PM1

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Antibody decisions and the written description requirement

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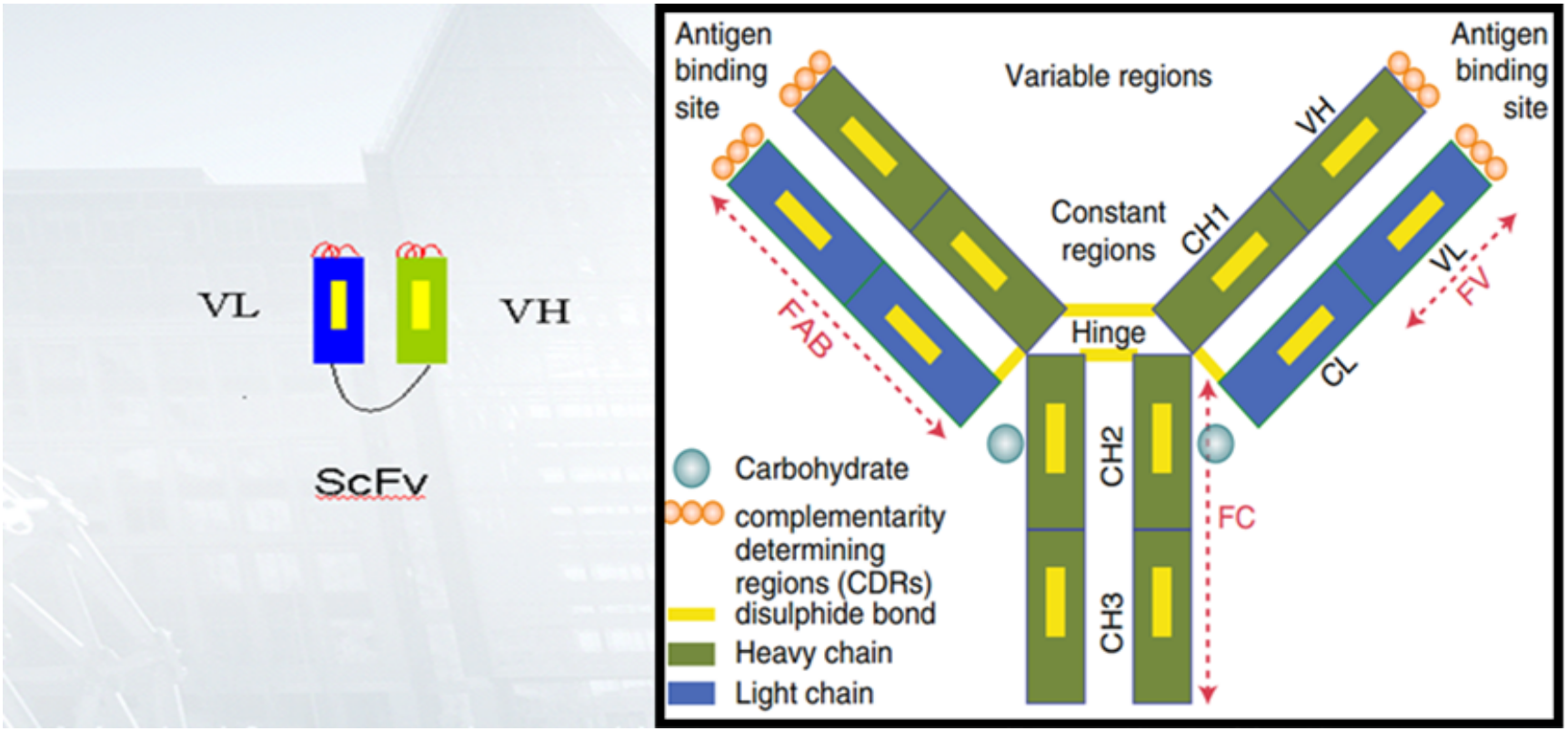
Overview

1. The written description requirement
2. *Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341 (Fed. Cir. 2011)
3. *AbbVie Deutschland GmbH v. Janssen Biotechnology, Ltd.*, 759 f.3d 1285 (Fed. Cir. 2014)
4. *Amgen Inc. v. Sanofi*, 872 F.3d 1367 (Fed. Cir. 2017)

