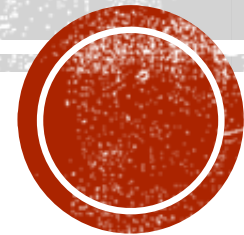


WRITTEN DESCRIPTION FOR ANTIBODIES

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WRITTEN DESCRIPTION

1. Section 112(a)'s grammatical structure makes that inescapable. It imposes the requirement of "a written description," followed by three sequential prepositional phrases ([1]-[3] below):

The specification

[A] shall contain *a written description*

[1] *of the invention*, and
[2] *of the manner and process* of
making and using it,

[3] *in such full, clear, concise, and
exact terms as to enable* any person
skilled in the art to which it pertains
* * * to make and use the same * * * .



QUID PRO QUO

- The statutory requirement for “written description” prevents overreaching
 - The law requires that the specification describe the invention in sufficient detail so “that one skilled in the art can clearly conclude that the inventor invented the claimed invention as of the filing date.”
 - *In re Alonso*, 545 F.3d 1015 (Fed. Cir. 2008), citing *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1556, 1572 (Fed. Cir. 1997)
- The requirement “serves a teaching function, as a *quid pro quo* in which the public is given ‘meaningful disclosure in exchange for being excluded from practicing the invention for a limited period of time.’”
 - *In re Alonso*, 545 F.3d 1015 (Fed. Cir. 2008), citing *Univ. of Rochester v. G.D. Seale & Co., Inc.*, 358 F.3d 916, 922 (Fed. Cir. 2004), citing *Enzo Biochem Inc. v. GenProbe Inc.*, 323 F.3d 956, 970 (Fed. Cir. 2002).



WRITTEN DESCRIPTION PRE-AMGEN

- *Noelle v. Lederman*, 355 F.3d 1343, 1348 (Fed. Cir. 2004) (“As long as an applicant has disclosed a ‘*fully characterized antigen*,’ either by its structure, formula, chemical name, or physical properties . . . , the applicant can then claim an antibody by its binding affinity to that described antigen.”)
- A claim directed to any antibody capable of binding antigen X would have sufficient support in a written description that disclosed a “*fully characterized antigen*” by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository, if the level of skill and knowledge in the art of antibodies at the time of filing was such that production of antibodies against such an antigen was *conventional or routine*.



ANTIBODY EXCEPTION

- The previous PTO written description guidelines included an antibody example.
- Referencing an immunology text published in 1976, the PTO guidelines indicated that a functional claim reciting ‘an isolated antibody capable of binding to [protein] X’ is adequately described where the specification fully characterizes protein X—even if there are no working or detailed prophetic examples of actual antibodies that bind to protein X.
- The PTO guidelines characterized ‘production of antibodies against a well-characterized antigen’ as ‘conventional’ and ‘routine,’ given ‘well developed and mature’ antibody technology.”
- U.S.P.T.O., Written Description Training Materials Revision 1 March 25, 2008 at 45–46 (available at <http://www.uspto.gov/web/menu/written.pdf>) (hereinafter PTO guidelines).



EPITOPE CLAIMS

- An isolated monoclonal antibody or an antigen binding fragment thereof, that specifically binds to an **epitope** within an amino acid sequence set forth as SEQ ID NO: 30, and wherein the isolated monoclonal antibody or an antigen binding fragment thereof binds to human 5B6 protein on the surface of a dendritic cell. (US Pat. No. 8,426,565, April 23, 2013): **supported by 4 exemplified antibodies.**
- An antibody or antigen-binding fragment thereof that specifically binds to an HMGB1 polypeptide consisting of SEQ ID NO:6, wherein said antibody or antigen-binding fragment binds an **epitope** comprising the sequence Cys-Ser-Glu. (US Pat. No. 8,354,106, January 15, 2013): **allowed with NO exemplified antibodies.**



AMGEN (REPATHA®) INC. V. SANOFI (PRALUENT®)

- In the case of a claim to antibodies, the correlation between structure and function may also be satisfied by the disclosure of a newly-characterized antigen by its structure, formula, chemical name, or physical properties if you find that the level of skill and knowledge in the art of antibodies at the time of filing was such that production of antibodies against such antigen was conventional or routine.
-
- **Final Jury Instrs.** at 25, *Amgen Inc., v. Sanofi*, Civ. No. 14–1317–SLR, 2016 WL 825671, at *4 (D.Del. March 2, 2016).
- An isolated monoclonal antibody, wherein, when bound to PCSK9, the monoclonal antibody binds to at least one of the following residues: S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, or S381 of SEQ ID NO:3, and wherein the monoclonal antibody blocks binding of PCSK9 to LDLR.



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- “newly characterized antigen” instruction was improper and not based on any binding precedent.
- In *Noelle*, we cautioned that “each case involving the issue of written description[] ‘must be decided on its own facts. Thus, the precedential value of cases in this area is extremely limited.’” *Id.* at 1349 (quoting *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1562 (Fed. Cir. 1991)).
- to satisfy the statutory requirement of a description of the invention, it is not enough for the specification to show how to make and use the invention, i.e., to enable it.
- The test thus contradicts the statutory “quid pro quo” of the patent system where “one describes an invention, and, if the law’s other requirements are met, one obtains a patent.”



