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Obviousness of Biologics Inventions: Strategies for Biologics Claims in the U.S., Europe, and China

TUESDAY, MARCH 9, 2021

1pm Eastern | 12pm Central | 11am Mountain | 10am Pacific

Today's faculty features:

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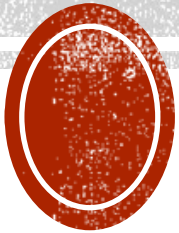
OBVIOUSNESS OF BIOLOGICS INVENTIONS: STRATEGIES FOR BIOLOGICS CLAIMS IN THE U.S



Strafford Webinars, March 9, 2021

Carla Mouta-Bellum, Ph.D.

Arrigo, Lee, Guttman & Mouta-Bellum, LLP

OBVIOUSNESS

- *Graham v. John Deere Co.*, 383 U.S. 1 (U.S. 1966)
  - Satisfying §103 is legal question with factual underpinnings:
    - the scope and content of the prior art;
    - differences between the prior art and the claims at issue; and
    - the level of ordinary skill in the pertinent art.
    - And "[s]uch secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., … may have relevancy."

"[if] the difference between the subject matter sought to be patented and the prior art… would have been obvious at the time to a person skilled in the art, then the subject matter cannot be patented."

OBVIOUSNESS

(A) COMBINING PRIOR ART ELEMENTS ACCORDING TO KNOWN METHODS TO YIELD PREDICTABLE RESULTS;
(B) SIMPLE SUBSTITUTION OF ONE KNOWN ELEMENT FOR ANOTHER TO OBTAIN PREDICTABLE RESULTS;
(C) USE OF KNOWN TECHNIQUE TO IMPROVE SIMILAR DEVICES (METHODS, OR PRODUCTS) IN THE SAME WAY;
(D) APPLYING A KNOWN TECHNIQUE TO A KNOWN DEVICE (METHOD, OR PRODUCT) READY FOR IMPROVEMENT TO YIELD PREDICTABLE RESULTS;
(E) "OBVIOUS TO TRY" – CHOOSING FROM A FINITE NUMBER OF IDENTIFIED, PREDICTABLE SOLUTIONS, WITH A REASONABLE EXPECTATION OF SUCCESS;
(F) KNOWN WORK IN ONE FIELD OF ENDEAVOR MAY PROMPT VARIATIONS OF IT FOR USE IN EITHER THE SAME FIELD OR A DIFFERENT ONE BASED ON DESIGN INCENTIVES OR OTHER MARKET FORCES IF THE VARIATIONS ARE PREDICTABLE TO ONE OF ORDINARY SKILL IN THE ART;
(G) SOME TEACHING, SUGGESTION, OR MOTIVATION IN THE PRIOR ART THAT WOULD HAVE LED ONE OF ORDINARY SKILL TO MODIFY THE PRIOR ART REFERENCE OR TO COMBINE PRIOR ART REFERENCE TEACHINGS TO ARRIVE AT THE CLAIMED INVENTION.

- What does it take to prove it? Most often (PTAB):
  - Rationale of teaching or suggestion of all claimed elements

    &
  - Showing that a skilled artisan would have been motivated to combine/modify the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.

  - https://www.uspto.gov/web/offices/pac/mpep/s2143.html#d0e209516

OBJECTIVE INDICIA SECONDARY CONSIDERATIONS

commercial success	long-felt need	failure by others
copying	teaching away	initial disbelief and subsequent acclaim by experts

ADDITIONAL EVIDENCE

- Unexpected results
  - Compare to closest prior art?
  - Compare to closest example within closest prior art?
  - Showing must be commensurate in scope with the claims

  - PTAB found that patentee did not sufficiently establish that "the efficacy of a subcutaneous 40 mg biweekly dosing regimen would have been unexpected. Nor [did] Patent Owner compare that dosing regimen to the closest prior art."
  - *Boehringer Ingelheim Int'l GmbH v. AbbVie Biotechnology Ltd.*, IPR2016-00408 and IPR2016-00409

NEXUS REQUIRED

- "Before delving into the specific arguments and evidence of secondary considerations, we note that it is not sufficient that a product or its use merely be within the scope of a claim in order for objective evidence of nonobviousness tied to that product to be given substantial weight. There must also be a causal relationship, termed a "nexus," between the evidence and the claimed invention. …A nexus is required in order to establish that the evidence relied upon traces its basis to a novel element in the claim, not to something in the prior art. …Objective evidence that results from something that is not "both claimed and novel in the claim," lacks a nexus to the merits of the invention. … All types of objective evidence of nonobviousness must be shown to have nexus. …The stronger the showing of nexus, the greater the weight accorded the objective evidence of nonobviousness."
- *Tandus Flooring, Inc. v. Interface, Inc.,* IPR2013-00527, Paper 48 (PTAB Feb. 12, 2015)

NOT WORKING VERY OFTEN AT PTAB

- Patent Owners having not much success so far with objective evidence of nonobviousness - not showing nexus (linking the objective evidence of obviousness to the merits of the claimed invention).
- PTAB was not persuaded by objective evidence of nonobviousness in a MOT patent, such as the commercial success of Humira® and long-felt need. The PTAB held that AbbVie did not sufficiently establish nexus between the objective evidence and the claimed dosing regimen rather than the (separately patented) humanized D2E7 antibody itself (nexus established here).

