No. _____

In the Supreme Court of the United States

GEVO, INC.,

Petitioner,

v.

BUTAMAX ADVANCED BIOFUELS LLC,

Respondent.

On Petition for Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

PETITION FOR A WRIT OF CERTIORARI

JAMES P. BROGAN
COOLEY LLP
380 Interlocken Crescent
Suite 900
Broomfield, CO 80021-8023
720-566-4000

MICHELLE S. RHYU
Counsel of Record
BENJAMIN G. DAMSTEDT
LORI R. MASON
KATHRYN D. DUVALL
COOLEY LLP
Five Palo Alto Square
3000 El Camino Real
Palo Alto, CA 94306
650-843-5000
mrhyu@cooley.com

Counsel for Petitioner Gevo, Inc.

April 22, 2014

Becker Gallagher · Cincinnati, OH · Washington, D.C. · 800.890.5001

QUESTION PRESENTED

Rule 52(a) of the Federal Rules of Civil Procedure provides that in matters tried to a district court, the court's "[f]indings of fact . . . must not be set aside unless clearly erroneous."

The question presented is as follows:

Whether a district court's factual finding in support of its construction of a patent claim term may be reviewed *de novo*, as the Federal Circuit requires (and as the panel explicitly did in this case), or only for clear error, as Rule 52(a) requires.

PARTIES TO THE PROCEEDING

Petitioner is Gevo, Inc., who was defendant-appellee below.

Respondent is Butamax Advanced Biofuels LLC, who was plaintiff-appellant below.

RULE 29.6 STATEMENT

Gevo, Inc. has no parent company. No publicly traded company owns 10% or more of Gevo, Inc.

TABLE OF CONTENTS

TABLE OF AUTHORITIES

CASES

STATUTE AND RULES

OPINIONS BELOW

The decision of the court of appeals (Pet. App. 1-33) is reported at 2014 WL 593486. The district court's claim construction decision (Pet. App. 36-102) is reported at 931 F. Supp. 2d 589.

JURISDICTION

The judgment of the court of appeals was entered on February 18, 2014. (Pet. App. 32-33.) The jurisdiction of this Court is invoked under 28 U.S.C. § 1254(1).

STATUTORY PROVISION INVOLVED

Rule 52 of the Federal Rules of Civil Procedure provides in pertinent part:

> **Findings and conclusions by the court; judgment on partial findings**
>
> (a) Findings and Conclusions.
>
> (1) *In General*. In an action tried on the facts without a jury or with an advisory jury, the court must find the facts specially and state its conclusions of law separately. The findings and conclusions may be stated on the record after the close of the evidence or may appear in an opinion or memorandum of decision filed by the court. Judgment must be entered under Rule 58
>
> ****
>
> (6) *Setting Aside the Findings*. Findings of fact, whether based on oral or other evidence, must not be set aside unless clearly erroneous, and the reviewing court must give due regard to the

trial court's opportunity to judge the witnesses' credibility.

INTRODUCTION

This Court recently granted the petition for writ of certiorari filed by *Teva Pharmaceuticals USA, Inc.* raising the same question presented as the Federal Circuit's decision in this case. (Supreme Court Case Docket No. 13-854, hereinafter "*Teva*"). By this petition, Gevo also seeks review of the Federal Circuit's practice of reviewing claim construction determinations *de novo*, without paying any deference to the factual findings of the district court, contrary to the "clearly erroneous" standard for review required by Rule 52(a)(6) of the Federal Rules of Civil Procedure.

This case presents an equally if not more appropriate vehicle for this Court's review of the question presented than the *Teva* case. In this case the district court conducted a painstaking claim construction, carefully reviewing voluminous evidence and testimony presented by the parties, including detailed expert declarations, and held multiple days of hearings. The district court construed the relevant claim twice, once after extensive evidentiary hearings on a preliminary injunction motion, which turned on claim construction issues, and again after remand from the Federal Circuit affirming denial of a preliminary injunction. The preliminary injunction hearing lasted two days, and the district court considered 13 depositions, 10 witness declarations, and hundreds of exhibits, as well as multiple rounds of briefing on claim construction. On remand, the district court again entertained extensive documentary and testimonial evidence, as well as lengthy arguments by counsel on

claim construction. By the time of the *Markman* hearing the parties had produced over 1.6 million pages of documents, taken more than 50 depositions, and submitted 26 expert reports. After concluding these proceedings, the district court made factual findings about historical, art-specific meanings and understandings of those skilled in the art. The Federal Circuit gave no deference to those findings when it reviewed the district court's construction *de novo*, and issued a new construction that changed the outcome of the case.