The written description requirement

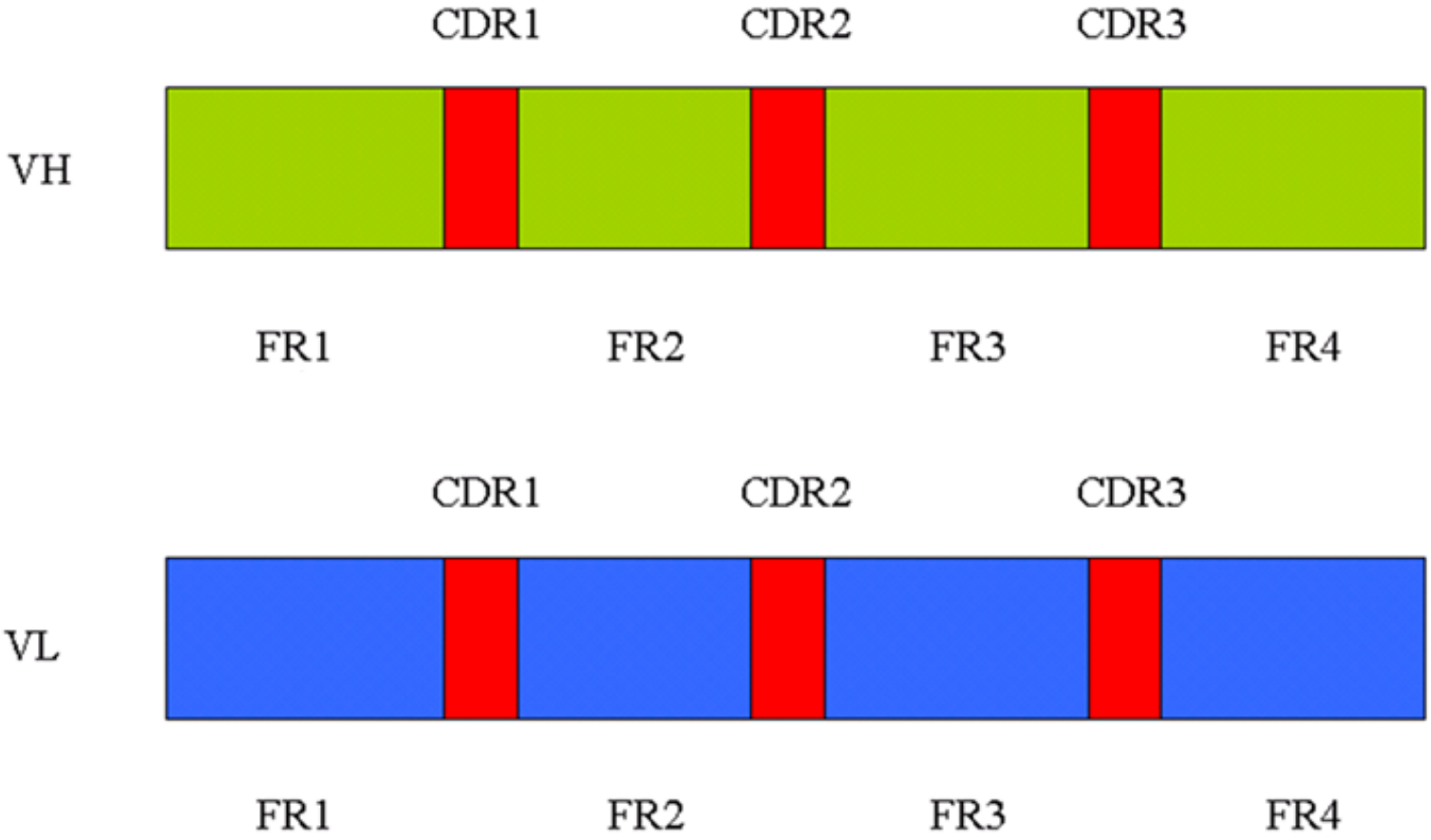
- MPEP 2163 provides guidance for complying with the written description requirement of 35 U.S.C. 112(a) that the "specification shall contain a written description of the invention . . . . ."
- This requirement is separate and distinct from the enablement requirement (*Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1355 (Fed. Cir. 2010)).