CLAIM TYPE CONCLUSIONS FOR ANTIBODY IPRS

- Composition/formulation claims have the best chance of withstanding an IPR challenge initially (lowest institution rate).

- If IPR instituted, method of treatment claims have highest rate of all claims surviving, but composition/formulation claims have the lowest rate of all claims canceled.

- An isolated human antibody that competes with a reference antibody for binding to human IL-4 interleukin-4 (IL-4) receptor, wherein the light chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:10 and the heavy chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:12.
- The claim construction dispute is this: in the context of this patent, must a "human antibody" be *entirely* human? Or may it also be "partially human," including "humanized"?
- Immunex filed TD seeking narrower Phillips construction. Too late. Purposefully.
- Court applied "broadest reasonable construction in light of the specification of the patent."
- Language of the claim: nothing in the claim restricts "humans" to fully humans. Dependent claims provide no further guidance.
- Specification: no express definition but usage confirms its breadth.
- "[t]he desired antibodies are at least partially human, and preferably fully human."

PHILLIPS V BRI

CLAIM CONSTRUCTION STANDARDS

Immunex Corp. v. Sanofi-Aventis U.S. LLC, 977 F.3d 1212, 1219 (Fed. Cir. 2020)

- Immunex, disagreeing that "fully" was necessary to convey an antibody's "completely human" nature, quotes approvingly a district court's remark in the accompanying litigation that "when one purchases . . . a German Shepherd, one assumes, absent further context, that the seller will not deliver . . . a poodle-Shepherd mix." Appellant's Br. 24 (quoting J.A. 9035).
- But to the extent that canine metaphors are apt, more on the nose is that "brown dogs" plainly include "partially brown" dogs, such as a mostly brown dog with a white spot

FOOTNOTE HUMOR

Immunex Corp. v. Sanofi-Aventis U.S. LLC, 977 F.3d 1212, 1219 (Fed. Cir. 2020)

PROSECUTION HISTORY

- ‘‘equivocal, at best’’?
- **Immunex** used both “fully human” and “human” within the same claim set in another patent application in the same family. “[T]he prosecution of related patents may be relevant to the construction of a given claim term.”
- **Immunex** provides no convincing explanation for its simultaneous use of the two terms beyond what is apparent: they are not interchangeable.
- As initially filed, claim 1 recited simply “an isolated antibody.” The word “human” was added later, at the same time that dependent claim 11, which recited “a human, partially human, humanized, or chimeric antibody,” was canceled. Surrender?
- Disavowal must be clear and unmistakable
- Only done to overcome anticipation by nonhuman abs
- Post-Amendment, Examiner expressly wrote that the amended “human” antibodies encompassed “humanized” antibodies.

EXTRINSIC EVIDENCE

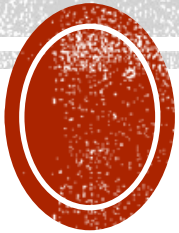
- experts' testimony, product catalogs, and a selection of journal articles—to establish whether “human antibody” had an established meaning to a person of ordinary skill in the art, independent of the specification.
- The patent drafter controls the content of the specification, writes the claims, and responds to office actions. The drafter, then, is in the best position to anticipate ambiguity or questions of scope and to write the patent accordingly. Indeed, we give the intrinsic evidence “priority,” *…*over extrinsic evidence with which it is “inconsistent.”
- Extrinsic evidence may be of assistance if the intrinsic record is equivocal, leaving us looking for further guidance.
- But here, the meaning of “human antibody” as discerned from the intrinsic evidence squarely conflicts with the meaning that **Immunex** would distill from its selected extrinsic evidence.
- intrinsic record trumps

PHILLIPS AT PTAB

- Rule changing the claim construction standard applied during *inter partes* review (IPR), post-grant review (PGR), and covered business method (CBM) review proceedings before the Patent Trial and Appeal Board (PTAB). Not Reexams, reissues.
- Applies to IPR, PGR, and CBM petitions filed on or after the effective date of the final rule, which is November 13, 2018
- Claim construction standard articulated by the United States Court of Appeals for the Federal Circuit in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (*en banc*).
- Narrower? Reduces the span of prior art
- More expert testimony than their own assessment of how POSITA understands the claim scope
- Takes into consideration prior claim construction in civil action or ITS if timely of record

- Greenleaf et al., "*How Different Are the Broadest Reasonable Interpretation and Phillips Claim Construction Standards?*" Intellectual Property Owners Association, 2018, p.1, available at https://ipo.org/wp-content/uploads/2018/10/BRI-v-Phillips-Final-1.pdf

EXAMPLES



MOTIVATION TO COMBINE

Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd., 821 F.3d 1359 (Fed. Cir. 2016)

1. *A method of labeling a nucleic acid molecule*, the method comprising incorporating into the nucleic acid molecule a nucleotide or nucleoside molecule, wherein the nucleotide or nucleoside molecule has a base that is linked to a detectable label via a cleavable linker and the nucleotide or nucleoside molecule has a ribose or deoxyribose sugar moiety, wherein the ribose or deoxyribose sugar moiety comprises a protecting group attached via the 2′ or 3′ oxygen atom, and said protecting group can be modified or removed to expose a 3′ OH group and the protecting group comprises an azido group.

- The RES requirement refers to the likelihood of success in combining the references to meet the limitations of the claimed invention. Board should have identified a reasonable expectation of making the claimed invention, not of combining the references for the purposes found in the prior art.

