2nd BCLT
Advanced Life Sciences Institute

Amgen One Year Out: What Have We Learned?

May 2024

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at Berkeley Law

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Douglas Behrens

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Douglas Behrens is Special Counsel at Covington & Burling LLP. He specializes in representing pharmaceutical and biotechnology companies in high-stakes patent litigation. Douglas focuses on litigating patent matters before the U.S. district courts, the Patent Trial and Appeal Board, and the Federal Circuit. He has played significant roles in all stages of litigation, from pre-suit diligence and case inception through trial and appeal. While Douglas handles cases involving a wide variety of technologies, including telecommunications and financial services, he specializes in small molecule and biologics cases.

Prior to joining Covington, Douglas served as a law clerk to the Honorable Kara F. Stoll of the U.S. Court of Appeals for the Federal Circuit and to the Honorable Richard G. Andrews of the U.S. District Court for the District of Delaware.

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Sabrina Poulos is a partner in Goodwin Procter LLP's Life Sciences group. While primarily focusing on US and ex-US patent strategy and prosecution, Sabrina approaches IP holistically, working with her clients on trade secret protection, licensing, sponsored research agreements, collaboration agreements, Bayh-Dole compliance, optimizing Patent Term Extension, developing company internal IP policies, advising companies on IP issues related to academic founders, and export matters.

Sabrina also represents investors in IP diligence matters and company creation, analyzing IP portfolios and creating pragmatic solutions to optimize the IP portfolio in order to maximize the return on an investment.

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Agenda

- State of the Law Post-*Amgen*
- USPTO Guidelines on Section 112 Post-*Amgen*
- Strategies and Business Impacts

State of the Law Post-Amgen

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Where Law Meets Innovation

Amgen v. Sanofi (S. Ct. 2023)

- Most recent Supreme Court pronouncement on enablement
- Technology related to antibodies for PCSK9, which is involved in the regulation of LDL cholesterol ("bad cholesterol")
  - Amgen's Repatha® and Sanofi's Praluent® were competing, FDA-approved antibody drugs that could inhibit PCSK9 from binding to LDL receptors
- Specification of Amgen's patent disclosed:
  - Amino acid sequence for 26 antibodies that perform the claimed functions;
  - Three-dimensional structures for 2 of these 26 antibodies; and
  - Two methods for making additional antibodies that would be encompassed by the claims (roadmap and conservative substitution)

Amgen – Representative Claim

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.

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.

Takeaways from *Amgen*

- Supreme Court affirmed judgment that claims were not enabled
- Enablement requirement: a "reasonable amount of experimentation" is permissible
- If the claims cover an entire class of compositions of matter, the specification "must enable a [POSA] to make and use the entire class"
  - But the specification need not describe with particularity how to make and use every embodiment within the claimed class
    - It may suffice to give one, or a few, examples if the specification also discloses a general quality that gives the class of claimed matter a "peculiar fitness for the particular purpose"
  - Amount of time required to exhaust the genus is not dispositive
- *Wands* factors were not addressed

Baxalta v. Genentech (CAFC 2023)

- First post-*Amgen* Federal Circuit case addressing antibody technology
- Asserted patent covered antibodies for Factor IX, which is part of the coagulation cascade that helps form blood clots
- Specification disclosed:
  - Hybridoma technique for preparing and screening antibodies (only 1.6% of 1,000+ screened antibodies demonstrated increased procoagulant activity); and
  - Amino acid sequence for 11 antibodies

Baxalta v. Genentech (CAFC 2023)

> 1. An isolated antibody or antibody fragment thereof that binds Factor IX or Factor IXa and increases the procoagulant activity of Factor IXa.

- As in *Amgen*, the claims recited the function, not structure, of the antibody
- Federal Circuit affirmed grant of summary judgment for lack of enablement
  - Court viewed this case as "materially indistinguishable" from *Amgen*
  - Nothing in the specification teaches a POSA how to identify infringing antibodies other than by repeating the trial-and-error screening process followed by the inventors
- *Amgen* did not overturn Federal Circuit's existing law on enablement, including *In re Wands*

Teva Pharms. v. Eli Lilly (D. Mass. 2023)

- Asserted patents covered methods of using antibodies for CGRP to prevent headaches
- Specification disclosed:
  - 1 humanized anti-CGRP antagonist antibody within the scope of the claims;
  - 84 antibody fragments (not within scope of claims); and
  - 12 mouse anti-CGRP antibodies (not within scope of claims)
- Jury rendered a verdict in favor of Teva and awarded $90M in lost profits, almost $37M in reasonably royalties, and just under $50M in future lost profits

