Enablement in the Chemical Arts

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• Whether U.S. Supreme Court case in *Amgen v. Sanofi* and USPTO Guidelines on Enablement impact examination and adjudication of chemical patent claims
Overview

• Historical perspective of the Enablement Requirement
• Enablement in the Chemical Arts Pre-Amgen
• Amgen v. Sanofi
• USPTO Guidelines on Enablement
• Enablement Cases Post-Amgen
Enablement Requirement has its origin in Section 2 of The Patent Act of 1790

[T]he grantee ... of each patent shall, ..., deliver ... a specification in writing, containing a description, ... to enable a workman or other person skilled in the art..., to make, construct, or use the same, to the end that the public may have the full benefit thereof, after the expiration of the patent term...
Enablement Requirement was Codified in the 1952 Patent Act

• 35 U.S.C. § 112, first paragraph
  – 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...

• The enablement requirement has stayed intact through several revisions of U.S. patent law
  – did not change in the America Invents Act (AIA)
  – 35 U.S.C. § 112(a) is the same as pre-AIA § 112, first paragraph
Representative Cases in the Chemical Arts

Pre-Amgen

• In re Wands, 858 F.2d 731 (Fed. Cir. 1988)
• Wyeth & Cordis Corp. v. Abbott Labs., 720 F.3d 1380 (Fed. Cir. 2013)
• Enzo Life Scis., Inc. v. Roche Molecular Sys., Inc., 928 F.3d 1340 (Fed. Cir. 2019)
• U.S. Patent Application No. 188,735
• Representative claim:
  – An immunoassay method utilizing an antibody to assay for a substance comprising hepatitis B-
    surface antigen (HBsAg) determinants which comprises the steps of: contacting a test sample
    containing said substance comprising HBsAg determinants with said antibody; and
    determining the presence of said substance in said sample; wherein said antibody is a
    monoclonal high affinity IgM antibody having a binding affinity constant for said HBsAg
    determinants of at least $10^9$ M$^{-1}$.

• Appeal from the Patent and Trademark Office Board of Patent Appeals and Interferences
  – Board upheld Examiner’s finding that claims were invalid for lack of enablement

• CAFC: Reversed
• Holding: Would not require undue experimentation to obtain antibodies needed to practice the claimed invention

*In re Wands*, 858 F.2d 731 (Fed. Cir. 1988)
Wands Factors to be considered in determining whether a disclosure would require undue experimentation include:

1. the quantity of experimentation necessary;
2. the amount of direction or guidance presented;
3. the presence or absence of working examples;
4. the nature of the invention;
5. the state of the prior art;
6. the relative skill of those in the art;
7. the predictability or unpredictability of the art; and
8. the breadth of the claims.

*In re Wands*, 858 F.2d 731 (Fed. Cir. 1988)
• Drug Product: rapamycin
• U.S. Patent Nos. 5,516,781 and 5,563,146
• Representative claim:
  • A method of treating (or preventing) restenosis in a mammal ... undergoing a ... [coronary angioplasty procedure]... administering an antirestenosis effective amount of rapamycin to said mammal...
• Rapamycin refers to a class of compounds
• A new use for an existing class of compounds
The structure of sirolimus includes a substituent group at the C-42 position (circled) and a macrocyclic triene ring:

The defendants market stent products that elute two drugs that have the same macrocyclic ring as sirolimus but different substituents at the C–42 position.