Gevo respectfully requests that this Court grant its petition for writ of certiorari, consider this case alongside the *Teva* case, and reverse the judgment of the Court of Appeals. Alternatively, Gevo requests that this Court hold the petition pending review in the *Teva* case and then grant the petition, vacate the Court of Appeals' judgment, and remand to the district court for further proceedings.

STATEMENT OF THE CASE

A. The Federal Circuit Reviews Factual Findings *De Novo* When They Are Made During Claim Construction

Beginning in 1995, the *en banc* Federal Circuit has held that factual findings made in support of a claim construction are reviewed *de novo* rather than for clear error. *Markman v. Westview Instruments, Inc.* (*"Markman I"*), 52 F.3d 967, 976-77, 979 (Fed. Cir. 1995) (en banc). The Federal Circuit rested its opinion on decisions of this Court regarding patent law that pre-date the Federal Rules of Civil Procedure.

The Federal Circuit read those cases as holding "that the construction of a patent claim is a matter of law exclusively for the court." *Id.* at 977. The Federal Circuit concluded that because "claim construction is a matter of law," factual findings underlying claim construction must be "reviewed *de novo* on appeal." *Id.* at 979. Three judges of the Federal Circuit wrote separately and would have held that factual findings made in connection with claim construction should be reviewed for clear error under Rule 52(a) of the Federal Rules of Civil Procedure. *Id.* at 989-98 (Mayer, J., concurring in the judgment); *id.* at 998-99 (Rader, J., concurring in the judgment); *id.* at 999-1026 (Newman, J., dissenting).

Although this Court reviewed the Federal Circuit's decision in *Markman I*, it did not address the standard of review for factual findings by a district court. The issue this Court addressed was whether the Seventh Amendment entitles the parties to a trial by jury on factual issues underlying claim construction. *Markman v. Westview Instruments, Inc.* (No. 95-26). The Court held that the Seventh Amendment does not require a jury trial of factual findings in this context. *Markman v. Westview Instruments, Inc.* ("*Markman II*"), 517 U.S. 370 (1996). The Court did not address the standard for reviewing a district court's findings of historical fact on appeal, but rather held that trial judges are better suited than juries to resolve evidentiary issues arising in the context of claim construction. *Id.* at 378, 390.

Four years later, the en banc Federal Circuit once again held that it was bound to review "any allegedly fact-based questions relating to claim construction" *de*

novo. Cybor Corp. v. FAS Techs., Inc., 138 F.3d 1448, 1456 (Fed. Cir. 1998) (en banc). The Federal Circuit held that this Court's decision in *Markman II* that claim construction is a purely legal question compelled the conclusion that *de novo* is the appropriate standard of review, even though the decision did not expressly address the issue. *Id.* at 1455-56. The Federal Circuit also found its own decision in *Markman I* was binding on the standard of review. *Id.* at 1456. Judges Rader, Newman, and Mayer concurred in the judgment, but wrote separately to dissent from the courts' pronouncements on claim interpretation. *Id*. at 1463-81.

The Federal Circuit granted en banc review again in *Phillips v. AWH Corp.,* 415 F.3d 1303 (Fed. Cir. 2005) (en banc), but ultimately elected not to reach the issue, leaving *Markman I* and *Cybor* "undisturbed." *Id.* at 1328. Judges Mayer and Newman dissented. *Id.* at 1330-35.

Most recently, the Federal Circuit again took up the standard of review en banc in *Lighting Ballast Control LLC v. Philips Electronics North America Corp.*, No. 2012-1014, 2014 WL 667499 (Fed. Cir. Feb. 21, 2014). As with each previous decision, the Federal Circuit divided on this issue, but ultimately continued to embrace the *de novo* standard. *Id*. at *16. Judges Rader, O'Malley, Reyna, and Wallach joined in dissent, advocating for applying the "clearly erroneous" standard of review for factual determinations, as required by Federal Rule of Civil Procedure 52(a)(6). *Id.* at *40.

Thus, all four en banc decisions on the appellate standard of review have resulted in the Federal Circuit

continuing to review *de novo* even quintessentially factual rulings.

B. In This Case, The Federal Circuit Disregarded the District Court's Factual Findings and Re-construed the Patent to Reach a Different Claim Construction That Contradicts Those Findings

Gevo is a leading renewable chemicals and advanced biofuels company located in Englewood, Colorado. Gevo's research has resulted in numerous innovations, including dramatic improvements to the yeast that transform sugar into isobutanol and processing innovations that efficiently separate isobutanol. These innovations enable the low-cost conversion of existing ethanol plants to make isobutanol. Gevo became a public company in 2011 and was the first company to open an industrial scale facility for producing isobutanol in microorganisms.

