the creation of a distinct group or sub-group of subjects (either end-users or patients) or the new use must involve new physical means/measures for its practise.

Decision of OD on EP 2 752 189 B1

- „effectively extends the progression free survival of the subject compared to the treatment of capecitabine alone“ defines a clinical situation
- Distinction between TTP and PFS has no bearing on the question of novelty
- At least 20 of the 106 patients in the XCALIBr study were treatment naive in the sense of the patent
- However, this subgroup was not assessed for TTP
- Since only median values were provided, treatment success of these 20 patients not disclosed

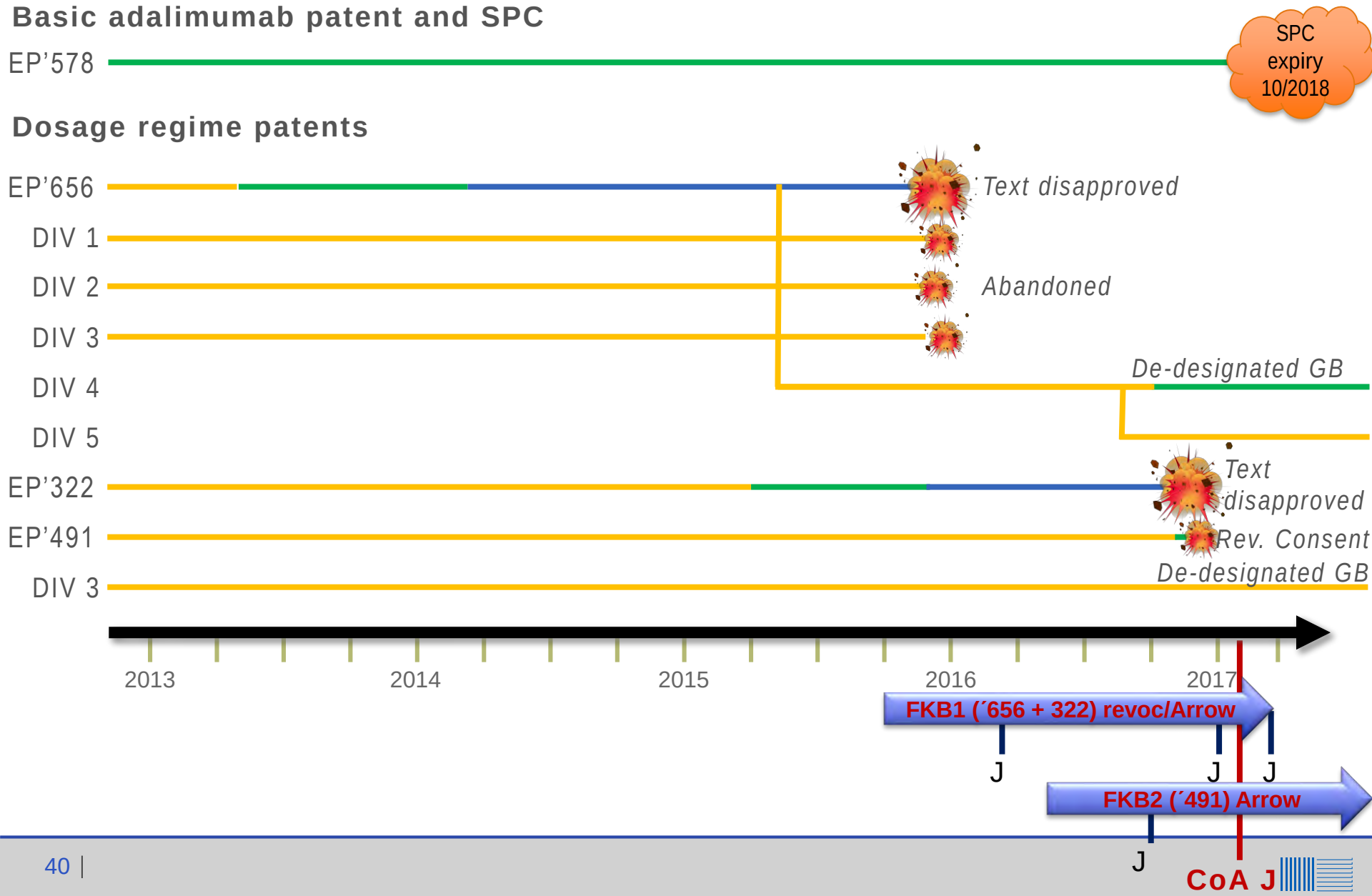
➢ Novel!