Antibody structure

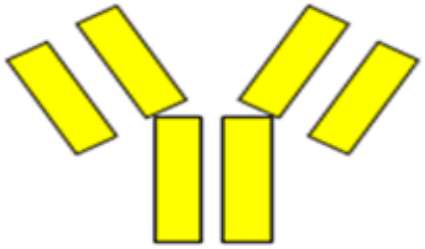


Adapted from http://people.cryst.bbk.ac.uk/~ubcg07s/gifs/IgG.gif

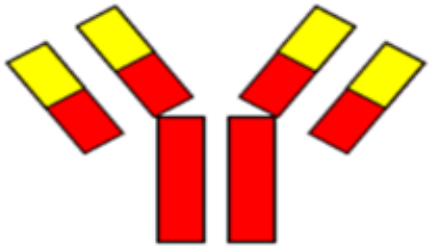
Antibody variable domains



Humanization of antibodies



Mouse



Chimeric

Humanized

Human

W.D. for claimed genus may be satisfied through sufficient description of a representative number of species

- Inverse function of the skill and knowledge in the art
- Depends on whether one of skill in the art would recognize necessary common attributes or features possessed by the members of the genus
- Generally, in an **unpredictable art**, adequate written description of a genus which embraces **widely variant species cannot be achieved by disclosing only one species within the genus**

See *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956 (Fed. Cir. 2002)*; Noelle v. Lederman*, 355 F.3d 1343 (Fed. Cir. 2004); *Regents of the University of California v. Eli Lilly Co.*, 119 F.3d 1559 (Fed. Cir. 1997)

W.D. is also satisfied when relevant identifying characteristics are disclosed

> [D]etermine whether the specification discloses other ***relevant identifying characteristics*** sufficient to describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize applicant was in possession of the claimed invention. For example, if the art has established a strong correlation between ***structure and function***, one skilled in the art would be able to predict with a reasonable degree of confidence the structure of the claimed invention from a recitation of its function. Thus, the written description requirement may be satisfied through disclosure of function and minimal structure when there is a well-established correlation between structure and function.

MPEP 2163 (emphasis added).

Claiming by function does not necessarily satisfy the written description requirement

> [A] generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others.
>
> . . . .
>
> A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. It is only a definition of a useful result rather than a definition of what achieves that result.

Regents of the *University of California v. Eli Lilly Co.,* 119 F.3d 1559 (Fed. Cir. 1997) (internal citations omitted).

Centocor Ortho Biotech, Inc. v. Abbott Labs., 636 F.3d 1341 (Fed. Cir. 2011)

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Claims in Centocor's U.S. Patent 7,070,775 ('775 Patent) (2006)

1. An isolated recombinant anti-TNF-α antibody or antigen-binding fragment thereof, said antibody or antigen-binding fragment comprising ***a human constant region***, wherein said antibody or antigen binding fragment (i) competitively inhibits binding of A2 (ATCC Accession No. PTA-7045) to human TNF-α, and (ii) binds to a neutralizing epitope of human TNF-α in vivo with an affinity of at least $1x10^8$ liter/mole, measured as an association constant (Ka), as determined by Scatchard analysis.

2. The antibody or antigen-binding fragment of claim 1, wherein the antibody or antigen binding fragment comprises ***a human constant region*** and ***a human variable region***.

(emphasis added)

Human anti-human TNF-α antibody

- Centocor sues for infringement, indicating that Abbott's TNF-a (Humira®) antibody is encompassed by Centocor's claim 2.

- Centocor's '775 patent filed July 18, 2002, claims benefit under 35 U.S.C. 120 to 08/570,674, filed 12/11/1995, which is a CIP of 08/324,799, filed 10/18/1994. It sought benefit (effective filing date) of this 1994 application, which would pre-date Abbott's earliest filing date for Humira® (1995).

Human anti-human TNF-α antibody (cont.)

- Centocor's '775 patent claims benefit of a 1991 application that discloses an antibody that was obtained by identifying a mouse antibody to human TNF-a that had high affinity and neutralizing activity ("A2 mouse antibody") and substituting the mouse constant region with a human constant region. The result was a chimeric antibody.

- Abbott's antibody (first filed 1995) was obtained from a phage display library that contained a large number of human variable regions. After identifying variable regions that bound to human TNF-a, "guided selection" was used to identify variable regions that had neutralizing activity (U.S. Patent 6,090,382).

Chimeric

Human

Human anti-human TNF-α antibody (cont.)

- Centocor files CIP applications (1993) that are rejected for lack of enablement because they are drawn to "less than an entire mouse variable region." The specification only teaches fully-mouse variable regions.

