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# Antibody Patenting:
# U.S. and European Perspectives

Meeting Patentability Requirements in the USPTO and EPO

THURSDAY, MAY 26, 2022

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# *Topics*

## Antibody Patenting in the U.S.

- Considerations relating to structural antibody claims
- Considerations relating to non-structure-based antibody claims
- Recent US case law relating to antibodies
- Practical considerations in the era of biosimilars

## European Perspective on claiming antibodies

- Antibody-specific updates to the EPO Guidelines for Examination
- Strategies to define antibodies in EP claims
- Inventive step and sufficiency considerations
- Recent EPO case law relating to antibodies

## *Claiming Antibodies in the U.S.*

## *Structural Antibody Claims: Prior Art Considerations*

- Generally, when claiming a novel sequence of an antibody, prior art is not a problem in the U.S. due to structural non-obviousness.

- Exceptions include:
  - When using humanized sequences and the CDRs are already known in the art
  - When claiming based on constant domain modifications that are already known to have beneficial properties

## *Structural Antibody Claims: § 112 Considerations*

- Generally, when claiming a sequence of an antibody, written description also will not be a problem in the U.S. provided there is evidence in the application that the claimed antibody has been made and tested

- However, some applicants may consider the scope of such sequence-based antibody claims too narrow

# *Other Options for Claiming Antibodies*

- Non-antibody sequence claim strategies include:
  - Binding site (epitope sequence)
  - Binding properties ($K_D$, $K_{off}$, etc.)
  - Binding function (block interaction/signaling)
  - Competitive binding

- These types of claims provide broader scope of protection than antibody sequence-based claims – but they can run into hurdles relating to § 112 and prior art

## *35 U.S.C. 112*

(a) The specification shall contain a written description of *the invention*, **and** of the manner and process of *making and using it*, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, …

- Must enable
- Must provide written description

- "Antibody Exception" discussed in USPTO's 2001 Written Description Guidelines was abrogated by Federal Circuit in 2017 *Amgen v. Sanofi* decision

# *AbbVie Deutschland v. Janssen (Fed. Cir. 2014)*

- The Product:
  - Stelara® (ustekinumab), an IL-12 antibody indicated for the treatment of adults with moderate-to-severe plaque psoriasis.
- Representative Claim:
  - A neutralizing isolated human antibody, or antigen-binding portion thereof, that binds to human IL-12 and disassociates from human IL-12 with a $K_{off}$ rate constant of $1x10^{-2}$ $s^{-1}$ or less, as determined by surface plasmon resonance.
- The specification taught ~300 fully human antibodies that bind and neutralize IL-12
  - All disclosed Abs have variable regions with at least 90% amino acid similarity to one starting Ab
  - More than 200 of the disclosed antibodies differed by only a single amino acid residue (99.5% similarity in variable regions).

# *AbbVie Deutschland v. Janssen (Fed. Cir. 2014)*

- Stelara® met the functional claim limitations:
  - fully human
  - anti-IL-12
  - neutralizes IL-12 activity
- But was structurally distinct from antibodies in the patent:

| | Stelara | J695 | Joe-9 |
|---|---|---|---|
| Sequence Similarity | 50% | 90% | 90% |
| CDR Length | Different | Identical | Identical |
| Epitope Binding Site | Side Binder | Bottom Binder | Bottom Binder |
| $V_H$ Family | $V_H5$ | $V_H3$ | $V_H3$ |
| Light Chain Type | Kappa | Lambda | Lambda |

# *AbbVie Deutschland v. Janssen (Fed. Cir. 2014)*

- What is sufficient description of a genus?
  - "AbbVie's patents need not describe the alleged infringing Stelara in exact terms."
- No prohibition of functional limitations:
  - if a **reasonable structure-function correlation** is established; or
  - if **representative examples** are provided.
- But "merely drawing a fence around a perceived genus is not a description of the genus. One needs to show … that one has conceived and described sufficient representative species encompassing the breadth of the genus."
- "AbbVie's patents only describe one type of structurally similar antibodies [sic] and [] those antibodies are not representative of the full variety or scope of the genus."