Issue: whether practicing the full scope of the claims requires excessive - and thus undue - experimentation.
Wyeth & Cordis Corp. v. Abbott Labs., 720 F.3d 1380 (Fed. Cir. 2013)

- **DC: Asserted claims are invalid due to lack of enablement**
  - claims cover *any* structural analog of sirolimus that exhibits immunosuppressive and antirestenotic effects
  - while the specification describes assays to ascertain whether a potential rapamycin compound exhibits the recited functional effects, the only species disclosed is sirolimus

- **CAFC: Affirmed**
  - Wyeth argued: (1) a skilled artisan could ascertain whether a candidate rapamycin compound has the same macrocyclic ring as sirolimus; (2) a skilled artisan could routinely determine whether a candidate has immunosuppressive and antirestenotic effects using the assays disclosed in the specification

- **Holding:**
  - Undue experimentation was required to practice the *full scope* of the claims where the specification "disclose[d] only a starting point for further iterative research in an unpredictable and poorly understood field"
    - Synthesizing and screening each of at least tens of thousands of candidate compounds constitutes undue experimentation
U.S. Patent Nos. 6,992,180 and 8,097,405

Claims of ‘180 patent:
- directed to non-radioactive labeling of polynucleotides where the label is attached at the phosphate position of a nucleotide
  - are not directed to any specific polynucleotide;
  - do not focus on the chemistry or linker used to attach a label, the number of labels to attach to a polynucleotide, or where within the polynucleotide to attach those labels
- encompass all polynucleotides with labels attached to a phosphate, as long as the polynucleotide remains hybridizable and detectable upon hybridization
Enzo Life Scis., Inc. v. Roche Molecular Sys., Inc.,
928 F.3d 1340 (Fed. Cir. 2019)

• Issue: whether the specification enables creation of a labeled probe that
is both hybridizable and detectable upon hybridization
• Claim requires both structure and function
• DC: Asserted claims are invalid due to lack of enablement
• CAFC: Affirmed
• Analogous to Wyeth
Enzo Life Scis., Inc. v. Roche Molecular Sys., Inc., 928 F.3d 1340 (Fed. Cir. 2019)

• **Wands** factors
  – claim scope is *broad*
  – specification’s guidance as to how such variables would or would not impact the functionality of the claimed probes is *sparse*
  – at the time of the invention, the art was *highly unpredictable*
  – example is insufficient to enable the breadth of the claims, especially in light of the unpredictability in the art
  – even if the example describes *one working embodiment* with the claimed functionality, *undue experimentation* would still be required with regard to the many other embodiments of the claims *based on the number of possible embodiments* and the unpredictability in the art

- Drug Product: sofosbuvir for treating hepatitis C virus (HCV) (Gilead)

- U.S. Patent No. 7,608,597
- Idenix sued Gilead for infringement
- Representative claim:
  - A method for the treatment of a hepatitis C virus infection, comprising administering an effective amount of a purine or pyrimidine 6-D-2'-methyl-ribofuranosyl nucleoside or a phosphate thereof, or a pharmaceutically acceptable salt or ester thereof.
  - claim has both structural and functional limitations
Nucleosides claimed have a specific chemical and stereochemical structure, e.g., a sugar ring having five carbon atoms, numbered 1’ (one prime) to 5’ (five prime) and a base.

At each carbon, substituent atoms or groups of atoms can be added in either the “up” or “down” position:

- 2’ and 3’ hydroxy “down” 2’
- 3’ hydroxy “down” methyl “up”
• Issue: whether a person of ordinary skill in the art would know, without undue experimentation, which 2'-methyl-up nucleosides would be effective for treating HCV

• DC: invalid for lack of enablement

• CAFC: Affirmed – applied Wands factors
  – the quantity of experimentation required to determine which 2'-methyl-up nucleosides meet claim 1 is very high - many thousands of candidate compounds
  – but, ... synthesis of an individual nucleoside was largely routine - weighs against a finding of non-enablement
  – specification fails to provide meaningful guidance as to which 2'-methyl-up nucleosides are or are not effective against HCV
  – only working examples provided are exceedingly narrow relative to the claim scope
  – the field of modifying nucleosides for anti-HCV activity was “in its infancy” and “unpredictable”
  – breadth of the claims weighs in favor of non-enablement
Drug Product: Repatha® (by Amgen)
- Cholesterol-lowering monoclonal antibody

U.S. Patents 8,829,165 and 8,859,741

Representative claim from ‘165 patent:
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 low density lipoprotein receptor (LDLR).

