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

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

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Obviousness of Biologics Inventions in the US

Carla Mouta-Bellum, Ph.D.
Biologic Commercial Products with the Most IPR Petitions Filed Against

Source: Finnegan research as of Jan. 28, 2018, on 112 filed antibody petitions.
Biologic Drug IPRs by Reference Product
Source: Finnegan research as of Jan. 28, 2018, on 112 filed antibody petitions.
Antibody Petitions Filed

- Granted (at least one claim), 37, 33%
- Denied, 32, 29%
- Pending, 29, 26%
- Adverse Judgment, 3, 3%
- Dismissed, 4, 3%
- Settled/Terminated (Prior to Institution Decision), 7, 6%

Grant rate: 54% (37/69)

Source: Finnegan research as of Jan. 28, 2018 on 112 filed antibody petitions.
Grant rate = granted/granted + denied.
Institution Rate in Antibody IPR Petitions by Type of Claim

Source: Finnegan research as of Jan. 29, 2018, on 73 institution decisions. Note: some petitions have more than one type of claim challenged.

Rate = granted on at least one claim/granted + denied. Does not include settlements, dismissals, adverse judgments, or pending petitions.

- “[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.”
- Not negatively impacted by KSR?
- 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.”
Evaluation of Obviousness

- Look for evidence of unexpected benefit or result (e.g., synergism).
- Obviousness to try: finite v. very large number of possibilities.
- Look for teachings away or disincentive to make a modification to arrive at claimed invention.
- *KSR* addressed motivation.
  - Obviousness requires motivation, rationale for change and reasonable expectation of success.
  - Try to establish no finite number of predictable solutions with anticipated success.
Diversity of Claim Types

- Biologic Compound *per se* (functional, structural, mix)
- Method of Treatment and Second Medical Use
- Formulations
- Patient Populations
- Combination Treatments
- Administration Routes
- Dosage Regimens
- Dosage Forms
- Purification Methods
- Generation Methods
What types of claims are being challenged?

Source: Finnegan research as of Jan. 29, 2018, on 118 filed antibody petitions. Note: some petitions have more than one type of claim challenged.
FWDs in Antibody IPRs

Patent Owner survival rate (by case): 33% (3/9).

Source: Finnegan research as of Jan. 28, 2018, on 37 granted IPRs. Of these, 9 have FWDs, 4 were settled, 24 are pending FWD.
RATIONALES FOR FINAL WRITTEN DECISIONS WHERE ALL INSTITUTED CLAIMS SURVIVED

- No reasonable expectation of success, 2, 50%
- No reasonable motivation to combine/modify, 2, 50%

Source: Finnegan research as of Jan. 29, 2018. May be more than one reason per FWD.
Basis for Petition Denial in Antibody IPRs

Source: Finnegan research as of Jan. 28, 2018, on 32 denials. May be more than one ground for denial.
Antibody Functional Claim

- Obvious to Try *(AbbVie v. Centocor/Stelara®)*

- 1. An isolated human antibody, or antigen-binding portion thereof that binds to human IL-12 and dissociates from human IL-12 with a $K_D$ of $1 \times 10^{-10}$ M or less and a $k_{off}$ rate constant of $1 \times 10^{-3}$ s$^{-1}$ or less, as determined by surface plasmon resonance.

  - “when a claim is functional, an [ordinary artisan] need not predict the structure of the embodiment, they simply must know how to use the methodology to achieve a functional result.”

- Market need

- Finite number of ways to achieve the goal (e.g., transgenic mice, phage display)

- Clear and convincing evidence that ordinary artisan would have expected to succeed


Obvious to try is erroneously equated with obviousness under §103:

1. When what would have been ‘obvious to try’ would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful; and

2. when what was ‘obvious to try’ was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. Id. (citing O’Farrell, 853 F.2d at 903).”
Kadcyla® Antibody-Drug Conjugate

- Not obvious: *Phigenix v. Immunogen*

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.

Nexus

- **Phigenix (con’t)**
  - PTAB: Claims not unpatentable.
    - “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.”
Herceptin® Combination Treatment

- Not obvious to exclude anthracyclin?
- 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.
  - First, denied: Hospira did not show why an ordinary artisan would have avoided anthracyclins when pursuing the combination of an anti-ErbB2 antibody with a taxoid. Although cardiotoxicity of anthracyclins was well known, it remained a common treatment of breast cancer.
  - Rehearing: instituted. Absence is not exclusion

Patient Population: No Institution

- Not obvious; *Phigenix v. Genentech*; Kadcyla®
  - No motivation to treat a patient that does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody with Kadcyla.