## *Amgen v. Sanofi (Fed. Cir. 2017)*

- Amgen owns two patents directed to anti-PCSK9 antibodies
  - PCSK9 (proprotein convertase subtilisin/kexin type 9) binds to receptors for low-density lipoprotein
- Claims recite isolated monoclonal antibodies that bind to specific residues on PCSK9 and block interaction with LDL receptors
- Examples in the specification provide testing data on the epitope contact residues of two antibodies that prevent LDLR signaling, as well as competitive binding experiments used to "bin" a series of additional antibodies based on epitope binding

## *Amgen v. Sanofi (Fed. Cir. 2017)*

- Amgen sued Sanofi for marketing an anti-PCSK9 antibody (Praluent™) used in treating high cholesterol
- Sanofi argued the claims were invalid for lack of written description and enablement because they covered a large genus of antibodies without providing sufficient examples or a structure-function correlation for antibodies targeting the claimed epitope, including the structure of Praluent™
- Amgen argued the claims were analogous to the "antibody exception"
  - discovered a newly characterized epitope "sweet spot" that effectively disrupts PCSK9 signaling

# *Amgen v. Sanofi (Fed. Cir. 2017)*

- CAFC rejected the antibody exception to the written description requirement
  - The "newly characterized antigen" test "flouts basic legal principles of the written description requirement"
  - Only court-approved tests for written description = representative examples or structure-function correlation
  - Identifying an epitope is not, by itself, enough to satisfy written description

- CAFC confirmed that pre- and *post-filing* evidence can be considered in assessing written description and enablement
  - **Remanded** because jury did not hear Sanofi's **post-priority-date** evidence (Praluent's structural differences from the antibodies in the patent and the "lengthy and potentially undue experimentation" required to identify Praluent and other antibodies falling within the scope of the claims)

# *Amgen v. Sanofi (Fed. Cir. 2021) – written description*

- On remand, District Court held Amgen's claims **not** invalid for lack of written description
  - Found the 3D structures of the antibodies disclosed in the specification are similar to those of the competitor antibodies
  - Found the amino acid sequences of the antibodies disclosed in the specification and the competitor antibodies (80% similarity) are more similar than those in *AbbVie*
  - Found the disclosed antibodies cover more classes of antibodies (8 families) than the classes disclosed in *AbbVie*
  - Found that Amgen presented substantial evidence of functional similarity (blocking PCSK9 binding to LDL-R)

# *Amgen v. Sanofi (Fed. Cir. 2021)*

- On remand, District Court held Amgen's claims invalid for lack of enablement, and the Federal Circuit affirmed
  - **NB**: jury found claims valid; District Court granted JMOL of invalidity for lack of enablement
- Both courts held that the functional diversity of the claimed embodiments exceeded the exemplification in the patents
  - Evidence suggested that only a small subset of antibodies could predictably be generated having the claimed functional properties
  - Undue experimentation to make and test all antibodies to determine if they bind as claimed
- The use of functional claim limitations raises the bar for enablement
  - Functional claiming is only permissible where there is a predictable relationship between structure and function, or where the applicant exemplifies a representative number of species

# *Amgen Petition for Certiorari (2021)*

Amgen poses two questions:

- Did the lower courts improperly invade the jury's role in evaluating enablement (question of fact vs. question of law)?

- Did the lower courts rely on an improper standard for enablement of genus claims?
  - Amgen argues that the new test requires applicants to identify and make all possible variations of the invention to satisfy the enablement
  - Amgen argues the specification only needs to teach how to "make and use" the claimed invention, not enable those skilled in the art to "reach the full scope" of the claimed invention without undue experimentation

## *Amicus briefs on appeal re enablement*

Many companies and scholars on both sides of this issue:

- Claims not enabled
  - Pfizer Inc.
  - Eli Lilly & Co.
- Claims enabled
  - Brisol-Myers Squibb Co.
  - Merck Sharp & Dohme Corp.
  - George Washington University Professors

SCOTUS has requested a brief from the SG

## *UCB v. Genetech (PGR 2019-00044)*

- Claims recite an isolated humanized monoclonal antibody that binds to an IL-17A/IL-17F heterodimer
- Patent claims priority to parent applications filed before March 16, 2013 that share essentially the same specifications
- The inventors used a humanized Her2 Ab as the template and generated a library of Fab fragments by introducing mutations to the heavy chain
- The specification discloses “the amino acid sequence of the region of the variable domain of the heavy chains that contains the three CDRs” from “34 Fab clones that encode distinct antibody heavy chain sequences that are able to bind to IL-17 A/F.”
- The specification does not disclose the sequence of any light chain.

## *UCB v. Genetech (PGR 2019-00044)*

- In the Institution Decision, the Board found the record supports the existence of other antibodies falling within the claimed genus that depart substantially from the sequences of the 34 clones
- The Board found that the disclosure of a common framework sequence is insufficient to represent the full scope of framework sequences within the claimed genus of antibodies
- The Board did not find disclosure of data showing that the 34 clones bind IL-17A/F
- PO abandoned the contest after the petition was instituted, and the Board entered adverse judgment against PO.