ARIAD PHARM., INC. V. ELI LILLY & CO., 598 F.3D 1336, 1351 (FED. CIR. 2010) (EN BANC)

- *Amgen v Sanofi*
- To show invention, a patentee must convey in its disclosure that it “had possession of the claimed subject matter as of the filing date.”
Id. at 1350.
- Demonstrating possession “requires a precise definition” of the invention. Id.
- To provide this “precise definition” for a claim to a genus, a patentee must disclose “**a representative number of species** falling within the scope of the genus or **structural features common** to the members of the genus so that one of skill in the art can ‘visualize or recognize’ the members of the genus.” Id.



AMGEN (REPATHA®) INC. V. SANOFI (PRALUENT®): VALID

Claim 7. An isolated monoclonal antibody that binds an epitope on PCSK9 comprising at least one of residues 237 or 238, and wherein the monoclonal antibody blocks binding of PCSK9 to LDLR, and wherein the epitope is a structural epitope.



AMGEN (REPATHA®) INC. V. SANOFI (PRALUENT®)

1. An isolated monoclonal antibody, wherein, when bound to PCSK9, the monoclonal antibody binds to at least one of the following residues: S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, or S381 of SEQ ID NO:3, and wherein the monoclonal antibody blocks binding of PCSK9 to LDLR.
 - 7. The isolated monoclonal antibody of claim 1, wherein the monoclonal antibody binds to at least D238.
 - 15. The isolated monoclonal antibody of claim 1, wherein the monoclonal antibody binds to at least V380.
 -
 - 19. The isolated monoclonal antibody of claim 1 wherein the isolated monoclonal antibody binds to at least two of the following residues S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, or S381 of PCSK9 listed in SEQ ID NO:3.
 -
 - 29. A pharmaceutical composition comprising an isolated monoclonal antibody, wherein the isolated monoclonal antibody binds to at least two of the following residues S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, or S381 of PCSK9 listed in SEQ ID NO:3 **and blocks the binding of PCSK9 to LDLR by at least 80%.**



ABBVIE DEUTSCHLAND GMBH V. JANSSEN BIOTECH, INC. (FED. CIR. 2014)

- 6,914,128,
 29. 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 $1 \times 10^{-2} \text{ s}^{-1}$ or less, as determined by surface plasmon resonance.

- 7,504,485
 1. A pharmaceutical composition comprising an isolated human antibody, or antigen-binding portion thereof, which is capable of binding to an epitope of the p40 subunit of IL-12, and further comprising an additional agent.

11. The composition of any one of claims 1-4, wherein the antibody, or the antigen binding portion thereof, dissociates from the p40 subunit of IL-12 with a K_{d} of 1×10^{-10} or less or a K_{off} of $1 \times 10^{-3} \text{ s}^{-1}$ or less, as determined by surface plasmon resonance.



ABBOTT'S DISCLOSURE

- More than 300 variants of a parental Ab were described by sequence and by binding affinity.
- Bind to an epitope located on the p40 subunit of IL-12.
- Many fell within functional claim limits.



NOT ENOUGH REPRESENTATIVE EXAMPLES

- Centocor presented evidence seeking to establish that the antibodies described in AbbVie's patents were not representative of other members of the functionally claimed genus, which included Stelara.

	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 _H 5	V _H 3	V _H 3
Light Chain Type	Kappa	Lambda	Lambda



MORE DIFFERENCES BETWEEN STELARA AND ABBOTT'S DISCLOSURE

- STELARA® and Abbott's Abs bind at different places.
- The dozens of contacts between STELARA® and IL-12 are all different than the dozens of contacts that [Abbott's Ab] makes with IL-12; no contact is the same at a chemical and structural level.
- The amino acid sequence of STELARA® and [Abbott's Abs] are about 50% different.
- The only antibody sequences described in the Abbott patents are in [a single] lineage and there is only about a 10% difference among the sequences.



ABBVIE DEUTSCHLAND GMBH V. JANSSEN BIOTECH, INC. (FED. CIR. 2014)

- When a patent claims a genus using functional language to define a desired result, "the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus."
- We have held that "a sufficient description of a genus . . . requires the disclosure of either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus" [citations omitted].



USPTO GUIDANCE

- Memorandum to the Examining Corps, issued in response to *Amgen*, explained that the March 25, 2008, Written Description Training Materials “should not be relied upon as reflecting the current state of the law regarding 35 U.S.C. §§ 101 and 112.”--Feb. 22, 2018, Memorandum to Examining Corps, 2 (emphasis in original)
- “In view of the *Amgen* decision, adequate written description of a newly characterized antigen alone should not be considered adequate written description of a claimed antibody to that newly characterized antigen, even when preparation of such an antibody is routine and conventional.”
- Rather, **Examiners should apply the conventional tests for written description spelled out in *Ariad* (reiterated in *AbbVie*).**



ARIAD V. LILLY, 598 F.3D 1336, 1351 (FED. CIR. 2010)

Predictability is key.