- The invention was not obvious because there was no motivation to combine the references since there was no credible explanation to why a POSITA would have expected Zavgorodny's group to meet the requirements of Tsien.

- Affirmed

REASONABLE EXPECTATION OF SUCCESS

Regents of the Univ. of Cal. v. Broad Inst., Inc., 903 F.3d 1286 (Fed. Cir. 2018)

The claims related to a method of cutting DNA molecules using the CRISPR-Cas9 system. System uses (1) crRNA; (2) a tracrRNA; and (3) Cas9 protein.

Board found no reasonable expectation of success in applying the system in eukaryotic cells.

Federal Circuit affirmed: substantial evidence supports lack of RES

- Too many differences between the two systems
- Concerns that it could work, could be degraded, toxic
- **UC's own expert** had concluded in 2012 that whether the CRISPR-Cas9 system will work in eukaryotes "remains to be seen" and "[o]nly attempts to apply the system in eukaryotes will address these concerns."
- **Inventor had stated** that their "2012 paper was a big success, but there was a problem. We weren't sure whether CRISPR/Cas9 would work in eukaryotes." Many frustrations. And success in doing so would be "a profound discovery."

OBVIOUS TO TRY

FC: Affirmed.

Supreme Court's *KSR* opinion.

> The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was 'obvious to try.' When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103."

OBVIOUS TO TRY

In re Kubin (561 F. 3d 1351) (Fed. Cir. 2009)

An isolated nucleic acid molecule comprising a polynucleotide encoding a polypeptide at least 80% identical to amino acids 22-221 of SEQ ID NO:2, wherein the polypeptide binds CD48.

The prior art disclosed:

1. The protein called "NAIL" encoded by the nucleic acid;
2. Antibodies specific to the protein; and
3. Cloning techniques for obtaining the polynucleotide.

OBVIOUS TO TRY

- *Kubin* (con't)
  - Board:
    - "one of ordinary skill in the art would have recognized the value of isolating NAIL cDNA, and would have been motivated to apply conventional methodologies, such as those disclosed in Sambrook and utilized in Valiante, to do so."
    - "appellants' claim was "'the product not of innovation but of ordinary skill and common sense,' leading us to conclude NAIL cDNA is not patentable as it would have been obvious to isolate it."

NON-OBVIOUSNESS OF AB-DRUG-CONJUGATE

- Antibody, linker, drug not known
- POSA not motivated to modify known components to make the ADC
- POSA would not have had a reasonable expectation of success
- Claimed ADC shows unexpected results

UNEXPECTED RESULTS

- 1. An immunoconjugate comprising an anti-ErbB2 antibody conjugated to a maytansinoid, wherein the antibody is huMAb4D5-8.

  - Prior art taught a mouse TA.1 mMab-DM1 conjugate.
  - POSITA would not have been motivated to replace TA.1 with Herceptin evidence at the time suggested such construct to have unacceptable levels of ADCC.
  - Immunogen also presented evidence of difficulty and unpredictability when preparing "any antibody-toxin immunoconjugate," lack of a reasonable expectation of success in the claimed invention.
  - In addition, Immunogen's objective evidence of nonobviousness related to the commercial success of T-DM1/Kadcyla® supported the patentability of other claims.

Phigenix, Inc. v. Immunogen, Inc., IPR2014-00676, Paper 39 (P.T.A.B. Oct. 27, 2015)

UNEXPECTED RESULTS NEXUS

- "In view of the specific components recited in claim 8, i.e., a specific antibody, linker, and toxin, which are the same as those in T-DM1/Kadcyla®, we are persuaded that Patent Owner establishes a sufficient nexus in relation to the cited objective evidence of nonobviousness."

- "The specification of the '856 patent discloses, and claim 8 recites, the very components that led to the unexpected results, praise and commercial success….Patent Owner sufficiently establishes that it is the exact combination of those components recited in claim 8, rather than different components previously combined in the prior art, that provided the unexpected results at issue, and led to praise and commercial success."

PRIOR ART TEACHES AWAY FROM THE PROPOSED MODIFICATION OR COMBINATION

- Proceeding contrary to the accepted wisdom in the art represents "strong evidence of unobviousness"

- "Trade-offs often concern what is feasible, not what is, on balance, desirable. Motivation to combine requires the latter."
  - *Winner Int'l Royalty Corp. v. Ching-Rong Wang*, 202 F.3d 1340 (Fed. Cir. 2000).

- Merely because a reference does not describe a particular feature does not automatically mean it teaches away from the claimed invention.
  - *In re Inland Steel Co.*, 265 F.3d 1354, 1361 (Fed. Cir. 2001).

- Mere disclosure of alternative designs does not teach away.
  - *In re Fulton*, 391 F.3d 1195 (Fed. Cir. 2004).

TEACHING AWAY

- *Boehringer Ingelheim Int'l GmbH v. AbbVie Biotechnology Ltd.*, IPR2016-00408, HUMIRA®

1. A method for treating rheumatoid arthritis in a human subject, comprising administering subcutaneously to a human subject having rheumatoid arthritis a total body dose of 40 mg of a human anti-TNFα antibody once every 13–15 days *for a time period sufficient to treat the rheumatoid arthritis*, wherein the anti-TNFα antibody comprises [lists 6 CDRs].

"for a time period sufficient to reduce the signs, symptoms, and/or progression of RA."

"for a time period sufficient to reduce significantly the signs and symptoms of rheumatoid arthritis."