Biosimilars: Clearing the way in Europe

- Licensing
- Invalidation proceedings
  - National nullity proceedings
  - EPO opposition proceedings
- Negative declaratory judgments

Case: *Fujifilm Kyowa Kirin Biologics (FKB) v. Abbvie*

- Antibody adalimumab, sold by Abbvie as *Humira* is highest selling prescription drug in the world with more than US$ 12 billion net sales p.a.
- FKB and others are preparing for launch of biosimilars when SPC expires in October 2018
- Abbvie has a large portfolio of second generation patents which FKB probably sees as a **Hydra** – for every head chopped off, a couple of heads regrow:


Basic adalimumab patent and SPC
EP’578
SPC expiry 10/2018
Dosage regime patents
EP’656
DIV 1
DIV 2
DIV 3
DIV 4
DIV 5
EP’322
EP’491
DIV 3
Text disapproved
Abandoned
De-designated GB
Text disapproved
Rev. Consent
De-designated GB
2013
2014
2015
2016
2017
FKB1 (´656 + 322) revoc/Arrow
FKB2 (´491) Arrow
J
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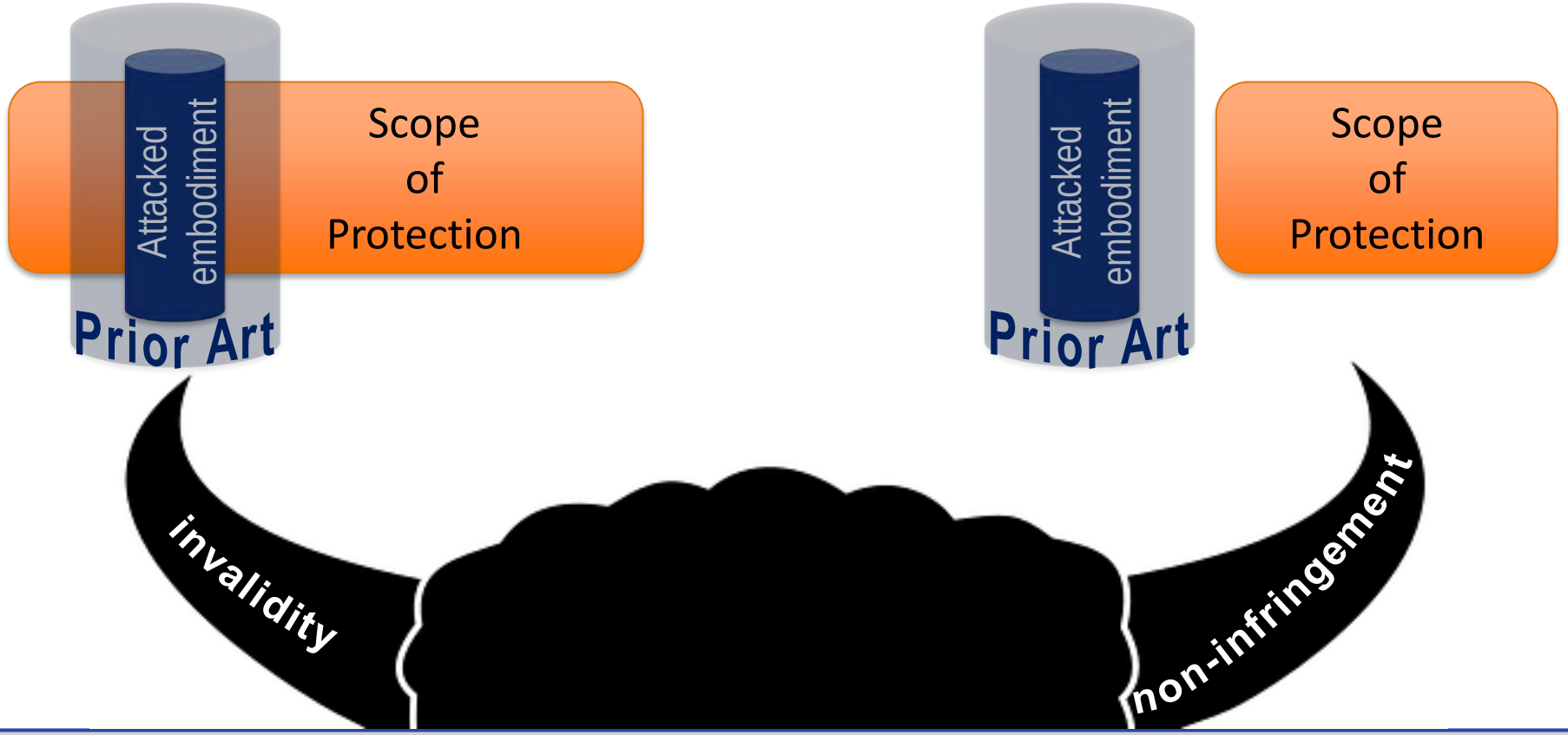
Motivation to request an Arrow declaration