- Not obvious; *BI v. Biogen*; Rituxan®
  - No motivation to use rituximab maintenance therapy to treat patients responding to CVP therapy.

- Not obvious; *Celltrion v. Genentech*; Rituxan®
  - No reasonable expectation of success in treating RA in inadequate responders to TNFα-inhibitor with the recited dosage regimen of Rituxan.
Dosage Regimen

- Genzyme Therapeutic Prods. Ltd. v. Biomarin Pharm., Inc., 825 F.3d 1360 (Fed. Cir. 2016)
  - Claim 1. A method of treating a human patient with Pompe’s disease, comprising intravenously administering biweekly to the patient a therapeutically effective amount of human acid alpha glucosidase, whereby the concentration of accumulated glycogen in the patient is reduced and/or further accumulation of glycogen is arrested.
  - PTAB FWD: instituted claims unpatentable as obvious.
    - Reference disclosed every claim limitation other than dosing schedule, and claimed dosing schedule would have been achieved by routine optimization.
Expectation of Success

- *Genzyme* (con’t)
  - FC: Affirmed.
    - No error in PTAB’s reliance on Petitioner’s expert:
      - “[W]e are persuaded by Dr. Pastores’s testimony that the knowledge in the art regarding the treatment of Pompe disease with human GAA would have provided the motivation to select a suitable dose and dosing schedule ... would have been informed by the clinical experience with Gaucher disease ... and that, because ‘it was well known that any enzyme replacement therapy for Pompe disease would be required for the rest of a patient’s life, ... repeated spaced administration of GAA to patients would be immediately understood upon reading [Reuser].’”).
  - Sufficient support of PTAB’s conclusion that a POSITA would have had a reasonable expectation of success combining the asserted references.
1. A method of treating rheumatoid arthritis in a human patient who experiences an inadequate response to a TNFα-inhibitor, comprising administering to the patient an antibody that binds to CD20, wherein the antibody is administered as two intravenous doses of 1000 mg.

- Petitioner did not establish that dose-sizing option (fixed vs. dosing based on surface area), total dose number of infusions, amount of each infusion, were result-effective variables such that a person of skill in the art would have reason to optimize (In Re Antonie, 559 F.2d 618, 620 (CCPA 1977).

Celltrion v. Genentech, Inc., IPR2016-01667
Difficult to Achieve Formulations

- High concentration (20 mg/ml) not obvious/no institution: Swiss Pharma v. Biogen (Tysabri®); Amgen v. AbbVie (Humira®)
  - 1. A stable, aqueous pharmaceutical formulation comprising from about 20 mg/ml to about 150 mg/ml of natalizumab, polysorbate 80 present in an amount of about 0.001% to 2% (w/v), about 10 mM phosphate buffer, and about 140 mM NaCl.

- Self-buffering not obvious/no institution: Coherus v. AbbVie (Humira®)
  - Claim 16. An aqueous pharmaceutical formulation comprising (a) [Humira], wherein the concentration of the antibody is 50 to 200 mg/ml and (b) water, wherein the formulation does not comprise a buffering system.
The Art of Formulating Monoclonal Antibodies Showed That:

- Monoclonal antibodies have unique formulation requirements, even when they have significant similarities in amino acid sequence.
- Small changes in antibody formulations can have enormous effects on protein aggregation, viscosity, and other factors. (e.g., citrate also has stabilizing properties)
Rebuttal 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?

- Other objective indicia of unobviousness/secondary considerations
  - Commercial success
  - Long-felt need
  - Failure by others
  - Copying
  - Teaching away
  - Initial disbelief and subsequent acclaim by experts
Teaching Away

- 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).
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).”
Consider Substantive Declarations During Prosecution

- Declarations need to be as solid as possible. PTAB has found that defective declarations relied on for patentability during prosecution can form an independent basis for instituting an IPR.
    - PTAB reviewed a § 1.131 declaration from the prosecution, found it deficient, and reapplied the prior art the declaration had antedated, instituting the IPR.
  - Case also had live testimony from inventor at oral hearing.
    - One might want declarations from the inventor during prosecution that can then by referred to by the Patent Owner in the optional Preliminary Response to try to ward off institution.
Load Up on Your Evidence During Prosecution!

The “objective evidence of non-obviousness” (also known as “secondary considerations,” as the term was coined in *Graham v. John Deere*) can, for example, include:

- Long felt but unsolved need,
- Failure of others,
- Commercial success,
- Unexpected results created by the claimed invention, and
- Skepticism of skilled artisans before the invention.