# *Juno v. Kite (Fed. Cir. 2021)*

- Juno received a patent on engineered CAR-T cell technology in 2002 (a time period one of the inventors called “the birth of the CAR-T field”)

- Representative claim:

A nucleic acid polymer encoding a chimeric T cell receptor, said chimeric T cell receptor comprising

(a) a zeta chain portion comprising the intracellular domain of human CD3 ζ chain,

(b) a costimulatory signaling region, and

(c) a [single chain antibody (“scFv”)] that specifically interacts with a selected target, wherein the costimulatory signaling region comprises the amino acid sequence encoded by SEQ ID NO:6.

- Specification disclosed two exemplary scFVs: one that binds CD19 and one that binds PSMA

# *Juno v. Kite (Fed. Cir. 2021)*

- Juno sued Kite over sales of its YESCARTA® product, which is a therapy in which a patient's T cells are engineered to express a CAR having the claimed structural features and targeting CD19

- District Court held patent valid and infringed, but Federal Circuit reversed finding patent invalid for lack of written description
  - Patent failed "to demonstrate to a skilled artisan that the inventors possessed and disclosed in their filing the particular species of scFvs that would bind to a representative number of targets."
  - Patent failed "to disclose structural features common to scFVs capable of binding specific targets, it also fails to disclose a way to distinguish those scFvs capable of binding from scFvs incapable of binding those targets."
  - In response to Juno's argument that the inventive concept was the backbone: "the '190 patent's claims are not limited to just the claimed backbone; they also include the functional scFv for binding the target."

# *Recently-Issued Epitope Claims*

**US 10,221,239:** TRPM4 Channel Inhibitors for Stroke Treatment (March 5, 2019)

**Claim**

**1.** An isolated antibody specific to the transient receptor potential melastatin 4 (TRPM4) protein, wherein:

the antibody specifically binds to a peptide consisting of the amino acid sequence of SEQ ID NO: 1, a peptide consisting of the amino acid sequence of SEQ ID NO: 2, or a peptide consisting of the amino acid sequence of SEQ ID NO: 3,

the antibody specifically binds to an epitope comprising amino acids 949-952 and 985-1008 of SEQ ID NO: 11 or amino acids 955-958 and 991-1014 SEQ ID NO: 12, and

the antibody inhibits TRPM4 activity.

# *Recently-Issued Epitope Claims*

**US 10,221,239:** Prosecution History

- Claims to antibody binding TRPM4 rejected on WD and enablement grounds, citing *Amgen v. Sanofi*.
- Applicant amended claims to recite precise epitope sequences and explained 3D model was used to map epitope to exemplary antibody disclosed in specification, along with data showing ability to disrupt TRPM4 activity after binding to that epitope.
- Examiner accepted this as sufficient characterization of structure-function correlation (WD), along with arguments about routine production of similar antibodies based on information provided about the epitope (enablement).

# *Will method claims meet with more success?*

**Perhaps:**

**US 11,066,472:** Methods of Treating Cardiovascular Disease with an anti-ASGR Antibody or Binding Fragments Thereof

**Claim**

1. A method of treating or preventing a cardiovascular disease comprising administering to a patient in need thereof a therapeutically effective dose of an isolated antigen binding protein that binds to ASGR-1 (asialoglycoprotein receptor 1), wherein the isolated antigen binding protein is a neutralizing antibody or a neutralizing antigen binding fragment thereof.

# *Will method claims meet with more success?*

**But see:**

**US 12/615,033:** Compositions And Methods For The Inhibition Of Cripto / Grp78 Complex Formation And Signaling (Appeal 2017-001821 (decided November 30, 2018)

**Claim**

**15.** A ***method of treating a hyperproliferative*** disease in a human subject comprising administering to the subject an amount of a selective targeting compound that is ***effective to inhibit Cripto signalling*** in hyperproliferative cells that express glucose regulated protein 78 (GRP78) on their surfaces and thereby reduce the cells' proliferation, wherein the selective targeting compound is an ***antibody that binds within the sequence region defined by amino acids 19-68 of GRP78 and inhibits the formation of complexes between human Cripto and GRP78***.

# *Will method claims meet with more success?*

**US 12/615,033**: PTAB Decision Affirming Examiner

- Claims to any antibody that binds a particular region of GRP78 and inhibits the formation of complexes between human Cripto and GRP78
- Specification describes only one antibody and offer no evidence that antibody is representative of the claimed genus or otherwise identifies structures that correlate with the claimed function required by the method claim.