- Centocor files CIP applications (1993-1994) drawn to "less than an entire mouse variable region." This comprises new matter that Centocor relies on as evidence to support the asserted claims of '775. While these additions were made, no claims were drawn to human variable regions.

Humanized

Human anti-human TNF-α antibody (cont.)

- Following the Abbott patenting of Humira® in 2000 and its regulatory approval in 2002, Centocor files claims to fully-human antibodies. Upon withdrawal of the enablement rejection, Centocor's claims are patented in 2006 (U.S. Patent 7,070,775).

Issue of adequate written description is raised

Question raised in Centocor Federal Circuit decision:

- Does Centocor have written description support for human antibodies against TNF-α?

Abbott's position:

- To have the 1994 benefit, Centocor's 1994 CIP must provide written description for a human antibody with 1) a human constant region, 2) a human variable region, 3) high affinity for human TNF-α, 4) neutralizing activity, and 5) the ability to bind TNF-α in the same place as Centocor's A2 mouse antibody.
- Abbott points out that making human antibodies against human proteins is difficult (e.g. autoimmune issues) and thus an artisan would need to engineer a human antibody.

Centocor **Conclusions**

The court found that all Centocor really has support for is the A2 mouse antibody and the single chimeric antibody. This mouse sequence does not serve as a stepping stone for the human variable region. Further, it was shown that the sequence of the mouse variable region was different from that of the human. As such, Centocor lacked written description for the genus of human anti-TNF-α antibodies.

> Thus, while the ***patent broadly claims*** a class of antibodies that contain human variable regions, the ***specification does not describe*** a single antibody that satisfies the claim limitations. It does not disclose any ***relevant identifying characteristics*** for such fully-human antibodies or even a single human variable region. ***Nor does it disclose any relationship*** between the human TNF-α protein, the known mouse variable region that satisfies the critical claim limitations, and potential human variable regions that will satisfy the claim limitations.

Centocor, 636 F.3d at 1351 (emphasis added) (internal citations omitted).

Centocor conclusions (cont.)

> [A] "mere wish or plan" for obtaining the claimed invention is not sufficient.
>
> . . . .
>
> While our precedent suggests that written description for certain antibody claims can be satisfied by disclosing a well-characterized antigen, that reasoning applies to disclosure of newly characterized antigens where creation of the claimed antibodies is routine. . . . [O]btaining a high affinity, neutralizing, A2 specific antibody with a human variable region was not possible in 1994 using "conventional," "routine," "well developed and mature" technology.

Centocor, 636 F.3d at 1351-52 (internal citations omitted).

***AbbVie Deutschland GmbH v. Janssen Biotechnology, Ltd.*, 759 F.3d 1285 (Fed. Cir. 2014)**

AbbVie v. Janssen (2014)

- Human antibody against human IL-12
- AbbVie's patents U.S. 7,504,485 and U.S. 6,914,128 shared the same specification, and had claims directed to **fully human anti-IL-12** antibodies.
- Janssen produced Stelara® (ustekinumab) indicated for the treatment of adults with moderate-to-severe plaque psoriasis.

Claim from AbbVie's '128 patent:

> 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 $1x10^{-2}$ s^{-1} or less, as determined by surface plasmon resonance.

Issue of adequate written description is raised

- AbbVie's '128 and '485 patents taught ~300 fully human antibodies that bind and neutralize IL-12.
- All of AbbVie's patents disclosed antibodies were derived from 1st Gen antibody "Joe-9."
- Joe-09 CDR3 (VH/VL) mutated to increase affinity and neutralizing activities.

Issue of adequate written description is raised (cont.)

All disclosed AbbVie antibodies have:

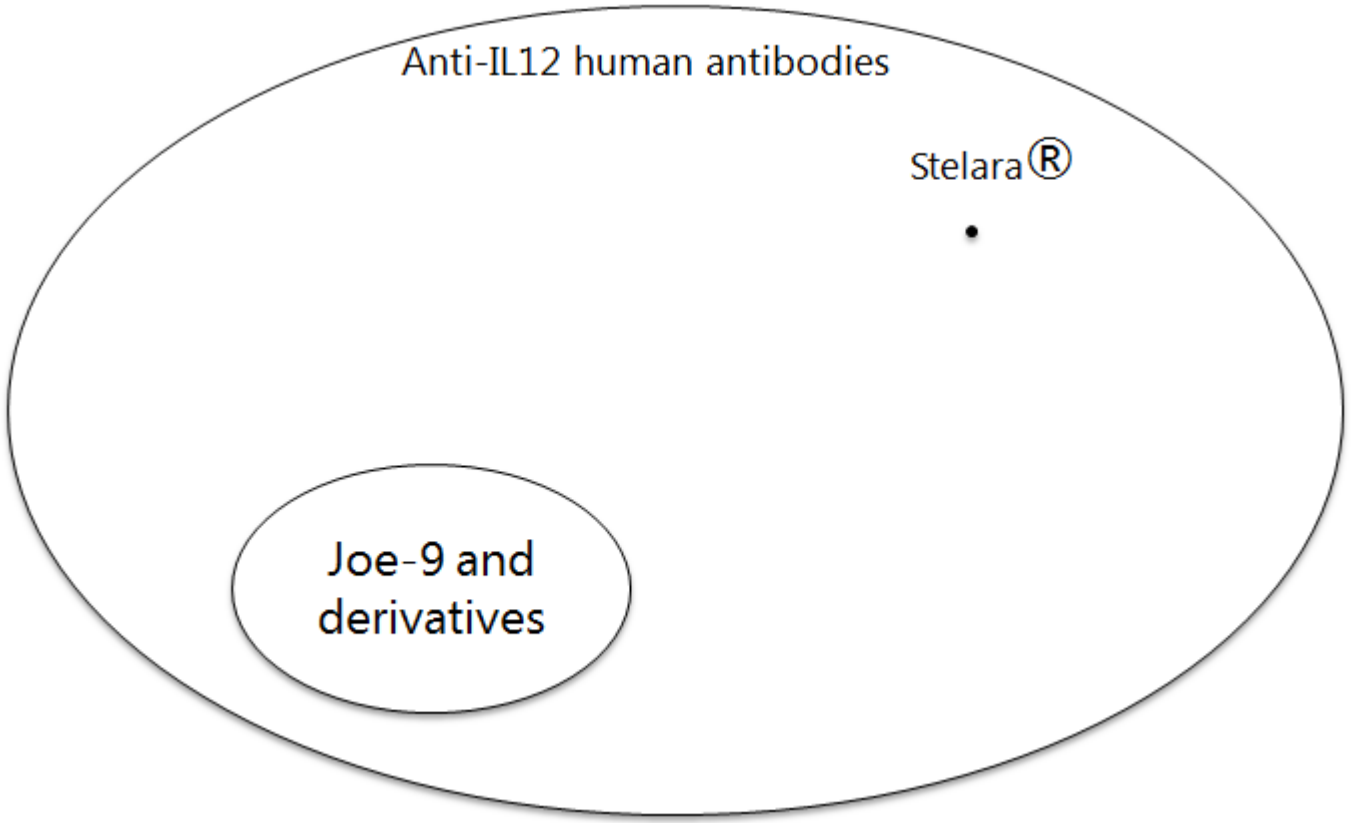
1. VH3 heavy chains
2. Lambda light chains
3. At least **90% similarity** with Joe-9 in variable regions
4. More than 200 of the antibodies differ from the 2nd gen Ab (Y61) at a single amino acid residue (**99.5% similarity** in variable regions)

Issue of adequate written description is raised (cont.)

- **Stelara® met the functional claim limitations:**
  - Fully human
  - Anti-IL-12
  - Neutralize activity of IL-12
- **But is structurally distinct from Joe and Joe-derived antibodies.**

	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

Stelera® is not encompassed by Joe-9 and its derivatives



Issue of adequate written description is raised (cont.)

Representative number and/or common structural features

- "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*****"** (*Capon v. Eshhar*, 418 F.3d 1349 (Fed. Cir. 2005)) (emphasis added).

- "***[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" (*AbbVie,* 759 F.3d at 1299, reiterating *Eli Lilly*, 119 F.3d at 1568-69) (emphasis added).

Issue of adequate written description is raised (cont.)

Functional limitations are not strictly prohibited.

- "It is true that functionally defined claims can meet the written description requirement if a ***reasonable structure-function correlation*** is established, whether by the inventor as ***described in the specification or known in the art at the time of the filing date***" (*AbbVie*, 759 F.3d at 1301, reiterating *Enzo Biochem, Inc.*, 323 F.3d at 964) (emphasis added).

Issue of adequate written description is raised (cont.)

