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Agilent Technologies Inc. v. Synthego Corp. (Fed. Cir. 2025)

An argument could be made that one of the most significant Supreme Court decisions in U.S. patent law over the last thirty years was *Dickinson v. Zurko*[1]. In that case, the Court held that the Federal Circuit was bound by the provisions[2] of the Administrative Procedures Act to defer to factual determinations made by administrative agencies within the area of their expertise. (It should be understood that the Supreme Court's more recent decision in *Loper Bright Enterprises v. Raimondo*[3] did not disturb this statutory standard, being limited to agency interpretations of the laws under which they were established or administered.) The effects of this interpretation of the laws governing judicial review can be observed (as it has been applied) in the Federal Circuit's subsequent opinions, particularly ones regarding Patent Trial and Appeal Board decisions and especially as applied in *inter partes* review (IPR). The most recent application of this standard can be found in *Agilent Technologies Inc. v. Synthego Corp*.

Synthego challenged two Agilent patents in its IPRs: U.S. Patent Nos. 10,337,001 and 10,900,034. These patents were directed to CRISPR-Cas9[4] systems for gene editing. Claims 1 for each patent are set forth in the opinion:

> The '001 patent:
>
> A synthetic CRISPR guide RNA having at least one 5′-end and at least one 3′-end, the synthetic guide RNA comprising:

(a) one or more modified nucleotides within five nucleotides from said 5′-end, or
(b) one or more modified nucleotides within five nucleotides from said 3′-end, or
(c) both (a) and (b);

> wherein said guide RNA comprises one or more RNA molecules, and has *gRNA functionality comprising associating with a Cas protein and targeting the gRNA:Cas protein complex to a target polynucleotide*, wherein the modified nucleotide has a modification to a phosphodiester linkage, a sugar, or both.
>
> (*emphasis* added).
>
> The '034 patent:
>
> A synthetic CRISPR guide RNA comprising:

(a) a crRNA segment comprising (i) a guide sequence capable of hybridizing to a target sequence in a polynucleotide, (ii) a stem sequence; and
(b) a tracrRNA segment comprising a nucleotide sequence that is partially or completely complementary to the stem sequence,

> wherein the synthetic guide RNA has *gRNA functionality comprising associating with a Cas protein and targeting the gRNA:Cas protein complex to the target sequence*, and comprises one or more modifications in the guide sequence, wherein the one or more modifications comprises a 2′-O-methyl.
>
> (*emphasis* added).

The opinion characterizes "[t]he key prior art" supporting Synthego's challenge on anticipation grounds to be an International Application, Publication No. WO 2015/026885, filed on August 20, 2014, by Pioneer Hi-Bred International. This application disclosed "compositions and methods" for performing CRISPR featuring "guide polynucleotide[s]["gRNA"]" in both single- and dual-molecule forms; specific disclosure included Example 4, for "modifying the nucleotide base, phosphodiester bond linkage or molecular topography of the guiding nucleic acid component(s) of the guide polynucleotide/Cas endonuclease system . . . for increasing cleavage activity and specificity." Also disclosed were modified RNA molecules comprising "nucleotide and/or phosphodiester bond modifications [that] may be introduced to reduce unwanted degradation." With regard to Synthego's contentions of invalidity for obviousness, two additional references were asserted: a first scientific publication by Threlfall *et al*.[5] and a second scientific publication by Deleavey *et al*.[6] The Threlfall reference discloses specific nucleotide modifications using PACE (phosphonoacetate)- or thioPACE (phosphonothioacetate)-modified phosphate groups, and the Deleavey reference discloses "a vast array" of nucleotide modifications to stabilize oligonucleotides (including RNA oligonucleotides).

The PTAB found all claims in each patent to be unpatentable.[7] The Board found that the Pioneer Hi-Bred reference disclosed a functional gRNA and was enabling, and that those claims that were not anticipated were obvious. This appeal followed.

The Federal Circuit affirmed, in a decision by Judge Prost, joined by Judges Linn and Reyna. In referencing the "substantial evidence" standard for the Board's factual determinations (which included anticipation, citing *St. Jude Med., LLC v. Snyders Heart Valve LLC*[8]), the opinion relies on *In re Bayer Aktiengesellschaft*[9] for the principle that "[w]here two different conclusions may be warranted based on the evidence of record, the Board's decision to favor one conclusion over the other is the type of decision *that must be sustained by this court as supported by substantial evidence*" (*emphasis* added).

Agilent propounded three arguments in its appeal: first, that the Board's anticipation determination was not supported by substantial evidence; second, that the Pioneer Hi-Bred application was not enabling; and third, that the skilled worker would not have had a reasonable expectation of success (with regard to the Board's obviousness determinations) that the PACE and thioPACE modifications would have been successfully used to modify gRNA in a CRISPR-Cas9 system. Regarding Agilent's first argument, the panel determined that the Board's anticipation decision was supported by substantial evidence. The opinion enumerates the facts the Board relied upon concerning the Pioneer Hi-Bred disclosure:

> "Pioneer Hi-Bred discloses that the guide polynucleotides described therein can: (1) form a complex with a Cas endonuclease; and (2) enable the endonuclease to recognize a DNA target site. That disclosure reads on both the associating and targeting aspects of the 'gRNA functionality' recited" in the challenged claims.