Respondent Butamax was formed in 2009 as a joint venture between DuPont and BP Biofuels North America LLC. (Pet. App. 8.) Butamax is the owner of United States Patent No. 7,851,188 B2 ("the '188 patent") entitled "Fermentive Production of Four Carbon Alcohols", which issued on December 14, 2010. (Pet. App. 41.) Butamax is also the owner of U.S. Patent No. 7,993,889 ("the '889 patent"), which shares the identical disclosure and title of the '188 patent, and issued on August 9, 2011. (*Id.*) Butamax filed suit against Gevo in 2011, asserting infringement of these two patents (the "patents-in-suit"). (Pet. App. 37.)

1. The Patents' Claims Relate to Production of Isobutanol in a Recombinant Organism Through a Five-Step Pathway Catalyzed By Known Enzymes

The patents-in-suit cover recombinant microorganisms that use a particular biosynthetic pathway to produce isobutanol, which is useful as a fuel or fuel additive. The primary pathway for producing isobutanol was well known long before the mid-2000s. Microorganisms naturally consume sugars and produce alcohols, including drinking alcohol and "fusel alcohols" like isobutanol. Microorganisms transform sugars into alcohols through a series of chemical reactions called a "pathway." The ingredients for the pathway steps are called "substrates."

The claimed biosynthetic pathway of the patents-in-suit comprises essentially five steps. Each step involves converting a substrate into a new product, with each conversion being catalyzed by a particular enzyme. The key reaction for this appeal is the second step of the five-step biosynthetic pathway to produce isobutanol, which converts acetolactate ("AL") to 2,3-dihydroxy-isovalerate ("DHIV"). In each of the patents-in-suit, an enzyme called "acetohydroxy acid isomeroreductase" ("AAIR") is claimed as the enzyme that catalyzes this step.[1] *Isomeroreductase* includes a reduction step, which means adding an electron to the substrate. Reduction requires a "cofactor" or "coenzyme" that donates an electron to the reaction.

---

[1] AAIR enzymes are a subset of enzymes in a broader category of "ketol-acid reductoisomerase" ("KARI") enzymes.

Two molecules called NADPH and NADH are fundamental molecules used by all life to transfer electrons, and thus can act as the necessary "cofactor" or "coenzyme" in these reactions.

The key question below was the meaning of "acetohydroxy acid isomeroreductase," as used in claim 1 of each of the patents-in-suit, and whether its definition is limited by the cofactor used with the AAIR enzyme.[2] The district court considered this question multiple times and on an extensive record, both in connection with a motion for preliminary injunction and again later during full *Markman* claim construction proceedings.

Ultimately the district court construed "acetohydroxy acid isomeroreductase (known by E.C. number 1.1.1.86)" to mean "an enzyme known by the EC number 1.1.1.86 that catalyzes the conversion of [AL] to [DHIV] and is NADPH-dependent." (Pet. App. 60.)

---

[2] Butamax and the lower courts imprecisely use the term "KARI" interchangeably with the claim term "AAIR." The inexact substitution is consequential here, as Gevo asserted counterclaims in this lawsuit, asserting its own patents in which a key claim term is "KARI." The Federal Circuit improperly relied on Gevo's construction of that term (which had express support in its own patents) to support a broader construction of the "AAIR" term in the patents-in-suit. (Pet. App. 13-14 (citing JA10240, Proposed Claim Construction for Gevo's 8,017,375 and 8,017,376 patents).)

2. The District Court Construed the AAIR Term as NADPH-Dependent After Extensive Briefing and Evidentiary Hearings in Connection With Preliminary Injunction Proceedings

After filing suit, Butamax moved for a preliminary injunction based on claims 1, 13, and 14 of the '889 patent. The district court granted both parties the opportunity to take extensive discovery. The record considered by the district court for Butamax's preliminary injunction motion included 13 depositions, 10 witness declarations, and hundreds of exhibits. The parties also submitted a full round of briefing before a two-day evidentiary hearing, where the district court heard live and video-recorded testimony. Following the hearing, the parties submitted another round of briefing. At the heart of the preliminary injunction discovery and hearings was the meaning of the AAIR term.

In a detailed opinion, the district court denied Butamax's motion, "conclud[ing] that plaintiff does not hold a valid patent, nor would the defendant infringe if it did." *Butamax Advanced Biofuels LLC v. Gevo, Inc.*, 868 F. Supp. 2d 359, 375 (D. Del. 2012). The district court construed the term "acetohydroxy acid isomeroreductase" to refer to "an enzyme that is solely NADPH dependent (as opposed to NADH-dependent or NADH and NADPH-dependent)." *Id*. at 367. Because Gevo's KARI enzymes are NADH-dependent, the district court found that Butamax had not shown a likelihood of success on infringement. *Id*. at 368. The district court also held that Gevo had raised a substantial question that several references anticipated

the asserted claims and that claim 13 was invalid for lack of written description. *Id*. at 372-74.