- just because other doses might have had better efficacy than the claimed dose does not represent a teaching away
- "[a] reference teaches away from the claimed invention if it criticizes, discredits, or would have discouraged a person of ordinary skill in the art from 'following the path set out in the reference,' or if a person of ordinary skill 'would [have been] led in a direction divergent from the path that was taken by the applicant.' In re Gurley, 27 F.3d 551, 553 (Fed. Cir. 1994); see In re Fulton, 391 F.3d 1195, 1201 (Fed. Cir. 2004). The mere disclosure of alternative designs, however, does not teach away. In re Mouttet, 686 F.3d 1322, 1333–34 (Fed. Cir. 2012)." IPR2016-00408

OBVIOUSNESS OF RANGES

E. I. du Pont de Nemours & Co. v. Synvina C.V. (Fed. Cir. 2018)

court recognized "several ways by which the patentee may rebut that presumption."

- If the claimed process parameter "produce[s] a new and unexpected result which is different in kind and not merely in degree from the results of the prior art." (based on *Aller)*
- If the prior art taught away from the claimed range
- If the parameter was not recognized as "result-effective." (based on *In re Applied Materials, Inc.*, 692 F.3d 1289 (Fed. Cir. 2012))
- If the prior art discloses "very broad ranges" which "may not invite routine optimization." (based on *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291 (Fed. Cir. 2011))

GENENTECH, INC. V. HOSPIRA, INC., 946 F.3D 1333 (FED. CIR. 2020)

1. A method of purifying a protein which comprises CH2/CH3 region, comprising subjecting a composition comprising said protein to protein A affinity chromatography at a temperature in the range from about 10°C to about 18°C.

- WO '389 teaches that "[a]ll steps are carried out at room temperature (18–25°C)."
- A prior art reference that discloses an overlapping but different range than the claimed range can be anticipatory, even where the prior art range only partially or slightly overlaps with the claimed range
- Once the patent challenger has established, through overlapping ranges, its prima facie case of anticipation, "the court must evaluate whether the patentee has established that the claimed range is critical to the operability of the claimed invention." Id. at 871; see also E.I. DuPont de Nemours & Co. v. Synvina C.V., 904 F.3d 996, 1008 (Fed. Cir. 2018) (" 'where there is a range disclosed in the prior art, and the claimed invention falls within that range, the burden of production falls upon the patentee to come forward with evidence' of … criticality")
- If the relevant comparison between a disputed claim limitation and the prior art pertains to a range of overlapping values, "we and our predecessor court have consistently held that even a slight overlap in range establishes a prima facie case of obviousness."
- No criticality, T known to be result-effective variable
- Presentation had no sufficient nexus

RELATIVE TERMS

- 1. A method for the treatment of a human patient with a malignant progressing tumor or cancer characterized by overexpression of ErbB2 receptor, comprising administering a combination of an intact antibody which binds to epitope 4D5 within the ErbB2 extracellular domain sequence and a taxoid, in the absence of an anthracycline derivative, to the human patient in an amount effective to extend the time to disease progression in said human patient, without increase in overall severe adverse events.

- *[T]he expressions "extend the time to disease progression" and "response rate" are clear from the specification (see, in particular, page 15, lines 15-17; and pages 42-43) and would be readily understood by a skilled oncologist. Clearly, the combination of an anti-ErbB2 antibody and a taxoid is administered in an amount effective to extend the time to disease progression relative to an untreated patient.*
- "The public notice function of a patent and its prosecution history requires that a patentee be held to what he declares during the prosecution of his patent."
- Terms "in an amount effective to extend the time to disease progression in the human patient" and "an effective amount," as set forth in patent claims directed to method for treating cancer patients who overexpress certain gene, were measured relative to an untreated patient; claims did not provide explicit comparator, specifications discussed several drugs and drug combinations that could be viable comparators, and patentee made comparator choice during prosecution
- Genentech, Inc. v. Iancu, 809 F. App'x 781, 783 (Fed. Cir. 2020)

NON-OBVIOUNESS STRATEGIES

Unpredictability can be important: show that invention was not predictable.

- Show no reasonable expectation of success.
- Show there was not a "finite number of identified, predictable solutions."
- Show unexpected results
- Other objective indicia of nonobviousnes??
- Will that affect scope of enablement?

Show teaching away, particularly in so-called predictable results.

Showing lack of predictability or expectation of success may require submitting data and/or declarations earlier in prosecution; evidence to destroy, not rebut, the prima facie case.

THANK YOU

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Obviousness of Biologics Inventions in Europe

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Summary - inventive step at the EPO

- Problem and solution approach
  - What problem is solved by the structural differences compared to known products?
  - Is the claimed product just an **alternative** to the known products, or does it lead to any **unexpected advantage**?
  - Is the problem solved across the scope of the claims
- EPO takes a particularly strict view in the antibody field
- New (March 2021) edition of EPO Guidelines for Examination now formally sets out the EPO's particular approach in relation to antibody inventions

Mathys&Squire

Much is considered routine by the EPO

"Knowledge of the structure-function relationships of antibodies allows the provision of a number of derivatives for a multitude of applications. Variants of antibodies, antibody fragments, bispecific or multispecific antibodies, antibody fusion products are commonly designed and produced"

2021 Guidelines, G-II-5.6.1

- Is there any technical reason why this product would not have been found by routine/trial and error methods?