# *Daiichi Sankyo v. Alethia (IPR2015-00291)*

- Representative claim:

  A method of ***impairing osteoclast differentiation*** in a mammal in need thereof, the method comprising administering an antibody or antigen binding fragment which ***specifically binds*** to human Siglec-15 (SEQ ID NO:2) or murine Siglec-15 (SEQ ID NO:108) to said mammal.
- Issue: Are claims entitled to priority date?
- Parent application disclosed:
  - Siglec-15 protein sequence as a potential target
  - assay for screening potential inhibitory compounds
  - conventional methods of producing antibodies
- Parent application did NOT disclose:
  - epitopes/unique antigenic regions of Siglec-15
  - working examples of a Siglec-15 antibody having the claimed ***functional properties***

## *Daiichi Sankyo v. Alethia (IPR2015-00291)*

- PTAB found inadequate written description and enablement
  - Distinguished from antibody exception cases because claims at issue contain a ***functional limitation***
  - Citing *Centocor*, found that full characterization of the antigen (Siglec-15) did not suffice to provide adequate written description support for a Siglec-15 antibody that also produces a desirable biological result

# *Merck v. Genetech (PGR 2021-0036)*

- Technology overview:
  - The patent is directed to a combination therapy comprising the administration of a PD-1 axis binding antagonist and an agent that decreases or inhibits TIGIT expression and or activity to treat cancer.
- 10,611,836 representative claim 1:
  - A method of treating or delaying progression of a cancer in an individual, the method comprising administering to the individual an effective amount of (i) a PD-L1 binding antagonist that inhibits the binding of PD-L1 to PD-1 and/or B7-1, a PD-1 binding antagonist that inhibits the binding of PD-1 to PD-L1 and/or PD-L2, or a PD-L2 binding antagonist that inhibits the binding of PD-L2 to PD-1 and (ii) an agent that inhibits and/or blocks the interaction of CD226 with TIGIT, wherein the agent is an inhibitory anti-TIGIT antibody or antigen-binding fragment thereof.
- Issue:
  - TIGIT antagonist
  - PD-1 axis binding antagonist
  - types of cancer

## *Merck v. Genetech (PGR 2021-0036)*

- The Board denied institution of PGR.
- The Board focused on the fact the claims are directed to methods of treatment, not the compounds used in the method claims
- The Board stated that all claims require co-administration of compounds from two known classes "with established functionality and is not claiming any new composition."
- The data in the specification purportedly demonstrated to one of skill in the art that such a co-administration provided a therapeutic benefit.

# *Post-Grant Prior Art Challenges*

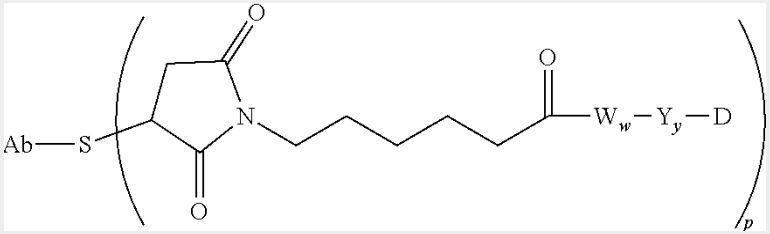
***Sanofi-Aventis v. Immunex Corp*, IPR2017-01884:** prior art murine Ab renders humanized Ab obvious

- Claims recite an isolated human antibody that competes with a reference antibody for binding to human IL-4 interleukin-4 (IL-4) receptor
- The prior art discloses (1) a mouse anti-hIL-4R blocking antibody, (2) humanization techniques, and (3) anti-IL-4R antibodies could be therapeutic entities for allergy
- The Board concluded that the term “human antibody” does not exclude partially human antibodies.
- The Board found that a POSA would have had a reason to humanize the prior art mouse Ab using known humanization technique to create the claimed antibodies with therapeutic potential with a reasonable expectation of success

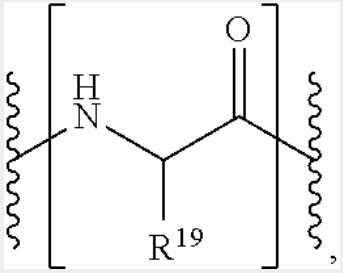
# *Daiichi Sankyo v. Seattle Genetics (PGR 2021-00030)*

## Representative claim

An antibody-drug conjugate having the formula:




or a pharmaceutically acceptable salt thereof, wherein Ab is an antibody, S is sulfur, each –Ww- unit is a tetrapeptide, wherein each –W- unit is independently an amino acid unit having the formula denoted below in the squared bracket:




wherein R19 is hydrogen or benzyl,

Y is a spacer unit,

y is 0, 1, or 2

D is a drug moiety, and

p ranges from 1 to about 20,

wherein S is a sulfur atom on a cysteine residue of the antibody, and

wherein the drug moiety is intracellularly cleaved in a patient from the antibody of the antibody-drug conjugate or an intracellular metabolite of the antibody-drug conjugate.