Examples 4 and 5 of the Pioneer Hi-Bred disclosure were specifically called out in the opinion for referring to "modified guide nucleotides," which the Board interpreted as "indicating that those sequences have [the claimed gRNA] functionality," supported by several additional statements in the Pioneer Hi-Bred disclosure. The Board had rejected (and the Federal Circuit affirmed as being supported by substantial evidence) Agilent's argument that the purported lack of cleavage activity using such modified gRNA nucleotides "demonstrate[d] that Pioneer Hi-Bred does not disclose gRNA functionality," the rejection of this argument being based in part on admissions by Agilent's expert that "just because a gRNA in Table 4 [in Pioneer Hi-Bred] lacks cleavage activity does not demonstrate that it also lacks the ability to bind a Cas protein and target that complex to target polynucleotide." Taken in its totality, the panel held that the Board's decision that the Pioneer Hi-Bred application anticipated certain of the claims of the '001 and '034 patents was supported by substantial evidence.

The opinion then turns to Agilent's argument that the disclosure of the Pioneer Hi-Bred application was not enabling, where the panel "[saw] no error" in the Board's conclusion that the reference *was* enabling. One basis for the Court's decision in this regard was recognition that for assertion as an anticipating reference only an enabling disclosure, not evidence of actual reduction to practice is required, under *inter alia*, *Schering Corp. v. Geneva Pharms.*[10], *Rasmusson v. SmithKline Beecham Corp.*[11], and *In re Morsa*[12] (cited in the opinion). Moreover "[p]rior art disclosures are presumed enabling" under *Impax Labs., Inc. v. Aventis Pharms., Inc.*[13] according to the Court. The panel appreciated that the Board performed its enablement assessment under the conventional rubrics set forth in *In re Wands*[14] and that the Pioneer Hi-Bred disclosure passed muster under those standards (while recognizing that certain disclosures, including Examples 4 and 5 were prophetic). Regarding the relative novelty of CRISPR-Cas9 systems when the Pioneer Hi-Bred application was filed the Board stated that

> [W]hile the art was somewhat unpredictable in December 2014, it was far from a blank slate with a [person of ordinary skill in the art] understanding how the different elements of a CRISPR/Cas system are used and function together, including the role of gRNA; the types of chemical modifications that had been successfully used in other systems to reduce RNA degradation, while preserving functionality; and standard techniques for making gRNAs with the modifications disclosed and exemplified in Pioneer Hi-Bred.

The Federal Circuit in affirming the Board's holding that the Pioneer Hi-Bred disclosure was enabling, rejected Agilent's argument that the factual circumstances in the Court's *Impax* decision were analogous. There, the issue was enablement of a disclosure of "hundreds or thousands of compounds and several diseases," as well as "broad and general" dosage guidelines "without sufficient direction or guidance to prescribe a treatment regimen. Here, on the other hand, "Pioneer Hi-Bred exemplifies particular crRNA sequences having the recited chemical modifications at the recited locations and teaches that gRNA comprising such may be used as guide polynucleotides in a CRISPR Cas system." In addition the Board had supported its enablement holding because "the particular types of chemical modifications disclosed in Pioneer Hi-Bred and recited in the challenged claims had been known and used for decades to stabilize RNA against unwanted degradation in other systems." Also unavailing was Agilent's reliance on the Supreme Court's *Amgen Inc. v. Sanofi*[15] decision, the opinion noting distinctions "in two meaningful ways." First, the Court's *Amgen* decision involved "whether the asserted claims were sufficiently enabling to be valid under 35 U.S.C. § 112, not whether a prior-art reference was enabling and could thus support anticipation" which are "two separate inquiries," citing *Novo Nordisk Pharms., Inc. v. Bio-Tech. Gen. Corp.*[16] According to the panel, enablement under Section 112 requires a disclosure to enable the skilled worker to be able to use the claimed invention, whereas for Section 102 purposes, no such disclosure of utility is required. Second, the Board found that the Pioneer Hi-Bred disclosure would have been understood by the person of ordinary skill in the art with regard to "how the different elements of a CRISPR/Cas system are used and function together, including the role of gRNA; the types of chemical modifications that had been

successfully used in other systems to reduce RNA degradation, while preserving functionality; and standard techniques for making gRNAs with the modifications disclosed and exemplified in Pioneer Hi-Bred" and that this disclosure was enabling. In addition the Federal Circuit rejected Agilent's argument regarding Pioneer Hi-Bred's purported disclosure of "many inoperable guide [RNAs]" because the data Agilent relied upon for this argument related to synthetic DNA sequences not modified RNA recited in the challenged claims. The last specific Agilent argument rejected by the Board and affirmed by the panel was that the Pioneer Hi-Bred disclosure did not enable a "single guide RNA" (sgRNA), which according to the opinion, was expressly disclosed in the reference.