Following the district court's denial of the preliminary injunction, Butamax appealed to the Federal Circuit. The panel affirmed, concluding that Gevo had raised a substantial question as to invalidity. *Butamax™ Advanced Biofuels LLC v. Gevo, Inc.*, 486 F. App'x 883 (Fed. Cir. 2012).

The panel noted in its opinion that the "trial court should reconsider its construction when it holds a *Markman* hearing," without further instruction. *Id*. Questioning at the hearing suggested that one panelist objected to the use of the term "solely," which could be misinterpreted to require the enzyme to use the NADPH cofactor exclusively. (Pet. App. 117-18.) As Gevo's counsel noted at the hearing, "solely" was not necessary to Gevo's construction, and was intended only to describe dependency. (Pet. App. 121.) The district court did not include "solely" in its subsequent construction, but did maintain the "NADPH-dependent" requirement.

3. After Carefully Considering the Entire Record, Including Expert Testimony Regarding the Understanding of a Person of Ordinary Skill in the Art, the District Court Again Construed the AAIR Term as NADPH-Dependent

The parties continued to engage in fact and expert discovery both during the appeal and on remand to the district court. The parties produced over 1.6 million pages of documents, took more than 50 depositions, and submitted 26 expert reports. The parties briefed claim

construction again and submitted summary judgment cross-motions on noninfringement and invalidity. The court held an extensive hearing on claim construction and the summary judgment motions.

Ultimately, after considering anew the parties' claim construction positions, the district court construed the AAIR term as "an enzyme known by the EC number 1.1.1.86 that catalyzes the conversion of acetolactate to 2,3–dihydroxyisovalerate and is NADPH-dependent." (Pet. App. 60.) In reaching this construction the district court began its analysis by recognizing that the patents expressly defined "AAIR" in the specification as an enzyme "using NADPH." (Pet. App. 45-46.) The crux of the dispute centered on two factual issues — the understanding of a person of ordinary skill in the art at the time of the invention regarding the AAIR term known by E.C. number 1.1.1.86, as well as the meaning of "using NADPH" as specifically recited in the patent's definition of AAIR.

To answer these questions the district court examined the patents' definitions, which distinguish enzymes by their use of NADPH and NADH (Pet. App. 51-52), and the prosecution history, which shows that the patentees amended their claims to recite specific enzymes to overcome repeated rejections, including by limiting the claimed enzymes as defined by EC number. (Pet. App. 49-51.)

The district court determined, as a matter of fact, that the Enzyme Commission ("EC") numbering system classifies enzymes by the reactions they catalyze. (Pet. App. 53.) The district court also determined that for enzymes that use nicotinamide cofactors, the EC Rules require specifying the cofactor and providing separate

EC numbers for naturally occurring enzymes with different cofactor preferences: "For oxidoreductases using NAD+ or NADP+, the coenzyme should always be named [as the acceptor] . . . . Where the enzyme can use either coenzyme, this should be indicated by writing NAD(P)+." (Pet. App. 53-54.)

The district court also carefully considered the extrinsic evidence, performing an exhaustive analysis of the documentary and expert testimony presented by the parties on the meaning and scope of the AAIR term and its express definition. The court reviewed the EC Rule 18 relating to the convention for citing cofactor usage, the entry for the EC number cited by the patent, EC 1.1.1.86, all of the references cited in that entry, and all the databases linked within the EC entry, including the BRENDA database. (Pet. App. 54-57.) The vast majority of these references described AAIR as NADPH-dependent.

The district court then reviewed all the references in the BRENDA database: "In the 43 pages of information contained on the BRENDA database for EC 1.1.1.86, NADH is mentioned in only 16 entries, all of which refer to one or more of only five literature references." (Pet. App. 56.) The court found that four of the five references expressly characterized the studied enzymes as NADPH-dependent. (Pet. App. 56-57.)

In addition to its comprehensive review of the many references confirming that all AAIR were known to be NADPH-dependent, the court also specifically analyzed the only two pieces of extrinsic evidence cited by Butamax in support of its contention that non-NADPH-dependent AAIRs were known (Rane and Xing) but

found, as a matter of fact, that they did not support Butamax's construction:

> [T]he scientific references almost exclusively characterize KARI enzymes as NADPH-dependent. Of the two references relied on by Butamax to support the use of NADH by KARI enzymes, one (Xing) included a single conclusory sentence with no data or other literature references to support it, and the other (Rane) described having to construct a "quadruple mutant" in order to change a KARI enzyme from being NADPH-dependent to NADH-dependent.