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# *Daiichi Sankyo v. Seattle Genetics (PGR 2021-00030)*

- The Board initially denied institution before granting a rehearing and ultimately instituting PGR.
  - In the Board's initial denial, it cited overlap between concurrent district court litigation and the Fintiv factors. The Board explained that although there was a strong likelihood of success, the fact that the district court would likely rule on the same invalidity grounds prior to the Board issuing a final decision outweighed the likelihood of success.
  - Petitioner filed a request for rehearing and argued institution should be instituted because the claims challenged in the PGR were not at issue in the district court litigation.
  - Relying on this, and the conclusion of the district court litigation, the Board instituted PGR.

## *Daiichi Sankyo v. Seattle Genetics (PGR 2021-00030)*

- Daiichi challenges the patent for, *inter alia*, lack of written description and enablement.

- In the decision on rehearing request, the Board pointed out that the specification focuses on particular dolastatin/auristatin ADCs and does not describe ADCs having other drug moieties or antibodies.


# *Practical Considerations in the Biosimilars Era*



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# *FDA Biosimilar Guidance*

FDA will consider these factors in evaluating biosimilarity:

- Reference Product and Reference Standard (antibody sequence)
  - "In general, FDA expects that the expression construct for a proposed product will encode the same primary amino acid sequence as the reference product. However, minor modifications such as N- or C-terminal truncations that will not affect safety and effectiveness may be justified and should be explained by the sponsor."
- Receptor Binding and Immunochemical Properties (epitope)
  - "Three types of assays are of particular importance for biosimilar product development: ligand binding assays, concentration and activity assays, and PD assays. … Assays that rely upon antibody reagents and ***epitopes involved in pharmacological/biochemical interactions*** with targets are most likely to produce concentration data that are meaningful for target binding activity."

# *FDA Biosimilar Guidance*

FDA will consider these factors in evaluating biosimilarity:

- Assessment of Physiochemical Properties (antibody tertiary structure)
  - "[I]t will be important to understand the heterogeneity of the proposed biosimilar product and the reference product (*e.g.*, the nature, location, and levels of glycosylation) and the ranges of variability of different isoforms, including those that result from post-translational modifications."

- Expression System (manufacturing methods)
  - "Differences between the chosen expression system of the proposed biosimilar product and that of the reference product should be carefully considered because the type of expression system and host cell will significantly affect the types of process- and product-related substances and impurities (including potential adventitious agents) that may be present in the protein product."