Amgen disclosed amino acid sequences of only 26 antibodies

Amgen sued Sanofi because Sanofi’s monoclonal antibody (Praluent®) fell within the scope of the above claim

U.S. Supreme Court held that both Amgen patents were invalid for lack of enablement
Amgen seeks to *monopolize an entire class of things defined by their function*—every antibody that both binds to particular areas of the sweet spot of PCSK9 and blocks PCSK9 from binding to LDL receptors.

If a patent claims an entire class of processes, machines, manufactures, or compositions of matter, the patent’s *specification must enable* a person skilled in the art to make and use the entire class.

The specification must enable the *full scope* of the invention as defined by its claims

- The more one claims, the more one must enable

That is not to say a specification always must describe with particularity how to make and use every single embodiment within a claimed class

- For instance, it may suffice to give an example (or a few examples) if the specification also discloses “*some general quality . . . running through*” the class that gives it “a peculiar fitness for the particular purpose.”
- In some cases, disclosing that general quality may reliably enable a person skilled in the art to make and use all of what is claimed, not merely a subset

Nor is a specification necessarily inadequate just because it leaves the skilled artist to engage in some measure of adaptation or testing

- Specification may call for a reasonable amount of experimentation to make and use a patented invention. What is reasonable in any case will depend on the nature of the invention and the underlying art.
Summary - *Amgen v. Sanofi*

- Did not apply *Wands* factors
  - *Wands* is still good law
- Discounted so-called “roadmap”
- Applies to all genus claims (not just antibodies)

- For USPTO employees to use, regardless of the technology, for ascertaining compliance with the enablement requirement in view of *Amgen v. Sanofi*, and to inform the public of the USPTO's practices
  - do not constitute substantive rulemaking and therefore do not have the force and effect of law; not grounds for appeal
- Are not intended to announce any major changes to USPTO practice or procedure and are incorporating guidance *Amgen* and post-*Amgen* decisions that are consistent with current USPTO policy
- Relies, in part, on *Amgen Inc. v. Sanofi, Aventisub LLC*, 987 F.3d 1080 (Fed. Cir. 2021)
- Discusses post-Amgen cases
  - *Baxalta, Medytox, and Starrett*
- Concludes that USPTO personnel will continue apply *Wands* factors to ascertain whether the amount of experimentation required to enable the full scope of the claimed invention is reasonable
Representative post-Amgen Cases (e.g., after May 18, 2023)

• Baxalta Inc. et al. v. Genentech Inc., 81 F.4th 1362 (Fed. Cir. 2023)
  – Decided: September 20, 2023

• Medytox, Inc. v. Galderma S.A., 71 F. 4th 990 (Fed. Cir. 2023)
  – Decided: June 27, 2023

• In re Starrett, 2023 WL 3881360 (Fed. Cir. 2023) (non-precedential)
  – Decided: June 8, 2023

• United Therapeutics Corp. v. Liquidia Techs., Inc., 74 F.4th 1360 (Fed. Cir. 2023)
  – Decided: July 24, 2023
Drug Product: Genentech’s Hemlibra® (emicizumab)
– Emicizumab is a humanized bispecific antibody that binds to Factor IXa with one arm and Factor X with the other arm, thereby mimicking the function of Factor VIIIa in the coagulation cascade
– Hemlibra® is prescribed to prevent or reduce the frequency of bleeding episodes

U.S. Patent No. 7,033,590

Representative Claim:
– An isolated antibody or antibody fragment thereof that binds Factor IX or Factor IXa and increases the procoagulant activity of Factor IXa.
– The ’590 patent discloses the amino acid sequences of eleven antibodies that bind to Factor IX/IXa and increase the procoagulant activity of Factor IXa.