(Pet. App. 58-59.) The court further held that, "even if (or especially if) it was well known in the art that KARI enzymes could 'use' either NADH or NADPH or both, the patentees knew how to describe that and chose not to." (Pet. App. 59 n.15.)

After conducting this comprehensive analysis of the intrinsic and extrinsic evidence, the court found that the evidence strongly favored Gevo's proposed construction. In doing so the court expressly found "the expert opinions proffered by Gevo (and, therefore, Gevo's proposed construction) to be more consistent with the intrinsic record." (Pet. App. 58.) In particular the court credited the testimony of Gevo's expert, Dr. Jack Kirsch, in resolving several factual disputes, finding that "[a]s of October 26, 2005, all natural KARI enzymes were known to be NADPH-dependent" and that "a person of ordinary skill in the art would understand that an enzyme that 'uses NADPH' or that 'uses NADH' is 'NADPH-dependent' or 'NADH-dependent', respectively." (Pet. App. 53 (citing and quoting the Declaration of Jack Kirsch, Ph.D).)

Notably, the district court had received recorded deposition testimony of Dr. Kirsch on this topic during the preliminary injunction hearing.

In sum, following the resolution of several core factual disputes, the district court properly concluded that "a person of ordinary skill in the art would understand 'acetohydroxy acid isomeroreductase' to be 'an enzyme known by the EC number 1.1.1.86 that catalyzes the conversion of acetolactate to 2,3-dihydroxyisovalerate and is NADPH-dependent.'" (Pet. App. 60.)

During the pretrial conference, conducted the day after the claim construction and summary judgment opinion, Butamax conceded that it could not prove literal infringement under the district court's construction. Shortly thereafter, the parties stipulated that the accused Gevo microorganisms do not literally infringe. The district court issued a final judgment (Pet. App. 34-35), and Butamax filed its notice of appeal.

4. The Federal Circuit Reviewed the District Court Construction of the KARI Term *De Novo* and Found That It Was Not NADPH-Dependent

The Federal Circuit reversed the district court's claim construction, rejecting the district court's explicit finding that a person of ordinary skill would have understood that the AAIR enzyme was NADPH-dependent. Gevo argued that the Federal Circuit should review the district court's factual findings for clear error. (Appellee's Resp. Br. Non-Confidential, D.I. 42 at 30-31.) Instead, reviewing the record *de novo*

and without deference to the district court's factual findings, the panel concluded that the appropriate construction of the disputed AAIR term was "an enzyme, whether naturally occurring or otherwise, known by the EC number 1.1.1.86 that catalyzes the conversion of [AL] to [DHIV]." (Pet. App. 24.)

In reaching this conclusion, the panel began by holding that the plain meaning of AAIR was not limited by co-factor usage. In direct contradiction of the district court's factual findings, the panel stated "there is nothing in the record to indicate that persons of ordinary skill in the art in 2005 understood the plain meaning to be limited to dependence on NADPH as a cofactor." (Pet. App. 13.) In support of its broader construction, the panel referred to the proposed claim construction for "KARI" that Gevo had submitted for its counterclaim patents, U.S. Patents 8,017,375 and 8,017,376, which were filed years after the patents-in-suit and had different disclosures from the patents in suit. (Pet. App. 13-14 (citing JA10240).[3]) The panel thus rejected the district court's express finding that "the patentees' definition of 'AAIR' simply reflects the state of the art, that is, that the KARI enzyme known by the EC number 1.1.1.86 was generally understood to be NADPH-dependent." (Pet. App. 59.)

Contrary to the panel's statement, the district court had arrived at the conclusion that "the scientific references almost exclusively characterize KARI enzymes as NADPH-dependent" (Pet. App. 58) after carefully considering (1) the chemical reaction defining

---

[3] JA10240, Proposed Claim Construction of "ketol-acid reductoisomerase" or "KARI" in Gevo's '375 and '376 patents.

this class of enzymes, which specifically recites the NADPH cofactor, (2) each of the four references cited by the IUBMB[4] in connection with EC 1.1.1.86, (3) entries for EC 1.1.1.86 in four databases cited by the IUBMB, (4) 43 pages of listings for EC 1.1.1.86 in the BRENDA database, (5) each of five publications cited in the 43 pages that mentioned NADH (two of those had been cited by the IUBMB), and (6) the Xing reference, which had not been mentioned in the intrinsic evidence at all. (Pet. App. 53-58.)

Rejecting the ordinary meaning of "AAIR" adopted by the district court, the panel turned to the patentees' express definition of AAIR and addressed whether the phrase "using NADPH" in the definition meant "NADPH-dependent." The panel discussed the specification and claims, the prosecution history, and the extrinsic evidence, and rejected the district court's finding that "a person of ordinary skill in the art would understand that an enzyme that 'uses NADPH' or that 'uses NADH' is 'NADPH-dependent' or 'NADH-dependent,' respectively." (Pet. App. 53.)