*See In re Rouffet, 149 F.3d 1350, 1355 (Fed. Cir. 1998).*

These objective considerations, when present, are important evidence, as they protect against the prejudice of hindsight bias, which frequently overlooks the fact that “[t]he genius of invention is often a combination of known elements which in hindsight seems preordained.”

*McGinley v. Franklin Sports, Inc., 262 F.3d 1339, 1351 (Fed. Cir. 2001).*
Non-Obviousness Strategies

- Unpredictability is 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 nonobviousness?
  - 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.
Obviousness of Biologics Inventions in Europe

Hazel Ford, PhD
Finnegan Europe LLP
Inventive Step at the EPO

- Problem and solution approach
  - Identify the closest prior art
  - Identify the differences between the claimed invention and the closest prior art
  - What is the “problem solved” by those differences?
  - Is the claimed solution to that problem obvious?
Unexpected Advantage?

- What is the problem solved compared to the closest prior art?
- Is there an unexpected advantage that can be relied upon?
  - advantage compared to the closest prior art
  - if not, then the “problem” may be just finding an alternative to the closest prior art
- **Advantage** - would the skilled person looking for this advantage have found this variant?
- **Alternative** - would the skilled person have found this alternative based on routine/trial & error experimentation?
Predictability?

- How predictable is the technical field?
  - Will variations of this type generally be tolerated/predictable?
    - Conservative substitutions?
    - Changes in region linked to activity/function?
  - Are there other examples of good/bad variants that would influence expectations?
  - What is considered routine experimentation?
“In the Board's view, the skilled person in this field is well aware of the fact that even a small structural change in a product (e.g. a vector, a protein, a DNA sequence) or in a procedure (e.g. a purification process) can produce dramatic functional changes. Therefore, the said expert would constantly be conditioned by the prior art and, before taking action, would carefully ponder any possible modification, change or adjustment against the background of the existing knowledge. Under these circumstances, in the Board's view, the skilled person would adopt a conservative attitude. However, this must not be seen in the sense of being reluctant or opposed to modify or adjust a known product or process, but rather in the sense of being cautious. For example, the skilled person in question would neither go against an established prejudice nor try to enter into "sacrosanct" or unpredictable areas nor take incalculable risks. However, within the normal design procedures, the said expert would readily seek appropriate, manifest changes, modifications or adjustments which involve little trouble or work and no risks or only calculable risks, especially for the sake of obtaining a more handy or convenient product or of simplifying a procedure. In particular, the skilled person working in one field (e.g. expression in yeast) would regard a means conveniently adopted in a neighbouring field (e.g. the bacterial art) as being readily usable also in that field, if this transfer of technical knowledge involves nothing out of the ordinary.”
Obviousness of Antibodies

- EPO makes a number of assumptions about antibodies
  - antibody structure/function relationships well known
  - methods for producing, modifying, humanizing etc. all considered routine
  - routine antibody production methods allow production of large numbers of antibodies against a given target

- “Methods to obtain monoclonal antibodies, including human, chimeric or humanized monoclonal antibodies, directed against every well-known and defined antigen, and to screen said antibodies in order to select those presenting specific characteristics are considered routine in the art”
Structural Non-Obviousness?

- EP 2297206 (Eli Lilly) - Preliminary opinion of Board of Appeal
  - “the skilled person starting from the closest prior art, represented by document D1, and faced 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.”

- Structural non-obviousness is usually not enough for an antibody against a known target
Unexpected Properties - Antibodies

- Need to demonstrate an unexpected advantage over prior art antibodies
  - New or improved biological activity
  - Significant improvement in affinity
  - Cross-reactivity
  - Low immunogenicity
  - Pharmacokinetic properties
  - Expression level
  - Stability in solution
  - Reduced toxicity in vivo

- Even then, a “better” antibody against a known target is not necessarily patentable in Europe
  - “The skilled person with a knowledge of [other antibodies against the same target] and intent on producing further antibodies would produce a mixture of antibodies with different properties and select them according to their functionality or affinity, depending upon the intended application”
“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 37ºC”

- lack of inventive step because making and selecting high affinity antibodies was obvious over known antibodies against that target

Amendment to specify epitope 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
T 2045/09 (Anti-ErbB3 Antibody/Genentech)