Teva Pharms. v. Eli Lilly (D. Mass. 2023)

1. A method for treating headache in an individual, comprising:

administering to the individual an effective amount of a humanized monoclonal anti-Calcitonin Gene-Related Peptide (CGRP) antagonist antibody, comprising:

two human IgG heavy chains, each heavy chain comprising three complementarity determining regions (CDRs) and four framework regions, wherein portions of the two heavy chains together form an Fc region; and

two light chains, each light chain comprising three CDRs and four framework regions;

wherein the CDRs impart to the antibody specific binding to a CGRP consisting of amino acid residues 1 to 37 of SEQ ID NO:15 or SEQ ID NO:43.

6. The method of claim **1**, wherein the headache is a migraine.

Teva Pharms. v. Eli Lilly (D. Mass. 2023)

- Court granted JMOL on enablement and written description grounds
- A POSA could not predict whether an antibody will antagonize CGRP based on its amino acid sequence, so each candidate would need to be made and tested
  - Number of covered antibodies is unknowable but potentially "mind-boggingly large"
  - It did not matter that making/testing the antibodies was routine
- Court rejected Teva's written description arguments regarding common structural features (e.g., y-shape, humanization, and structural complementarity with CGRP)
  - The y-shape structure is common to all antibodies, the humanization process is not specific to anti-CGRP antagonist antibodies, and structural complementarity with CGRP does not describe the antibody's structure
  - These are not structural features that determine whether an antibody will fall within the scope of the claims

Regeneron v. Mylan (N.D. W. Va. 2024)

1. A vial comprising an ophthalmic formulation suitable for intravitreal administration that comprises:

a vascular endothelial growth factor (VEGF) antagonist

an organic co-solvent,

a buffer, and

a stabilizing agent,

wherein said VEGF antagonist fusion protein is glycosylated and comprises amino acids 27-457 of SEQ ID NO:4; and

wherein at least 98% of the VEGF antagonist is present in native conformation following storage at 5° C. for two months as measured by size exclusion chromatography.

2. The vial of claim **1**, wherein the concentration of said VEGF antagonist fusion protein is 40 mg/ml, and wherein said organic co-solvent comprises polysorbate.

4. The vial of claim **2**, wherein said organic co-solvent comprises about 0.03% to about 0.1% polysorbate 20.

Regeneron v. Mylan (N.D. W. Va. 2024)

- Mylan's enablement arguments focused on the fact that the claims did not specify the type or amount of organic co-solvent, buffer, or stabilizing agent
- Court applied *Wands* factors and found claims were enabled
  - POSA could practice claims with "minimal and routine" experimentation
- Notably, the court found that there was *no* expert testimony that undue experimentation would be necessary to practice the claims
- Distinguished *Amgen* on the grounds that the claims are directed to formulations of a specific protein at a specific concentration, not a whole kingdom of proteins

USPTO Guidance

Determining "Reasonableness of Experimentation"

- Published January 2024
- Wands factors are still probative of the essential inquiry in determining whether one must engage in more than a reasonable amount of experimentation
  - The explanation in an enablement rejection or in a PTAB determination that a claim is not enabled should focus on the Wands factors and the reasons and evidence that led the examiner or decision-maker to arrive at their conclusion
  - Examiners must provide sufficient explanation to facilitate clarity of the record, as well as consistency between examination and post-grant challenges

Strategies and Business Impacts

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Where Law Meets Innovation

Big Picture: Opportunities

- Opens development opportunities
  - Decreased risk of FTO roadblocks
  - Assume broader patents are invalid
- Early innovators may be less likely to put platform patents at risk of being invalidated with litigation
- Rebalances value of licenses to early stage IP
  - Evaluate likelihood that application will issue or patent is enforceable before licensing
  - More leverage over license terms

Big Picture: Threats

- Existence of platform technology and lack of appetite for litigation can create opportunities for follow-on innovators
  - Harder to protect platforms and new modalities/targets
  - Need to move faster to concrete embodiments = need more cash
  - Once you disclose (e.g. application publishes), followers may start working on their own variations (race to market favors well-funded companies)
  - Increased focus on trade secrets -> more complex license negotiations and stickier royalties