First, the panel gave no deference to the district court's findings that "NADH and NADPH are two important and *distinct* cofactors," that they "are not metabolically interchangeable," that the difference between these cofactors "is crucial for their distinctive functions," and that "[e]nzymes that depend on them for catalytic activity are frequently termed NADH- or NADPH-dependent." (Pet. App. 53.) Instead, the panel treated the two cofactors equally, merely noting "KARI

---

[4] The International Union of Biochemistry and Molecular Biology. (Pet. App. 54 n.9.)

needs a source for the added electrons. This electron source is known as the 'cofactor' or 'coenzyme.' Two such cofactors are NADH and NADPH." (Pet. App. 5.)

Second, the panel gave no deference to the district court's finding that "the limits of biology virtually guarantee that all KARI enzymes will have at least some ancillary activity with both factors." (Pet. App. 53.) This factual premise led the district court to conclude that to distinguish between an enzyme that "uses NADPH" and one that "uses NADH" a person of ordinary skill in the art would understand that the former means "NADPH-dependent" and the latter means "NADH-dependent." (*Id*.) The panel ignored this factual finding, and concluded that the term "uses NADPH" in the patent definition did not clearly express an intent to "redefine all KARI[s]" as "NADPH-dependent." (Pet. App. 16.)

Third, the panel gave no deference to the district court's comprehensive analysis of the factual record, expert reports, publications, and how one of ordinary skill would view the intrinsic record to understand that "use NADPH" meant "NADPH-dependent."

Instead, the panel focused on the patent specification's reference to a preferred enzyme from the species *Methanococcus mariplaudis*, and a single *extrinsic* publication (Xing et al.), which had not been referenced in either the patent or the EC database. (Pet. App. 19-20.) Here, the panel again discarded the district court's factual conclusion and substituted its own. The district court evaluated the reference and concluded that "neither a reference nor data" were noted to support the assertion that "NADH supported

60% of the methanococcal activity obtained with NADPH." (Pet. App. 57-58.)

Next, the panel attributed heightened importance to the only reference (Rane) in the 43 pages of information in the BRENDA database for EC 1.1.1.86 that did not describe a KARI enzyme as NADPH-dependent. The district court acknowledged this reference, but believed it to be minimally significant because it described a KARI that was *mutated* to reverse its cofactor specificity from its natural state of being NADPH-dependent, to preferring NADH. (Pet. App. 58-59.) The panel dismissed the court's conclusion, substituting its own conclusion that the mutants were important because Gevo's enzymes were also mutants. (Pet. App. 18-19.) This point was at odds with the panel's recognition that EC numbers are not given to non-naturally occurring, engineered enzymes. (Pet. App. 18.)

In sum the panel failed to acknowledge the district court's finding that, based on its consideration of the record evidence as a whole, "that the KARI enzyme known by EC number 1.1.1.86 was generally understood to be NADPH-dependent." (Pet. App. 59.)

REASONS FOR GRANTING THE PETITION

I. THIS CASE SHOULD BE CONSIDERED ALONGSIDE THE *TEVA* CASE IN WHICH THIS COURT RECENTLY GRANTED CERTIORARI TO REVIEW THE APPROPRIATE STANDARD OF APPELLATE REVIEW FOR CLAIM CONSTRUCTION FINDINGS

A. The Federal Circuit Continues To Apply a *De Novo* Standard of Appellate Review to Quintessentially Factual Issues, Contravening Rule 52(a)(6)

Federal Rule of Civil Procedure 52(a)(6) requires Courts of Appeals to review all factual findings by district courts for clear error, not *de novo*. The mandate of Rule 52(a)(6) is plain: "Findings of fact" cannot be set aside unless they are "clearly erroneous." Fed. R. Civ. P. 52(a)(6).

This Court has explained that Rule 52(a) applies to "*all* actions tried upon the facts without a jury." *United States v. U.S. Gypsum Co.,* 333 U.S. 364, 394-95 (1948) (emphasis added). "Rule 52(a) . . . *does not make exceptions* or purport to exclude certain categories of factual findings from the obligation of a court of appeals to accept a district court's findings unless clearly erroneous." *Pullman-Standard v. Swint*, 456 U.S. 273, 287 (1982) (emphasis added). The Federal Circuit's decisions applying *de novo* review to findings of historical fact made in connection with claim construction have created just such an impermissible exception. The Federal Circuit, however, lacks

authority to modify the Federal Rules of Civil Procedure.