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Structural non-obviousness not enough

- If the target antigen is known, then it would be routine to produce and screen large numbers of antibodies against that target

"If a novel antibody binds to the same antigen as known antibodies, inventive step is not acknowledged solely on the basis that the novel antibody is structurally different from the known antibodies. Arriving at alternative antibodies by applying techniques know[n] in the art is considered to be obvious to the skilled person. **The fact that the structure of the thus obtained alternative antibodies**, i.e. their amino acid sequences, **is not predictable is not a reason for considering these antibodies as non-obvious** … "

2021 Guidelines, G-II-5.6.2

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“Alternative” antibodies against a known target

“the skilled person … faced [with] the technical problem of providing additional monoclonal anti-CXCR-4 antibodies useful for treating diseases in which pathogenesis is mediated by CXCR4 and SDF-I … and having knowledge of how to prepare such antibodies … would have been motivated to apply those known techniques to arrive at antibodies that solve the technical problem in an obvious manner. **All such antibodies would therefore have been obvious to the skilled person, the claimed antibody being one of many potential anti-CXCR-4 antibodies, each of which representing an obvious solution to the technical problem**.”

EP 2 297 206, Preliminary opinion of the Board of Appeal

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Surprising technical effect/unexpected advantage

- “The subject-matter of a claim defining a novel, further antibody binding to a known antigen **does not involve an inventive step unless a surprising technical effect is shown by the application**.”
- “Examples of surprising technical effects when compared to known and enabled antibodies are, for example,
  - an improved affinity,
  - an improved therapeutic activity,
  - a reduced toxicity or immunogenicity,
  - an unexpected species cross-reactivity or
  - a new type of antibody format with proven binding activity.”

2021 Guidelines, G-II-5.6.2

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EP 1957106 Opposition (Labrys)

"An anti-CGRP antagonist that is a human antibody or a humanized antibody with a binding affinity (KD) to human alpha-CGRP of 50 nm or less as measured by surface plasmon resonance at 37°C"

- Making/selecting high affinity antibodies was obvious over known anti-CGRP antibodies
- Amendment to **specify epitope sequence** did not fix the problem
  - "…the specific selection of amino acids 25-37 of alpha-CGRP is considered arbitrary in the absence of data proving that said selection leads to a particular, unforeseeable technical effect"
- Amendment to **specify VH and VL sequences** did not fix the problem
  - "The particular antibody … in the absence of any particular technical effect which could not be derived from prior art, lacks inventive activity."
- Amended to **medical use** claim – for use in the prevention or treatment of headache
  - Claim upheld as an inventive new use

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Supporting data

- If inventive step is based on an unexpected effect, it must be technically plausible **from the information in the application as filed** that your invention does actually achieve that effect
  - did the application include **enough information to at least suggest** that the effect would be achieved?
  - did the application include a **plausible technical reason** why the effect would be achieved?
- Post-filing evidence can only be taken into account to show an advantage if that advantage was **at least plausible based on the information in the application as filed**

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T 2637/11 Anti-TIRC7 monoclonal antibody/CELLACT

- Alleged advantage = unexpected ability to induce immunotolerant T-cells
  - "The application does not **explicitly disclose** that the claimed antibodies induce immunotolerant T-cells."
  - "…the **examples** of the application do not point to the induction of immunotolerance"
  - "…the **common general knowledge** would not have prompted the skilled person to infer from the suggested use of the antibodies claimed for transplantation therapy that this is based, at least in part, on the antibodies' ability to induce immunotolerance"
  - "…it is not derivable from the application that the claimed antibodies induce immunotolerant T-cells and **this effect cannot accordingly be relied on for the formulation of the technical problem**"

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Claim scope

- If an inventive step is based on an unexpected advantage, then that advantage must be obtained across the scope of the claims
  - "When defining the objective technical problem an effect cannot be retained if it is not **credible that the promised result is attainable throughout the entire range covered by a claim** … If the inventive step of a claimed invention is based on a given technical effect, the latter should, in principle, be **achievable over the whole area claimed**" (Case Law of the Boards of Appeal I.D.4.3)