Rethinking Strategies – First Movers v Fast Followers

	First Movers	Fast Followers
Reevaluate university involvement; likely pivot to trade secret focus -> stickier royalties	✓	
Prioritize early need for large capital raise and strong team (set stage to win race to market)	✓	✓
Focus IP pitch on trade secrets and future strategy	✓	
Prioritize delay in disclosure (stay in stealth)	✓	
Use accelerated exam to avoid disclosure without patent protection (skip PRO; beat pub.)	✓	
Patent as many specific variations as you can (Data! Data! Data!)	✓	✓
Consider public disclosures of "non-enabled" variations (poison the well)	✓	✓
Prioritize patent spend on developing data (skip patenting secondary developments)	✓	✓
Prepare data showing lack of predictability within a genus/document unpredictability with eye to future litigation		✓
Prioritize PGRs – (tight deadline: 9 months from issuance)		✓

Rethinking Strategies – Investors

- Increased risk
  - Betting on companies without meaningful present patent protection; early platform filings provide less protection for your targets (do not assume target can block competitors)
  - Need to pony up large amounts of cash to fund race to market
  - Does company have team (and resources) that can quickly push into development
  - Is technology in place now to enable commercialization
- Decreased risk
  - Early platform filings provide fewer impediments for your targets
  - A well-funded, good team may be able to pass early innovators

Diligence Considerations – Understanding the Space

- Focus landscape searches on specific products or components of products
  - Broad platform searches now less informative
  - Save money by using narrower searches
  - Broad platform searches may uncover material prior art you need to disclose to the PTO; patents that may be invalid can still be prior art to your improvements
- Increase focus on disclosure strategy and trade secret strategy (control of information)

Adaptive Prosecution Strategies

- Load up specification with data and examples
  - Definite downside: very expensive and time consuming; delays filings (prior art concern); value of data/examples is unpredictable
  - Potential downside: examples/bad data could undermine patentability
- Limit claims to novel components
  - Potential downside: claims rejected or invalidated for missing essential elements/structure
  - Potential downside: claims limited to claimed component alone

Adaptive Prosecution Strategies

- Means-plus-function and Jepson claims
  - Means plus function – claim something by its function, with no structure ("means for binding human C5 protein")
  - Jepson – preamble states the known prior art, and the body specifies the improvements made over this prior art ("wherein the improvement comprises")
  - Definite downside
    - MPF claim scope limited to the examples in the specification and equivalents known at issuance
    - Jepson claims admit prior art; complicate obviousness analysis
  - Potential downside: limited litigation in life sciences space means law still being developed (outcomes unpredictable)

In re Xencor (Ex Parte Chamberlain)

- US 16/803,690
  - Claimed antibody functionally using Jepson and means-plus-function claims
  - MPF and Jepson claims rejected by PTAB for lack of written description; Xencor appealed to the Federal Circuit
  - Federal Circuit remanded to the USPTO for consideration by an Appeals Review Panel (ARP) on Jan. 23, 2024
- ARP Decision released on May 17, 2024
  - Panel – Katherine Vidal (Dir. Of USPTO), Vaishali Udupa (Commissioner of Patents), Scott Boalick (Chief Administrative Patent Judge)
  - Holding – Maintained PTAB rejections for lack of written description

In re Xencor (Ex Parte Chamberlain)

- Claim 8 – Jepson claim
  - 8. In a method of treating a patient by administering an anti-C5 antibody with an Fc domain, the improvement comprising said Fc domain comprising amino acid substitution M428L/N434S ... wherein said anti-C5 antibody with said amino acid substitution has increased in vivo half-life…
  - Preamble is limiting
    - Preamble of a Jepson claim is limiting, by necessity
    - Defines the context of the claimed invention and the scope of the claim
  - Where preamble is limiting, it must satisfy written description requirement
    - No written description for “anti-C5 antibody” based on the one example
    - No written description for “treating a patient” -> treating all patients and all diseases

In re Xencor (Ex Parte Chamberlain)

- Claim 9 – means-plus-function claim
  - 9. A method of treating a patient by administering an anti-C5 antibody comprising: a) means for binding human C5 protein; and b) an Fc domain comprising amino acid substitution M428L/N434S ... wherein said anti-C5 antibody with said amino acid substitution has increased in vivo half-life…
  - Written description for means-plus-function claims
    - Specification need only provide a single corresponding structure
    - Specification does not need to provide written description for equivalents
  - Preamble is limiting
    - Gives life to claim; “in vivo half-life” necessitates incorporating “treating a patient” into body of claim
    - No written description for “treating a patient” -> treating all patients and all diseases

Thank you for joining us.

2024 Advanced Life Sciences Institute Agenda: LINK

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