- FKB argued that due to Abbvie‘s conduct and the pendency of multiple divisionals it would not have a chance to clear the way prior to the intended product launch post SPC expiry in October 2018

- Thus relied upon Courts inherent jurisdiction / discretion to grant declarations

Arrow Declarations are based on ‘Gillette defense’:

- instead of asking whether a patent is valid and infringed, it is considered whether the potentially infringing product (“attacked embodiment”) is old or obvious:



Arrow Declarations are based on ‘Gillette defense’:

- Concept / terminology goes back to case *Arrow Generics v Merck, [2007] EWHC 1900 (Pat)*
- Similar circumstances, though not identical, e.g.:
  - parent patent previously invalidated by both UK courts and centrally at EPO, and generic market entry had, thus, already taken place
  - Merck‘s EP divisional applications thus posed a threat to Arrow‘s existing generics business in UK
- Arrow filed UK revocation action against next granted divisional, but Merck withdrew UK designation at last minute; further divs were pending
- UK Patents Court held that an action for a declaration that the generic product was old or obvious at a particular date was arguable.

Arrow is declaratory judgment regarding the product/use

Request in the FKB v Abbvie cases:

> products containing a biosimilar to adalimumab for the treatment of rheumatoid arthritis, psoriatic arthritis and/or psoriasis by the administration of 40mg every other week by subcutaneous injection would have been anticipated or obvious at the priority dates of Abbvie's two patents.

Declarations finally granted for the following reasons

- No granted patent to revoke and no preemption of decision on validity of future patents, thus no usurpation of UK statute or EPO‘s competence
- AbbVie’s threat to sue for infringement, while avoiding judicial scrutiny, but keeping multiple divisionals pending
- not otherwise possible for a company to clear the way for an intended product launch
- need for commercial certainty
- useful purpose in the UK

  (Court took into account effect of declarations in foreign jurisdictions only to extent that UK market affected – claimants’ supply chain in UK was protected by making injunctive relief in other jurisdictions less likely and settlements more likely)
- huge investment costs for clinical development
- potential damages risk in the event of launch at risk

Pfizer v Roche

- Roche holder of EP patent for bevacizumab and SPC (expiry 06/2020) and of various patent applications
- Pfizer manufactures biosimilar in Belgium and intends to bring biosimilar to the market in various European countries
- Pfizer filed “Arrow” claim in the UK
- Roche de-designated UK
- Pfizer reasoned that UK judgment would persuade courts in other countries to not grant a preliminary injunction
- Trial in April 2019; judgment expected shortly
- Judge suggested that abandoning UK patents may be enough to warrant a declaration

Pfizer v Roche

- Pfizer also tried an “Arrow” claim in NL
- Roche responded by filing a motion to decline jurisdiction
- Court dismissed Roche’s motion (May 10, 2019)
  - Hypothetical situation (no products on the market; divisionals not yet filed) does not preclude jurisdiction
  - Situation not merely hypothetical as Roche’s strategy seems to be focused on keeping open the possibility to file further divisionals

For any questions – JRenken@HoffmannEitle.com

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Thank you for your attention

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