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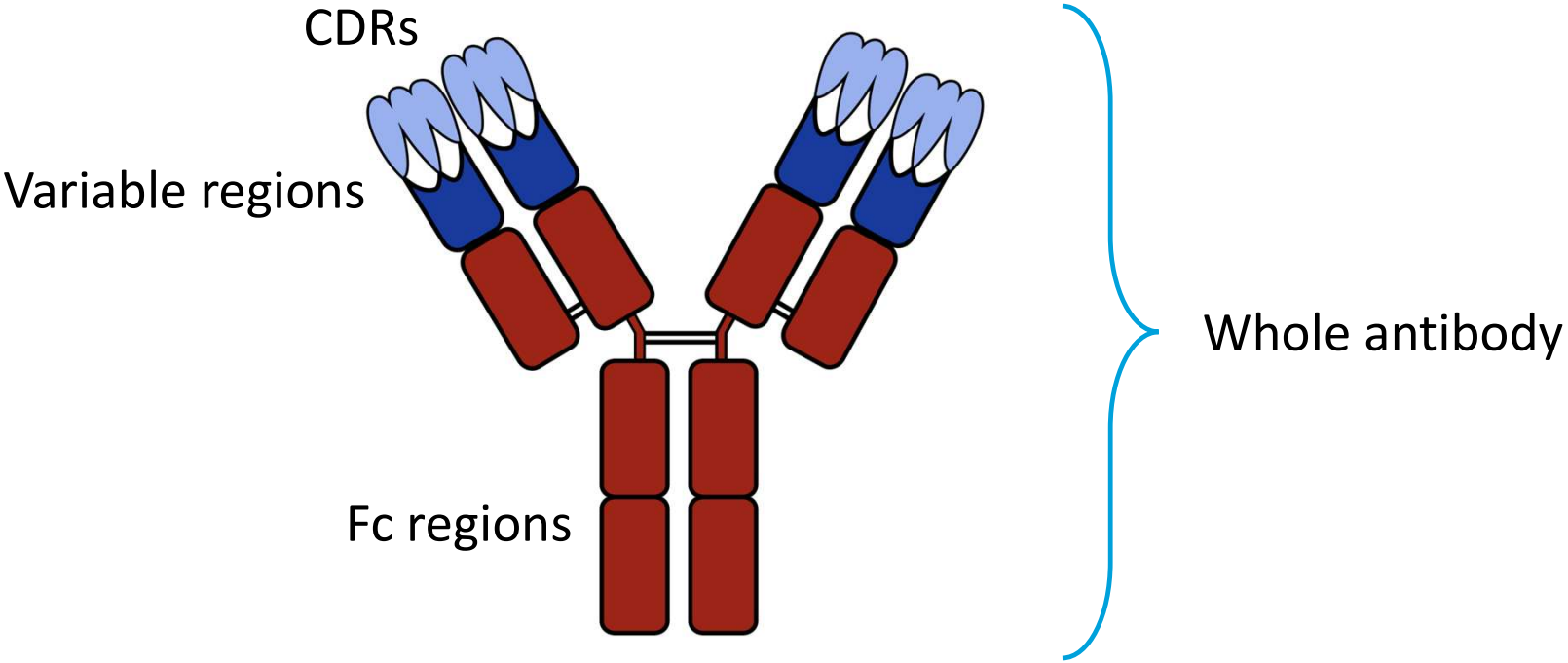
Which parts of your antibody are responsible for the advantage that you rely on?



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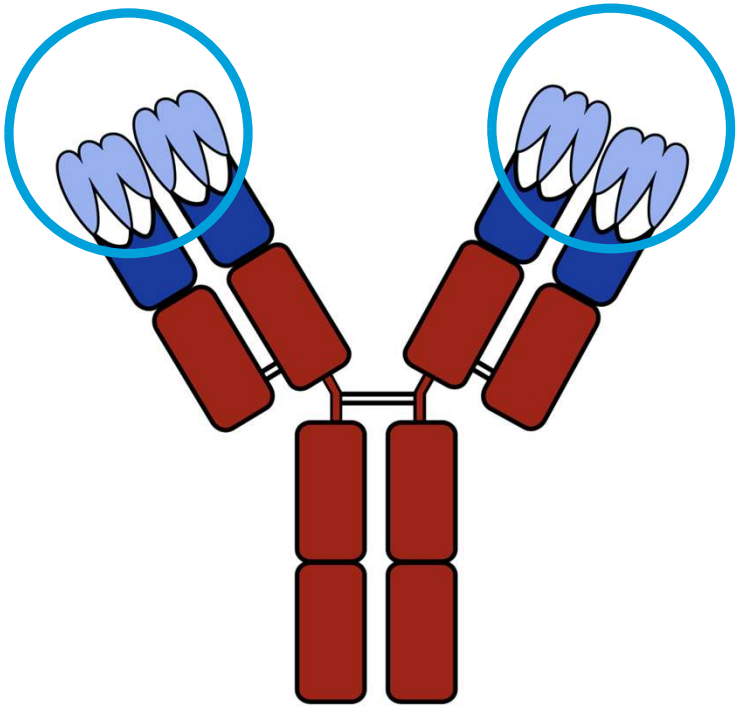
Improved binding specificity/selectivity

"Since the three CDRs of each of the variable domains of the light and heavy chains are normally responsible for binding to the antigen, the conventional antibody, **in order to** be uniquely defined by its structure only and **have its characteristic binding specificity, needs to be defined by at least these six CDRs** to fulfil the requirements of [clarity]"

"A claim to an antibody defined by its structure by fewer than six CDRs will be considered to fulfil the requirements of [clarity] only if it is **experimentally shown** that one or more of the six CDRs do not interact with the target epitope or if it concerns a specific antibody format allowing for epitope recognition by fewer CDRs"

2021 Guidelines G-II 5.6.1.1



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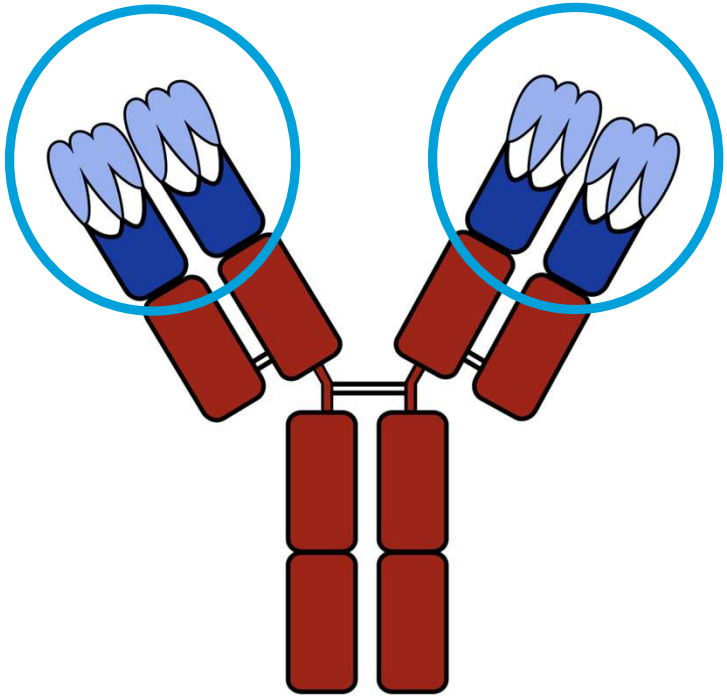
Improved affinity