For generic claims, we have set forth a number of factors for evaluating the adequacy of the disclosure, including “the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, [and] the predictability of the aspect at issue.” . . .

“functional claim language can meet the written description requirement when the art has established a correlation between structure and function.”



CAPON V. ESCHAR, 418 F.3D 11349 (FED. CIR. 2005): HIGHLY FUNCTIONAL

- 1. A chimeric DNA comprising:
 - a **first DNA segment** encoding a single-chain Fv domain (scFv) comprising a V_L linked to a V_H of a specific antibody by a flexible linker, and
 - a **second DNA segment** encoding partially or entirely the transmembrane and cytoplasmic, and optionally the extracellular, domains of an endogenous protein,

wherein said endogenous protein is expressed on the surface of lymphocytes and triggers the activation and/or proliferation of said lymphocytes, which chimeric DNA, upon transfection to lymphocytes, expresses both said scFv domain and said domains of said endogenous protein in one single, continuous chain on the surface of the transfected lymphocytes such that the transfected lymphocytes are triggered to activate and/or proliferate and have MHC non-restricted antibody-type specificity when said expressed scFv domain binds to its antigen.



CAPON V. ESCHAR, 418 F.3D 11349 (FED. CIR. 2005)

- Declarations stating that POSITA would readily know the structure of a chimeric gene made of a first segment of DNA encoding a single-chain variable region on an antibody, and a second segment of DNA encoding an endogenous protein.
- The invention is not in discovering which DNA segments are related to the immune response, for that is in the prior art, but in the novel combination of the DNA segments to achieve a novel result.
- The **Board erred** in holding that the specifications do not meet the written description requirement because they do not reiterate the structure or formula or chemical name for the nucleotide sequences of the claimed chimeric genes.



THE FACTORS TO BE USED

Written Description: Capon Factors

- 1) nature and scope of the claims
(Wands 4 & 8)
- 2) existing knowledge in the particular field and extent and content of the prior art (Wands 6)
- 3) maturity of the science or technology and scientific and technologic knowledge already in existence (Wands 5)
- 4) **predictability** of the aspect at issue (see Wands 7)

Enablement: Wands Factors

- 1) *quantity of experimentation*
- 2) *amount of direction or guidance*
- 3) *working examples*
- 4) nature of invention
- 5) state of art
- 6) relative skill in art
- 7) **predictability** of art
- 8) breadth of claims

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US10,221,239

TRPM4 CHANNEL INHIBITORS FOR STROKE TREATMENT 2019

- 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.
- Used 3D model to map epitope of exemplary antibody
- Data showing it inhibits TRPM4 activity
- Sufficient to establish structure-function correlation



NO FUNCTIONAL ELEMENT?

- US10,669,347 2020
- Antibodies comprising site-specific non-natural amino acid residues, methods of their preparation and methods of their use
- 1. An isolated antibody of the IgG class comprising a heavy chain and a light chain, wherein:
 - the heavy chain comprises at least one non-natural amino acid residue at a specific site selected from the group consisting of heavy chain residue 52 according to the Kabat numbering scheme and heavy chain residues 119, 222, and 241 according to the EU index of Kabat; or
 - the light chain comprises a non-natural amino acid residue at the light chain residue 152; or a combination thereof; or an aglycosylated variant thereof, wherein each non-natural amino acid residue is independently selected from the group consisting of ortho-substituted tyrosine, meta substituted tyrosine, para-substituted phenylalanine, ortho-substituted phenylalanine, and meta-substituted phenylalanine.



US10562966

ANTIBODIES OF THE CLASS IGG4

2020

- 1. An antibody of the class **IgG4**, comprising two [**at least one**] light chains and two heavy chains, wherein the heavy chains comprise a C_H1 domain and a hinge region comprising an IgG4 upper hinge and core region, wherein in each heavy chain:
 - (a) the inter-chain cysteine at position 127 in the C_H1 domain is substituted with [**another amino acid**] an amino acid selected from the group comprising serine, threonine, alanine, and glycine; and
 - (b) **one or more of the amino acids** at positions 227, 228, and 229 in the upper hinge region is substituted with cysteine, and wherein the amino acid numbering is according to the Kabat numbering system.



CONCLUSION

- Representative species
- Common structural elements
- “functional characteristics when coupled with a known or disclosed correlation between function and structure” may satisfy the written description requirement.
- “The precedential value of cases in this area is extremely limited.” Each case must be decided on its own facts.



THANK YOU

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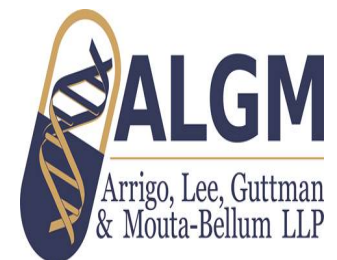
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