Baxalta sued Genentech alleging Hemlibra® infringes the ’590 patent
DC: the ‘590 patent is invalid due to lack of enablement
CAFC:

- Facts are materially indistinguishable from those in *Amgen* - process for generating and testing antibodies *similar to roadmap of Amgen*;
- ‘590 patent contains *no* disclosures—such as “*a quality common to every functional embodiment*,” that would allow a skilled artisan to predict which antibodies will perform the claimed functions;
- The patent does not disclose any common structural (or other) feature delineating which antibodies will bind to Factor IX/IXa and increase procoagulant activity from those that will not;
- Nor does the patent describe why the eleven disclosed antibodies perform the claimed functions, or why the other screened antibodies do not;
- The only guidance the patent provides is “to create a wide range of candidate antibodies and then screen each to see which happen to bind” to Factor IX/IXa and increase procoagulant activity;
- *Amgen* makes clear that such an instruction, without more, is not enough to enable the broad functional genus claims at issue here.

CAFC affirmed invalidity due to lack of enablement

- Moore, Clevenger, and Chen

Holding: the ‘590 patent fails to teach skilled artisans how to make and use the full scope of claimed antibodies without unreasonable experimentation.
Drug Product: animal-protein-free botulinum toxin composition for treating cosmetic and non-cosmetic conditions, such as glabellar lines, lateral canthal lines, and chronic migraines

U.S. Patent No. 10,143,728

Representative substitute claim:

19. A method for treating glabellar lines in a patient in need thereof, comprising: locally administering a first treatment of a botulinum toxin composition comprising a serotype A botulinum toxin in an amount present in about 20 units of MT10109L...; locally administering a second treatment of the botulinum toxin composition at a time interval after the first treatment; wherein said time interval is the length of effect of the serotype A botulinum toxin composition as determined by physician’s live assessment at maximum frown; wherein said botulinum toxin composition has a greater length of effect compared to about 20 units of BOTOX®, ...; and wherein said greater length of effect is determined by physician’s live assessment at maximum frown and requires a responder rate at 16 weeks after the first treatment of 50% or greater.

Galderma filed a petition requesting post-grant review

Appeal from the PTAB finding of, *inter alia*, invalidity due to a lack of enablement
**Medytox, Inc. v. Galderma S.A., 71 F. 4th 990 (Fed. Cir. 2023)**

- **Specification:**
  - Includes results of two clinical trials, which compared animal-protein-free botulinum toxin composition with botulinum toxin stabilized with human serum albumin purportedly supporting longer lasting efficacy

- **PTAB:**
  - After evaluating the *Wands* factors, found that the full scope of the claims was not enabled, particularly because a skilled artisan would not have been able to achieve higher responder rates under the guidance provided in the specification without undue experimentation

- **CAFC: affirmed**
  - Dyk, Reyna, and Stark
  - caselaw may not require disclosure of every possible working example of responder rates, but here, there are at most three examples of responder rates above 50% at 16 weeks: 52%, 61%, and 62%
  - though a specification *need not* always “describe with particularity how to make and use *every single embodiment* within a claimed class,” it must nevertheless “enable the *full scope* of the invention as defined by its claims”
    - for example, *by “disclosing [a] general quality” of the class*
In re Starrett, 2023 WL 3881360 (Fed. Cir. 2023) (non-precedential)

- U.S. Patent Application No. 15/299,124
  - Directed to methods, systems, media, and machines for maintaining augmented telepathic data for telepathic communication as a gadget-free extension of human senses
- Representative claim:
  - A non-transitory computer readable medium containing data representing either of or both data structures and program instructions for generating, analyzing, extending, communicating, integrating, storing, converting, editing, encoding, or maintaining said data structures...
- Appeal from the PTAB finding of, inter alia, invalidity due to a lack of enablement
- PTAB: Affirmed
  - Lourie, Dyk, and Taranto
- PTAB treated claim 1 as a genus claim containing forty-seven “or” clauses, thereby allowing it to cover over 140 trillion embodiments
  - Here, much is claimed, and little is enabled
- Application's disclosure of a broad and abstract organizational structure used to accomplish the maintenance of augmented telepathic data amounts to little more than a “research assignment” requiring a skilled artisan to undertake undue experimentation to discover what types of devices are encompassed by the claim limitations and how they would function
Drug Products:

- Tyvaso®, an inhaled solution formulation of treprostinil approved for treating pulmonary hypertension (United)
- Yutrepia™, a dry powder inhalation formulation of Treprostinil (filed NDA under § 505(b)(2)) (Liquidia)

U.S. Patent No. 10,716,793 (United)

Representative claim:

A method of treating pulmonary hypertension comprising administering by inhalation to a human suffering from pulmonary hypertension a therapeutically effective single event dose of a formulation comprising treprostinil or a pharmaceutically acceptable salt thereof with an inhalation device, wherein the therapeutically effective single event dose comprises from 15 micrograms to 90 micrograms of treprostinil or a pharmaceutically acceptable salt thereof delivered in 1 to 3 breaths

Five subgroups of pulmonary hypertension

Groups 1, 3, 4, and 5 are caused by conditions affecting the pulmonary arteries or precapillary vessels of the lungs (“precapillary PH”)

Group 2 typically develops as a result of a cardiac-based etiology (“postcapillary PH”)

- Due to differing etiologies, each group may require group-specific treatment
• DC: asserted claims were *not* invalid for lack of enablement
  – construed “treating pulmonary hypertension” as encompassing all five groups of pulmonary hypertension
    • specification of the ’793 patent expressly includes all five groups when describing “pulmonary hypertension”
  – found that a skilled artisan would not need to engage in undue experimentation to practice the full scope of the claimed treatment of pulmonary hypertension
  – the claims were not invalid and were infringed
    • the court stayed approval of Liquidia’s NDA for Yutrepia until May 5, 2027, the expiration date of the ’793 patent
CAFC: Affirmed
   – Lourie, Dyk, and Stoll

Did not cite *Amgen v. Sanofi* or apply *Wands* factors
   – Specification
     • provides details on administration, concentrations, and dosages of inhaled treprostinil for treating patients with pulmonary hypertension
     • describes an open label study upon acute safety, tolerability, and hemodynamic effects of inhaled treprostinil delivered over the course of a few seconds.
   – Record demonstrates that the claimed administration of treprostinil vasodilates the pulmonary vasculature and reduces pulmonary blood pressure even in Group 2 PH patients
   – The court properly relied on expert testimony and record evidence to conclude that a skilled artisan would understand that the claimed administration of treprostinil would vasodilate the pulmonary vasculature, improve hemodynamics, and in this way for a single dose, treat a patient’s elevated pulmonary blood pressure *independent of the type of pulmonary hypertension patient*
• *Wands* factors are still probative
  – Examining corps (in my experience) consistently apply the *Wands* factors
  – Courts appear to be inconsistent in doing so

• The USPTO views the guidelines as not intended to announce any major changes to USPTO practice or procedure
  – incorporating guidance from *Amgen* and post-*Amgen* decisions

• Will courts (and examining corps) apply rationale from *Amgen* to genus claims in chemical applications?
  – and, if so, will that impact examination and adjudication of chemical patent claims?
• Claims in the chemical arts can be distinguished from Amgen in that they typically provide structure and do not rely on function.

• But what about claims reciting both structure and function?
  – Look to Wyeth, Enzo, and Idenix for guidance.

• Broad chemical genus claims
  – Does Amgen narrow scope of claims or is scope the same as under Wands?

• Method of use claims
  – entire class of compounds for treating a specific disease
    • e.g., inhibitor of X for treating Y
  – generically claimed compounds for treating an entire class of disease(s) with a common mechanism of action
    • Compound of formula (X) for treating X, Y, and Z