## *FDA Biosimilar Guidance*

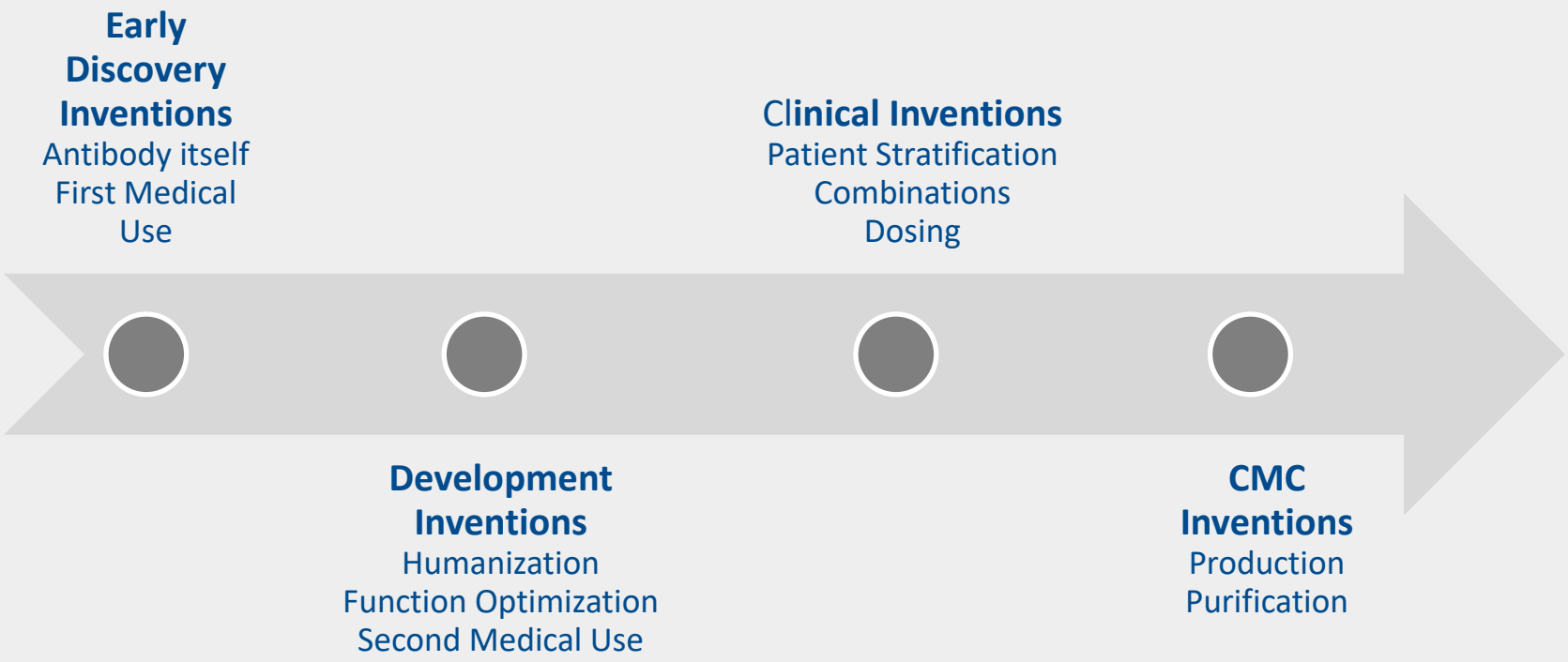
FDA will also consider these factors in evaluating biosimilarity:

- Manufacturing Process
- Functional Activities
- Impurities
- Finished Drug Product
- Stability

# *Best Practice Recommendations*

## When to file?

Therapeutic antibody life cycle:



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# *Best Practice Recommendations*

- Define your antibodies in the specification in many different ways and include data to support these types of claims
  - Structure
    - CDRs (in multiple formats), variable domains, full sequences
    - Isotypes, alternative antibody structures
    - Compositions, combinations
  - Epitope
    - Full/partial epitope, specific amino acids in the epitope
    - Competitive binding
  - Function/uses
    - Functional features
    - General and specific uses
    - Therapies
    - Patient groups
    - Dosages


# *Claiming Antibodies at the EPO*



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# *Claiming Antibodies at the EPO*

- How much data is needed in the application as filed?
- When can post-filing data be used?

- No US style written description requirement.
- Enablement/sufficiency of disclosure.
  - Can the invention as claimed be carried out across the scope of the claims?

- Inventive Step
  - Does your argument for inventiveness apply to substantially all embodiments falling within the claims?

## *Updated EPO Guidelines for Examination*

- High volume of cases at EPO = “antibody-specific” issues.
- A dedicated section of the EPO’s Guidelines for Examination (G, 11, 5.6) issued March 2021 and revised again March 2022 = an attempt to “standardise” approach.
- Guidance on:
  - Options for defining an antibody (Ab) in the claims;
  - Inventive step.

## *EPO Guidelines – defining an Antibody*

- Definition by:
  - Structure - defined by the CDRs required for binding
  - Target antigen - antigen must be clearly defined
  - Target antigen + functional features – further properties
  - Functional + structural features
  - Production process – immunisation protocol, cell line
  - Epitope – aa which are bound, guidance for definition of linear and discontinuous epitope
  - Hybridoma – deposited according to Budapest treaty

# *EPO Guidelines – Inventive step*

- Inventive step
- *"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 or unless there was no reasonable expectation of success of obtaining antibodies having the required properties"*

# *EPO Guidelines – Ab Inventive step*

- If inventive step of a functionally defined antibody relies on an improved property versus the enabled antibodies of the prior art, the main characteristics of the method for determining the property must also be indicated in the claim or indicated by reference to the description.
- If the surprising technical effect involves the binding affinity, the structural requirements for conventional antibodies inherently reflecting this affinity must comprise the six required CDRs and the framework regions because the framework regions also can influence the affinity (T 1628/16).

# *EPO Guidelines – Ab Inventive step*

- 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, *i.e.,* structural non-obviousness is usually not enough for an antibody against a known target.
- Arriving at alternative antibodies exclusively by applying techniques know 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 (see T 605/14, section 24; T 187/04, section 11).
- Nevertheless, antibodies can be inventive if the application overcomes technical difficulties in producing generating or manufacturing the claimed antibodies.