The Federal Circuit's leading decisions on the standard of review do not even cite, much less discuss, Rule 52(a). This is so even though concurring opinions in those cases stressed the conflict between the rule and the *de novo* standard of review. *Markman I*, 52 F.3d at 991 (Mayer, J., concurring in the judgment); *see also Cybor*, 138 F.3d at 1464 (Mayer, J., concurring in the judgment).

The Federal Circuit has avoided Rule 52(a)(6)'s mandate by reasoning that claim construction involves *no* factual findings. *See, e.g., Lighting Ballast*, 2014 WL 667499, at *9 ("Claim construction is a legal statement of the scope of the patent right; it does not turn on witness credibility, but on the content of the patent documents . . . the elaboration of experts or tutorial explanation of technical subject matter does not convert patent claim construction into a question of fact."); *Cybor*, 138 F.3d at 1456 ("[A]s a purely legal question, we review claim construction *de novo* on appeal including any allegedly fact-based questions relating to claim construction."). The Federal Circuit has even characterized claim construction as mere "document construction." *Id.* (quoting *Markman II*, 517 U.S. at 389).

Although this Court has held that claim construction is ultimately a legal conclusion, it does not follow that the district court makes no factual findings that provide an underpinning for that ultimate legal determination. Construing claims does, in fact, frequently require the district court to make findings of fact along the way to reaching its ultimate conclusion.

Construing a patent claim is in this way similar to construing technical terms in a contract. As this Court explained in *Great Northern Railway Co. v. Merchants' Elevator Co.,* 259 U.S. 285, 291-92 (1922), a district court may need to resort to extrinsic evidence to determine the meaning of a technical term used in a contract. *Id.* Although the meaning of a contract is a question of law, "the function of construction is necessarily preceded by the determination of the matter of fact." *Id.* at 292.

Claim construction involves determining what a person of ordinary skill in the art would have understood the patent to mean. The underlying questions of historical fact involved in claim construction will include questions as to the qualifications of someone who is of ordinary skill in the relevant scientific art; what that person would know; and what that person would have understood the patent to mean in light of their knowledge. This Court, for example, has expressly recognized the "level of ordinary skill in the pertinent art" to be a "basic factual inquir[y]." *Graham v. John Deere Co.,* 383 U.S. 1, 17 (1966). Because district court judges are not themselves persons of ordinary skill in the relevant art, they must determine, as a matter of fact, what a person of ordinary skill would have known.

To answer the questions of fact raised on claim construction, district courts frequently must weigh conflicting evidence presented by the parties in the form of expert scientific testimony. And the district courts must assess the witnesses' credibility. As discussed in detail below, this case involved just such a clash of experts, and the district court credited the

testimony of Gevo's expert regarding the meaning of disputed claim terms.

The district courts are better suited to resolve factual questions than the Courts of Appeals are. As now Chief Judge Rader explained in his concurring opinion in *Cybor*, district courts have "institutional advantages" over appellate courts in finding the facts that underpin claim construction. *Cybor,* 138 F.3d at 1478 (separate opinion of Rader, J.). "Trial judges can spend hundreds of hours reading and rereading all kinds of source material, receiving tutorials on technology from leading scientists, formally questioning technical experts and testing their understanding against that of various experts, [and] examining on site the operation of the principles of the claimed invention . . . ." *Id.* at 1477.

By contrast, "[a]n appellate court has none of these advantages": it holds parties to "strict time and page limits in oral and written presentations," and it examines only "a sterile written record [that] can never convey all the nuances and intangibles of the decisional process." *Id.* at 1477-78. While district courts can spend "several days" on hearings, as the district court did in this case, an appellate court has only "mere minutes . . . to devote to live exchanges with counsel." *Retractable Techs., Inc. v. Becton, Dickinson & Co.,* 659 F.3d 1369, 1374 (Fed. Cir. 2011) (O'Malley, J., dissenting from denial of rehearing en banc).

Because the district courts are better suited to resolve factual questions than the courts of appeals are, Rule 52(a)(6) requires deferential appellate review of factual findings. The factual findings that underpin claim construction should be treated no differently.

B. This Case Presents an Ideal Vehicle to Address the Question Presented in Conjunction With the *Teva* Case

This case is exactly what Judge Rader had in mind in his separate decision in *Cybor*. The district court received 90 pages of claim construction briefing, an additional 8 declarations from 6 different experts and 100 exhibits (not including the joint appendix patents and their file histories), in addition to conducting two days of hearings. The appellate standard of review made all the difference in this case. If the Federal Circuit had reviewed for clear error, we believe it would have affirmed the district court's judgment. Moreover, the district court's decision was outcome determinative. As it stands, however, under the Federal Circuit's new construction, the parties must continue to litigate the issues of infringement and validity.