"If the surprising technical effect involves the binding affinity, the structural requirements for conventional antibodies inherently reflecting this affinity **must comprise the six CDRs and the framework regions** because the framework regions also can influence the affinity"

2021 Guidelines, G-II-5.6.2



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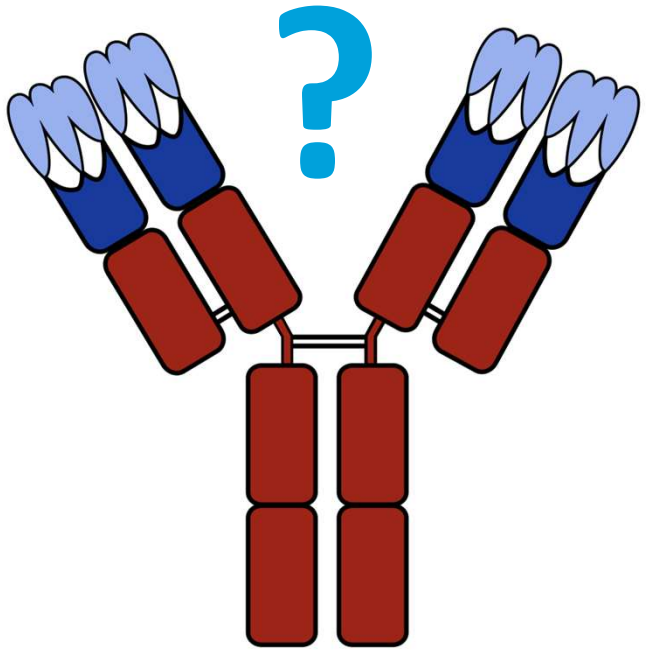
Other advantageous properties

- Improved physical properties, e.g. stability, production yield
- Improved pharmacokinetic properties
- Improved effector function
- Improved therapeutic efficacy

- Which parts of the antibody structure are responsible for those properties?



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Takeda v Roche [2019] EWHC 1911

- Alleged technical contribution = increased fucosylation of an antibody would reduce ADCC to background, even at high antibody concentrations
- Court found that data in the patent
  - make it plausible that the **tested** antibody reduces ADCC
  - make it plausible that no ADCC was found **at the concentration tested**
  - do not make plausible that the same effect would be seen at **higher concentrations or with other antibodies**
- Does the patent plausibly demonstrate a technical contribution to the art?
  - Is it disclosed in the patent?
  - Is it plausible?
  - Is it true?
  - Is it a technical advance?
  - **Does it support claims of this breadth?**

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Conclusions

- Structural non-obvious unlikely to be enough for an inventive step at the EPO
- A new antibody against a known target will probably need an unexpected advantage over any known antibodies against that target
  - Plausible technical pointer to that advantage in the application as filed
- An advantage relied on for inventive step must exist across the scope of the claim
  - Technical reasons or data to support a broader claim scope
- Be prepared…
  - What supporting data might you need?
  - What claim limitations might you need to make?

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Biologics Patent Claims & Obviousness in China

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March 9, 2021

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Definition for Inventiveness

Article 22, paragraph 3 of the Chinese Patent Law:

Inventiveness means that, as compared with the prior art, the invention has prominent substantive features (i.e., non-obviousness) and represents a notable progress (beneficial technical effects).

Post-filing data is acceptable to establish the inventiveness of an invention under certain scenarios according to the amended Guidelines for Patent Examination entering into force as of January 15, 2021.

Assessment of Non-obviousness

Assessment of Non-obviousness (“three-step” approach):

- Identifying the closest prior art;

- Determining the distinguishing technical features and the technical problem actually solved by the invention on the basis of the technical effects achieved by the distinguishing technical features; and

- Determining whether the prior art as a whole provides motivation to apply the distinguishing technical features to the closest prior art to solve the technical problem actually solved by the invention.

Assessment of Beneficial technical effects

Assessment of beneficial technical effects:

- the invention produces a better technical effect over the prior art such as improved quality, increased yield, etc.
- the invention provides a technical solution having different inventive concept, and can produce a **technical effect of substantially the same level as in the prior art**
- the invention represents a new trend of technical development
- the invention produces clearly positive technical effect in some aspects, in spite of the negative effect in other aspects

Assessment of Unexpected technical effects

Unexpected technical effects:

- the invention represents a “qualitative” change, that is, new performance;
- the invention represents a “quantitative” change that is unexpected;

The “qualitative” change or “quantitative” change cannot be expected or inferred by a person skilled in the art

Amendments to the Guidelines Regarding Inventiveness of Biologics

The amended Guidelines for Patent Examination enters into force as of January 15, 2021. In comparison with the previous version of the Guidelines for Patent Examination, the following two amendments would affect the determination of biologics inventions:

1. Acceptance of Post-filing test data under certain scenarios

2. The level of technical effects required for monoclonal antibody

Amendments to the Guidelines Regarding Inventiveness of Biologics

1. Acceptance of Post-filing test data

Principle of examination

The technical effect to be proven by the post-filing test data shall be obtainable from the disclosure of the patent application by a person skilled in the art.