- “1. An antibody which binds to ErbB3 protein and (i) reduces heregulin-induced formation of an ErbB2-ErbB3 protein complex in a cell which expresses ErbB2 and ErbB3, and (ii) reduces heregulin-induced ErbB2 activation in a cell which expresses ErbB2 and ErbB3”
  - Not inventive - no evidence that these antibodies showed any advantage over prior art anti-ErbB2 antibodies, obvious to target any part of the ErbB2-ErbB3 complex

- “…and (iii) increases the binding affinity of heregulin for ErbB3 protein”
  - Inventive - unexpected that anti-ErbB3 antibodies would increase the binding affinity of heregulin for ErbB3, rather than inhibiting/interfering with its binding

- “7. An antibody which binds to the epitope bound by the 8B8 antibody obtainable from the hybridoma cell line ATCC no. HB-12070”
  - Inventive - plausible that the advantage relied upon for inventive step of claim 1 would be shared by other antibodies binding the same epitope
Is the Problem Actually Solved?

- If inventive step is based on an unexpected advantage or effect, it must be technically plausible that your invention does actually achieve that effect
  - was the advantage demonstrated in the application as filed?
  - 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 data 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
  - “…even if supplementary post-published evidence may in the proper circumstances be taken into consideration, it may not serve as the sole basis to establish that the application solves indeed the problem it purports to solve.” - T 1329/04 (Factor-9/John Hopkins)
Combination of rituximab and methotrexate for treating RA

Patentee argued for unexpected synergy and filed post-published evidence

Board of Appeal:
- effect cannot be taken into account if it could not be deduced by the skilled reader of the application as filed
- nothing in the application as filed suggested synergy
- post-published evidence not taken into account
- closest prior art described other combination RA therapies using methotrexate - problem to be solved is finding an alternative agent to be used in combination with MTX
- rituximab was a new RA agent so was obvious to try
“Compounds described in the following Examples have been tested in one or more of these assays, and have shown activity”
- Examples reporting the production of 580 compounds
- Patent claimed single compound, supported by post-filing data

“a mere verbal statement that “compounds have been found active” in the absence of any verifiable technical evidence is not sufficient to render it credible that the technical problem is indeed solved” – particularly “where the invention is directed to a very broadly defined class of compounds encompassing millions of structurally rather different candidates with unknown properties”

“If, as in the present case, the nature of the invention is such that it relies on a technical effect, which is neither self-evident nor predictable or based on a conclusive theoretical concept, at least some technical evidence is required to show that a technical problem has indeed been solved”

Post-filing data not taken into account, claims lacked an inventive step
Comparative Data?

- “…to be relevant, such comparative tests must meet certain criteria. These include in the present case the choice of a microsphere formulation according to the claimed invention and of a comparative powder formulation taken from the closest state of the art; at the same time, the pair being compared should possess maximum similarity with regard to the materials and the drugs used, the structure and the application … Moreover, the nature of the comparison with the closest state of the art should be such that any alleged advantages or beneficial effects are convincingly shown to have their origin in the distinguishing feature of the invention vis-à-vis the closest state of the art” - T 955/96 (Microspheres/West Pharmaceutical Services)
“…inventive step could only be acknowledged for an antibody which would have a technical effect that sets it apart from the … antibodies of the prior art. Such an antibody would however have to be defined by the structural features which are responsible for achieving this particular effect, i.e. the sequences of all its six CDR regions in the structural context of its corresponding framework regions which are well known in the art to provide the correct conformation of the CDRs and have a significant effect on the antibody’s affinity.”

Which characteristics of your product are responsible for the advantage that you rely on?

Which variations would the skilled person expect to retain the advantage?

- variations in particular parts of the molecule
- particular types of variation (e.g. conservative substitution)
- do you provide a technical explanation for the effect?
Conclusions?

- Usually need an unexpected advantage over the closest prior art to establish an inventive step at the EPO
  - consider predictability of the technical field
  - particularly difficult in antibody cases where the EPO makes many assumptions about what can be found routinely: routine to mass-produce antibodies against a known target and screen for best affinity

- Be prepared to prove that your invention does actually have the advantage that you are relying on
  - across the whole scope of your claims
  - enough experimental support in the application to give a technically plausible reason why it would work (across the scope of the claims)
  - make the right comparisons
  - be prepared – include a variety of fallback positions in your application in case the EPO considers the claims are broader than the invention, or issues arise with a particular claim type
Hazel Ford is a European patent attorney, chartered UK patent attorney and Higher Courts patent litigator. Hazel works with clients in the life sciences and pharmaceuticals fields to develop and coordinate global patent strategies. Named a “patent star” in the UK by Managing Intellectual Property, Hazel directs portfolio assessments and strategic counsel in view of a client’s business goals.
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Obviousness of Biologics Inventions in China

Amy Feng

January, 2018
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 (unexpected technical effects).