Finally, the opinion assessed and rejected Agilent's arguments that the Board erred in finding certain other claims[17] in each patent to be invalid for obviousness. The grounds for these arguments were that the Pioneer Hi-Bred disclosure "did not expressly disclose the functionality of the claimed PACE- or thioPACE-modified guides" and that the Board did not explain its findings concerning whether there had been a reasonable expectation of success by the skilled worker. Regarding the former argument, the opinion states that Agilent conflated the requirements for anticipation with those for obviousness, wherein the lack of PACE- or thioPACE-modified guides disclosure in the Pioneer Hi-Bred reference was remedied by combination with the Threlfall and Deleavey disclosures, as supported by expert testimony adduced by Synthego. Regarding Agilent's latter argument, the panel considered as "thorough" the Board's analysis that the person of ordinary skill would have reasonably expected success from the combination of the Pioneer Hi-Bred reference with either the Threlfall or Deleavey disclosures. The opinion sets forth the Board's reasoning to illustrate its decision to affirm:

> [B]y December 2014, several studies had shown that the CRISPR/Cas system could successfully tolerate modifications. While these studies describe different types of modifications than those in the challenged claims, such evidence nevertheless supports Dr. Furneaux's testimony that a [person of ordinary skill in the art] would have expected that chemical modifications could be made at the 5[′] and 3[′]-ends of a gRNA while preserving the Cas enzyme's gene editing function.
>
> The record further demonstrates that shortly after the discovery of the CRISPR/Cas system for gene editing and prior to December 2014, there were already a number of researchers in addition to the authors of the Pioneer Hi-Bred publication suggesting the use of the claimed chemical modifications to improve the resistance of gRNA to degradation. [Agilent's] expert, Dr. Marshall, conceded as much on cross-examination. The fact that multiple groups of researchers independently suggested the same types of gRNA modifications re cited in the challenged claims evidences that a [person of ordinary skill in the art] would have had a reasonable expectation those modifications could be successfully employed in a CRISPR/Cas system. Moreover, while [Synthego] points to multiple references suggesting such modifications to gRNA, neither [Agilent] nor Dr. Marshall identify any reference expressing doubt that such modifications could be successfully implemented in a CRISPR/Cas system. This contrast undermines [Agilent's] argument that a [person of ordinary skill in the art] would not have reasonably expected the prior art modifications to work in a CRISPR/Cas system.

This record was sufficient for the Federal Circuit to affirm the Board's decision as being supported by substantial evidence. This outcome is unsurprising in view of the panel's compliance with *Zurko* in making its decision, although it provides something of a cautionary tale for Patent Owners when facing invalidity challenges before the PTAB that might have a more difficult time satisfying the standards applied in district court litigation.

Footnotes

1 Dickinson v. Zurko, 527 U.S. 150 (1999).

2 5 U. S. C. § 706

3 Loper Bright Enterprises v. Raimondo, 603 U.S. 369 (2024).

4 The opinion in a footnote informs that “CRISPR” stands for “clusters of regularly interspaced short palindromic repeats.”

5 Threlfall et al., Synthesis and Biological Activity of Phosphonoacetate- and Thiophosphonoacetate-modified 2′-O-methyl Oligoribonucleotides, 10 Org. Biomol. Chem., 746–54 (2011)

6 Deleavey et al. Designing Chemically Modified Oligonucleotides for Targeted Gene Silencing, 19 Chem. & Bio. Review, 937–54 (2012).

7 Claims 1–7, 9–10, 12–15, 17–18, 20–25, and 27–30 of the ’001 patent and claims 1–5, 8–21, and 24–33 of the ’034 patent were anticipated, and claims 8, 11, 16, 19, and 26 of the ’001 patent and claims 6–7 and 22–23 of the ’034 patent were obvious over the cited references.

8 St. Jude Med., LLC v. Snyders Heart Valve LLC, 977 F.3d 1232, 1238 (Fed. Cir. 2020).

9 In re Bayer Aktiengesellschaft, 488 F.3d 960, 970 (Fed. Cir. 2007).

10 Schering Corp. v. Geneva Pharms, 339 F.3d 1373, 1380 (Fed. Cir. 2003).

11 Rasmusson v. SmithKline Beecham Corp., 413 F.3d 1318,1326 (Fed. Cir. 2005).

12 In re Morsa, 803 F.3d 1374, 1376 (Fed. Cir. 2015).

13 Impax Labs., Inc. v. Aventis Pharms., Inc., 545 F.3d 1312, 1316 (Fed. Cir. 2008).

14 In re Wands, 858 F.2d 731 (Fed. Cir. 1988).

15 Amgen Inc. v. Sanofi, 598 U.S. 594 (2023).

16 Novo Nordisk Pharms., Inc. v. Bio-Tech. Gen. Corp., 424 F.3d 1347, 1355 (Fed. Cir. 2005).

17 Specifically, claims 8, 11, 16, 19, and 26 of the ’001 patent and claims 6–7 and 22–23 of the ’034 patent.