## *Inventive Step at the EPO*

- Problem and solution approach.
  - What is the difference between your invention and the closest prior art and what problem does that difference solve?

- Invention based on new antigen/target.
  - If your antigen is new, you may get a broad claim at the EPO to any antibody that specifically binds that antigen.
  - Inventive step derives from the new antigen.

- Invention based on new antibodies to a known target.
  - More difficult…

# *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***"

# *Unexpected properties/surprising technical effect*

Listed in EPO guidelines:

- Improved affinity
- Improved therapeutic activity
- Reduced toxicity
- Reduced immunogenicity
- Unexpected species cross-reactivity
- New Ab format with proven binding activity

- Other:
- Pharmacokinetic properties
- Expression level
- Stability in solution
- Novel specificity

# *Enablement/Sufficiency at the EPO*

- Methods for producing, modifying, humanizing antibodies are all considered routine.
  - If the antibody target is provided, then most new antibodies against that target will be considered enabled.

- If the antibody is defined using further functional features or effects, then further information may be needed.
  - Does the application explain how to obtain/screen for those features/effects?
  - Is it at least plausible that antibodies across the scope of the claims, having those features or effects, could be produced?
  - If a therapeutic use of the antibody is claimed, then is it plausible from the application as filed that the therapy would be achieved across the scope of the claim?

- Post-filing data can only be used to confirm what was already at least plausible from the application as filed.

## *Scope of the Claims*

- An unexpected advantage which gives an inventive step must be one which can be **fairly assumed to be produced by substantially all the claimed embodiments.**
  - If you are relying on an advantage for your inventive step, your claim can only cover the antibodies that would share that advantage.

- *"…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."*

# *Are Some Advantages Better Than Others?*

- "*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*"

- A "better" antibody against a known target might not be patentable at the EPO.

# *Supporting the Scope of the Claims*

- Which characteristics of your antibody 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)

- Include specific description of these characteristics and variations in your application as filed.

- Post-filing evidence can only be taken into account if it is **already plausible from the disclosure in the application as filed** that the problem is solved.
  - When drafting, think carefully about the evidence or statements that should be included to support this.

# *Supporting the Scope of the Claims*

- Structural information for at least one exemplary antibody
  - CDRs required for binding + positional numbering e.g. Kabat

- Functional data to show binding and specificity
  - *E.g.* surface plasmon resonance, method described

- Further functional data to show that the antibody has a surprising effect
  - at least include a description of the functional characteristics of the antibodies, ideally with exemplification

- May be necessary to provide comparative data. This might be provided as post-filed data if the surprising effect relied on is plausible in the application as filed.

## *Recent EPO case law*

- Despite the large number of EP applications filed relating to “antibody inventions” there are relatively few EPO decisions.
- Backlog and lag
- Decisions discussed here were published 2020-2022 but applications filed 2003-2010

## *Recent EPO case law*

(T 1964/18) – Epitope + function - Jan 2022

- mAB that: a) specifically blocks NKG2A but not NKG2C/E; and b) binds same NGK2A epitope as a deposited Ab, such that binding of the antibody to its target on NK cells activates NK-cell killing
- Prior art Ab binds NGK2A/C/E
- Tech effect = specific binding and improvement in NK-cell mediated cell killing
- Obvious to modify prior art Ab to block NGK2A only?
- Prior art taught that Abs binding NGK2A/C/E would activate NK-cells, and so not obvious to modify
- Currently back with the OD but likely to be granted.

## *Recent EPO case law*

(T 966/18) – pre-clinical data and plausible therapeutic effect – Nov 2020 and Jan 2022

- Claim 1 related to the use of α-synuclein (α-SN) fragments or anti-α-synuclein antibodies to treat or protect against Lewy Body disease, particularly Parkinson's disease.
- Published literature showed that α-SN aggregation was likely linked to Parkinson's disease pathology.
- Considered plausible at the filing date that anti-α-SN antibodies would treat Parkinson's Disease.

## *Recent EPO case law*

(T 966/18) – pre-clinical data and plausible therapeutic effect – Nov 2020 and Jan 2022

- The Patent included data showing reduction of α-SN aggregates in a mouse model of Lewy Body disease following administration with α-SN in order to elicit production of α-SN antibodies (low n and statistical significance not assessed).
- The application as filed also included data showing the *in vitro* binding effect of the claimed anti-α-SN antibodies.
- The patentee further submitted post-filed evidence from clinical trials for Prasinezumab showing a clinical effect.
- The Board of Appeal found the data provided in the application as filed, in combination with the common general knowledge, to be good enough to support the claimed therapeutic use without recourse to the post-filed data.