Amendments to the Guidelines Regarding Inventiveness of Biologics

1. Acceptance of Post-filing test data

Two Examples were included in the amended Guidelines to demonstrate “technical effect to be proven by the post-filing test data shall be obtainable from the disclosure of the patent application by a person skilled in the art”.

Amendments to the Guidelines Regarding Inventiveness of Biologics

Example 1:

The claims are directed to Compound A.

The description recites:

- the preparation examples,
- the antihypertensive effect, and
- experimental method for measuring the antihypertensive activity for Compound A, but does not provide the experimental result data.

The applicant submits the supplemental test data for the antihypertensive effect of Compound A.

Based on the original specification, the antihypertensive effect of Compound A has been disclosed, and the technical effect to be proved by the supplementary data is obtainable from the disclosure of the patent specification by a person skilled in the art.

Amendments to the Guidelines Regarding Inventiveness of Biologics

Example 2:

The claims are directed to a compound of general formula I.

The description recites:

- the general formula I and the preparation method thereof, and the preparation examples for multiple specific compounds within the general formula I such as A, B and etc.
- the anti-tumor effect of the compound of general formula I,
- the experimental method for determining the anti-tumor activity and the experimental result data, which is expressed as an IC_{50} value of Compound A against tumor cells ranging from 10 to 100 nM.

The applicant submits post-filing comparative test data showing that the IC_{50} value of Compound A is 15 nM, while the IC_{50} value of the compound of D1 is 87 nM.

Based on the original specification, Compound A and the anti-tumor effect thereof have been disclosed, and the technical effect to be proved by the supplementary data is obtainable from the disclosure of the patent specification by a person skilled in the art.

Amendments to the Guidelines Regarding Inventiveness of Biologics

2. Inventiveness of monoclonal antibody (Part II, Chapter 10, Section 9.4.2.1 of the Guidelines)

A monoclonal antibody of a known antigen involves an inventive step, if

- the monoclonal antibody of the antigen characterized by the structural features differs from the known monoclonal antibody in terms of the key sequences determining the function and use,
- The prior art does not provide any technical motivation to obtain the key sequences, and
- The monoclonal antibody has produced the **beneficial technical effect**.

Definition of Antibodies

How can a monoclonal antibody claim be defined

(Yes) By the producing hybridoma
(Yes) By structural features, with or without functional features
(No) By functional features only: epitope, competitive binding, Kd…- will be rejected for lacking support

※ For definition by hybridoma, the relevant hybridoma must be deposited prior to filing.

※ For definition by structure, at least all of the six CDRs have to be specified.

Exemplary Structural Definitions

- Sequences of 6 CDRs (Yes)
- H and L chain variable region sequences (Yes)
- H and L chain sequences (Yes)
- 6 CDRs from a given H-L chain pair (Yes)
- H chain CDR3 only (No)
- H or L chain only (No)
- CDRs from a CDR pool (No)

Inventiveness of Gene

Inventiveness of a gene encoding known protein (Part II, Chapter 10, Section 9.4.2.1 of the Guidelines)

If the amino acid sequence of a protein is known, an invention of a gene encoding the protein does not involve an inventive step. However, if the gene has a particular base sequence and has unexpected technical effects over other genes having a different base sequence encoding the same protein, the invention of said gene involves an inventive step.

Inventiveness of structural gene

Inventiveness of structural gene (Part II, Chapter 10, Section 9.4.2.1 of the Guidelines)

An invention of a structural gene encoding the following protein involves an inventive step:

In comparison with the known protein, the protein has different amino acid sequence and has different types of properties or improved properties; and
The prior art does not provide any technical motivation of the property change brought about by the sequence difference.

Case 1: PRB Decision No. 87391

- Claim: a humanized Ab defined by H chain and L chain variable region sequences
- D1: a murine Ab having the same CDRs (the parent Ab)
- Spec shows the Kd of the claimed Ab (3.17nM) is slightly lower than the parent Ab (4.19 nM), whereas another humanized Ab has higher Kd.

Applicant's arguments

- The impact that humanization has on the binding affinity is unpredictable. PHOSITA could not foresee the decreased Kd (hence improved affinity) of the claimed antibody
- Submitted supplemental data to show the claimed Ab has superior effect to parent Ab

PRB affirms, holding

- Humanization is common knowledge. Sequence of a particular humanized Ab cannot make it patentably distinct from other potential humanized antibodies.
- Fluctuation of affinity among humanized Abs is within PHOSITA's expectation. The slightly decreased Kd **does not amount to unexpected technical effect**.
- Supplemental data rejected

Hypothetical Decision of the Same Case

For this particular case, a different decision would have been delivered if the amended Guidelines were applied to the case for the following two reasons:

1) No unexpected technical effect is required for monoclonal antibody; and/or

2) Supplemental data might be accepted to establish the inventiveness of the claimed antibody.

Thanks for your attention!

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