Post-filing data is generally not acceptable to establish the inventiveness of an invention.
Approach for Determining Inventiveness

The “Three-Step” Approach Under the Guidelines For Determining the Inventiveness of an Invention

- Identifying the closest prior art;

- Determining the distinguishing technical features and the technical problem actually solved by the invention; and

- Determining whether the invention is non-obvious to a person skilled in the art, i.e., whether the prior art provides motivation to apply the distinguishing technical features to the closest prior art to solve the technical problem actually solved by the invention.
Inventiveness of Antibodies

How can a monoclonal antibody claim be defined

(😊) By the producing hybridoma
(😊) By structural features, with or without functional features
(😊) 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 (😊)
- H and L chain variable region sequences (😊)
- H and L chain sequences (😊)
- 6 CDRs from a given H-L chain pair (😊)
- H chain CDR3 only (😊)
- H or L chain only (😊)
- CDRs from a CDR pool (😊)
Inventiveness of Antibodies

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

If an antigen is known and it is clearly known that the antigen has immunogenicity, the invention of a monoclonal antibody of the antigen does not involve an inventive step. However, if the invention is further defined by other features, and hence has unexpected technical effects, the invention of that monoclonal antibody involves an inventive step.
Inventiveness of Antibodies

Inventiveness of antibodies defined by 6 CDRs

The structural differences in the CDRs are not enough to establish the inventiveness of an antibody defined by 6 CDRs.

An antibody defined by 6CDRs does not involve an inventive step if no unexpected technical effect of the antibody is disclosed in the description as filed.
Inventiveness of Antibodies

Unexpected technical effects (UTE)

Structural differences in the CDRs are not enough to establish the inventiveness of an antibody defined by 6 CDRs.

An antibody defined by 6CDRs does not involve an inventive step if no unexpected technical effect of the antibody is disclosed in the description as filed.
UTE is key. How to assess it?

Guidelines says that UTE means, compared to prior art, the invention provides

- a new, unpredictable technical effect (kind)
- A known technical effect at a level beyond PHOSITA’s expectation (amount)

How to choose the “prior art” for comparison remains opaque

- the closest prior art as used in the obviousness assessment?
- the prior art having the best effect?
- Conveniently chosen from the art in general?
Case 1: PRB Decision No. 109361

- **Claim**: an anti-EGFR mAb (m175) defined by 6 CDRs
- **Spec**: contains data comparing m175 and m806
- **D1**: anti-EGFR mAb (m806) for the same epitope, each CDR differing from that of m175 by 1 amino acid
Reasoning of Final Rejection

• Alternative antibodies for a known epitope are presumed obvious
• PHOSITA could easily make m175 from m806 by conventional substitution
• mAb1 does not produce UTE, as the description shows m175 has lower antitumor effect than m806 in a cell type
Substitution of CDRs is no routine practice as changing CDRs unpredictably affects activity.

m175 is non-obvious over m806 by virtue of distinct CDRs.

m175 outperforms m806 in at least one aspect (the description shows m175 had better effect in another cell type), which could not have been unpredicted from their structural differences. UTE is thus recognized.
Case 2: PRB Decision No. 113596

- **Claim**: anti-EpCAM antibody defined by epitope sequence & hybridoma deposit No.

- **Description**: presents data showing tumor-inhibiting effect of the antibody.

- **D1**: hybridoma antibodies raised with the same antigen peptide. No disclosure of tumor inhibition.
Reasoning of Final Rejection

• The description does not show better specificity or affinity of the claimed antibody over D1’s.

• Many anti-EpCAM antibodies capable of treating tumors are known in the art, thus the tumor-inhibiting effect is not a UTE.
PRB reverses, holding

- Although hybridoma technology is well-established, obtaining a particular mAb is contingent and random.
- Whether a particular mAb has therapeutic effect is unpredictable. The spec has data to prove the effect while D1 has not. PHOSITA cannot predict the claimed antibody has such an effect from D1. UTE recognized.
Case 3: 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)
- The description 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

• Supplemental data submitted 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 UTE.

• Supplemental data rejected
Summary

• UTE is more relied on for showing inventiveness in biotech than in other areas

• UTE must be explicitly disclosed & supported by data in the application as filed

• Abs having new CDRs fare better than those having not. PRB takes a more liberal approach in assessing UTE of Abs with new CDRs than it does in other areas (e.g. does not require head-to-head comp with prior art).
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