But, genus claims need core structure or representative examples.

"The asserted claims attempt to claim ***every fully human IL-12*** antibody that would ***achieve a desired result***, i.e., high binding affinity and neutralizing activity, and cover an antibody as ***different as Stelara®***, whereas the patents do not describe representative examples to support the full scope of the claims." Jury's decision of invalidity for lack of adequate written description for the claimed genus affirmed (AbbVie, 759 F.3d at 1301) (emphasis added).

Genus-Species guidance in MPEP 2163. MPEP includes citations of Noelle v. Lederman, 355 F.3d 1343 (Fed. Cir. 2004), Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956 (Fed. Cir. 2002), and Regents of the University of California v. Eli Lilly Co. 119 F.3d 1559 (Fed. Cir. 1997).

***Amgen Inc. v. Sanofi*, 872 F.3d 1367 (Fed. Cir. 2017), *cert. denied*, Jan. 7, 2019 (No. 18-127)**

Amgen v. Sanofi (2017)

- **Monoclonal antibodies targeting proprotein convertase subtilisin kexin type 9 (PCSK9), a protein that destroys LDL receptors in liver cells**
- **Amgen produced Repatha® (evolocumab) for the reduction of high levels of LDL cholesterol**
  - Claim from Amgen's '165 patent:
    An isolated monoclonal antibody, wherein, when bound to PCSK9, the monoclonal antibody binds to at least one of [15 residues] of SEQ ID NO:3, and wherein the monoclonal antibody blocks binding of PCSK9 to LDL-R.

Issue of adequate written description of Amgen's '165 patent is raised

- '165 patent described trial-and-error screening process leading to Repatha®
- 3,000 human mAbs screened for binding to wild-type PCSK9 to confirm stability
- Narrowed to 85 mAbs that blocked PCSK9/LDL-R interaction at greater than 90%
- Three-dimensional structures of 2 mAbs bound to PCSK9 (one is Repatha®)
- Amino acid sequences of 22 other antibodies that compete with Repatha® for binding to PCSK9

Issue of adequate written description of Amgen's '165 patent is raised

- Sanofi wished to provide post-filing date evidence of antibodies (including Praluent®) that fall into '165 patent's claimed genus but were developed after Amgen's filing date.
- "Evidence showing that a claimed genus does not disclose a **representative number of species** may include evidence of species that fall within the claimed genus but are not disclosed by the patent, and evidence of such species is likely to postdate the priority date."

Issue of adequate written description of Amgen's '165 patent is raised

- "We cannot say that this particular context, involving a 'newly characterized antigen' and a functional genus claim to corresponding antibodies, is one in which the underlying science establishes that a finding of 'make and use' (routine or conventional production) actually does equate to the required description of the claimed products." *Amgen*, 872 F.3d at 1378.

Issue of adequate written description of Amgen's '165 patent is raised

- "[T]he 'newly characterized antigen' test flouts basic legal principles of the written description requirement. Section 112 requires a 'written description of the invention.' But this test allows patentees to claim antibodies by describing something that is not the invention, i.e., the antigen." *Amgen*, 872 F.3d at 1378.

Issue of adequate written description of Amgen's '165 patent is raised

- "[W]e have generally eschewed judicial exceptions to the written description requirement based on the subject matter of the claims." Amgen, 872 F.3d at 1378-79 (citing *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 925 (Fed. Cir. 2004).
- "Congress has not created a special written description requirement for antibodies as it has, for example, for plant patents." *Amgen*, 872 F.3d at 1379 (citing 35 U.S.C. § 162).

The difference between written description and enablement

- Written description requires description, while enablement is satisfied with disclosure of how to make and use.

- MPEP 2163 (written description): "A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, ***even when accompanied by a method of obtaining the claimed sequence"*** (emphasis added).

The difference between written description and enablement (cont.)

- MPEP 2164 (enablement): The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art.

Which rejection addresses the issue at hand?

Claim under examination: A peptide having 95% identity to SEQ ID NO. 1, wherein the peptide activates protein X.

Written description
What structure, or 95% of the sequence, needs to be preserved to maintain the peptide's function?

Enablement
Can an artisan predict which 95% of the sequence needs to be intact to maintain the peptide's function?

Applicant's response: make amino acid mutants and screen for the ones that activate protein X (i.e., an argument on how to make).

Result: Enablement rejection withdrawn; written description maintained.

Questions?

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