# *Recent EPO case law*

(T 0032/17) – hybridomas R 31 EPC – July 2020

- The hybridoma must be made available to the public in the form of a biological deposit and referenced in the application as filed (Rule 31 EPC).
- Claims related to product-by-process claims by reference to hybridomas.
- The relevant hybridomas were deposited before the priority date of the patent.
- The hybridomas were also mentioned in a product catalogue pre-dating the patent application.
- The Board of Appeal found that the deposit information referenced in the application as filed did not provide any technical information about the structure of the antibodies produced by the hybridomas, either explicitly or implicitly.
- As such, the claim could not be said to be limited by reference to these hybridomas, and so the prior mention of the hybridomas was novelty destroying.

## *Recent EPO case law*

(T 0032/17) – hybridomas R 31 EPC – July 2020

- Claims to hybridoma *per se* (not Ab produced by hybridoma)
- Deposited hybridomas are made available to the public when the patent application is published.
- The Board found that the public availability of the deposited hybridomas post-dated the filing date of the application, and that the depositing of the hybridomas before the priority date was not novelty destroying to the hybridoma product claim.
- Currently in examination with the Opposition Division.

# *Recent EPO case law*

T 0096/20 – medical use of Ab - April 2021

- Claims related to any anti-C5 antibody inhibitor of complement C5 for treating myasthenia gravis (MG).
- During proceedings the patentee limited the claims to focus on a specific antibody by name (eculizumab).
- The Board held it to be obvious to use anti-C5 antibody inhibitor of complement C5 to treat MG, with a reasonable expectation of success given a published announcement / protocol for a phase II safety/efficacy trial of eculizamb for MG.
- There was no change to this expectation just because there had been no new treatment for MG for a long time, nor that trials for other complement directed therapies for other diseases had failed.
- Take home - clinical trial protocol publications can often be extremely difficult prior art to overcome, similar to the situation for non-antibody pharmaceuticals.
- Cannot rely on grace period outside US.

# *Recent EPO case law*

T 0033/19 – medical use of Ab - April 2021 – related to previous case

- Same antibody (eculizumab) as above.
- The examining division had rejected the case under Article 83 EPC, sufficiency, because the application did not demonstrate experimentally that treatment of aHUS (Atypical Hemolytic Uremic Syndrome) was achieved.
- However, The Board reversed this decision on the basis that the application does identify aHUS as complement associated and explicitly suggests treatment with eculizumab, referring to the amelioration of some symptoms.
- The Board also found that specific documents considered to be representative of common general knowledge (CGK) showed that the etiology of aHUS is known to be complement-mediated and that use of anti-C5 antibodies was thus a potential treatment option.
- The Board indicated that there is no requirement for direct experimental proof, provided the skilled person has no reason to doubt that the agent achieves the claimed effect, with due regard to CGK.

# *Recent EPO case law*

T 0033/19 – medical use of Ab - April 2021

- The Board went on to review Article 56 EPC (inventive step) over the same CGK documents. The suggestions in the CGK relied upon for Article 83 EPC (i.e. to use anti-C5 for aHUS) were held not enough to provide reasonable expectation of success, whereas the application included an explicit statement that eculizumab has been found to ameliorate some aHUS symptoms.
- The Board found there was no reason to doubt this statement (despite lack of data in the application), and also that subsequently published data was supportive of the statement.
- Thus, the Board concluded there is an inventive contribution over these specific CGK documents.
- The case was remitted to the examining division to consider patentability over other cited documents and accepted for grant. Presently, it is open to third party opposition.

# *Ab claim type summary*

Broad claims

- New or challenging target/antigen
- Target/antigen with new medical use

Focused claims

New/improved technical effect

- Specificity
- Affinity
- Epitope
- Immunogenicity
- Other surprising effects

Development of medical use

- Bispecific
- Patient group
- combi/co-admin
- dose/formulation
- Admin route

Comparative data and/or arguments for technical effect may be required

# *EPO Conclusions*

- Increasingly difficult to establish an inventive step for a new antibody against a known target.
  - Structural non-obviousness very unlikely to be enough.
  - Need some kind of unexpected advantage or surprisingly technical effect.

- Scope of the claims should match the technical contribution that had been made plausible at the filing date.

- How much data in the application?
  - Enough to make it plausible that the effect can be achieved.
  - Enough to give a technical reason why it might work across the claims.

- Post-filing data only considered if it supports what was plausible at the filing date.

# Your Presenters

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