Of specific importance to the decision in *Teva*, as well as here, were the district court's factual findings regarding the understanding of persons of ordinary skill in the art. Of key importance here was the determination of how a person of ordinary skill in the art would understand the patents' definition of the AAIR enzyme by reference to EC number 1.1.1.86, and the express recitation of the enzyme as "using NADPH." The district court made specific factual findings regarding the general knowledge and understanding in the art as of 2005 regarding what was specifically known about AAIR enzymes at that time, as well as the understanding of references to cofactor "use" by enzymes generally.

Specifically the district court found that:

- "NADH and NADPH have distinct chemical structures," are "not metabolically interchangeable," and contain differences in chemical structure that a "crucial for their distinctive functions." (Pet. App. 52-53.)
- All AAIR or KARI enzymes will have at least some ancillary activity with both NADH and NADPH due to the limits of biology. (Pet. App. 53.)
- Enzymes that depend on NADH or NADPH for "catalytic activity are frequently termed NADH- or NADPH-dependent." (Pet. App. 52-53.)
- "A person of ordinary skill in the art would understand that an enzyme that 'uses NADPH' or that 'uses NADH' is 'NADPH-dependent' or 'NADH-dependent', respectively." (Pet. App. 53.)
- The Enzyme Commission classification system requires that an enzyme that can use either NADH or NADPH be indicated as such. (Pet. App. 53-54.)
- EC number 1.1.1.86 describes a reaction with NADPH. (Pet. App. 54.)
- "The scientific references almost exclusively characterize KARI enzymes as NADPH-dependent." (Pet. App. 58.)
- As of October 26, 2005, all natural KARI enzymes were known to be NADPH-dependent. (Pet. App. 53.)

In making these findings, the district court specifically credited the testimony of Gevo's experts. While Butamax presented expert testimony of its own, the district court found Gevo's testimony more persuasive because it was more consistent with the intrinsic record. (Pet. App. 58.) While the Federal Circuit focused its analysis on what it deemed the intrinsic record, the district court recognized that the expert testimony and documentary evidence presented was in this instance "instructive, if not imperative" to the understanding of one of skill in the art. (Pet. App. 52, n.6.)

The Federal Circuit failed to properly credit the district court's findings by relying on two lone references out of many that the district court in fact directly addressed. The district court found those two references either insufficiently supported by data to attribute any weight, or not relevant enough to overcome the overwhelming weight of the contradictory evidence showing AAIRs known by E.C. number 1.1.1.86 were NADPH-dependent. Yet the Federal Circuit, by reviewing the construction *de novo*, attributed significant additional value to these two references, despite the district court's own consideration and determination that they were not persuasive against the backdrop of all the remaining evidence.

Because of the district court's extensive consideration of claim construction and the particular importance of expert testimony to the claim construction inquiry, this case presents an equally appropriate vehicle for consideration of the question presented here as in *Teva*. This case, however, also

presents a slightly different framework for consideration of the question presented in *Teva,* making it particularly suited for consideration alongside *Teva.* In that case the claim construction dispute centered around whether the claim was indefinite, which implicates additional legal standards not at issue in this case. Indefiniteness calls into question additional considerations of whether a claim is "insolubly ambiguous." Here the dispute is plainly and cleanly an issue only of the proper construction of the disputed term. While both cases involve the appropriate deference to a district court's factual findings in relation to claim construction, this case presents a different set of circumstances that will complement this Court's consideration of the question presented.

II. ALTERNATIVELY, THE COURT MAY WISH TO HOLD THE PETITION FOR RESOLUTION OF THE *TEVA* CASE, FOLLOWED BY AN ORDER TO GRANT, VACATE AND REMAND

Should this Court determine that it will not consider a plenary review of Gevo's petition in conjunction with *Teva*, it should hold this petition pending decision in that case. If, upon resolution of *Teva*, this Court determines that factual findings by the district court during claim construction must be reviewed only for clear error, then Gevo's petition should be granted, the court of appeals opinion vacated, and remanded for further proceedings in light of that decision. Such orders are particularly appropriate when an intervening decision has issued that could affect the lower court's determination. *Lawrence v.*

Chater, 516 U.S. 163, 166-67 (1996) (explaining that GVR is appropriately exercised in light of intervening developments such as decisions of this Court). This would be particularly appropriate in this case, if the Court decides not to conduct a plenary review. A reversal of the Federal Circuit's standard of review for claim construction would constitute just such an intervening decision the GVR power is intended to address.

The Federal Circuit here conducted a *de novo* review of the district court's claim construction. If this court determines that standard was incorrect, there is "a reasonable probability that the decision below rests on a premise that the lower court would reject if given the opportunity for further consideration." *Id*. at 167-68. Moreover, a redetermination of the claim construction "may determine the ultimate outcome of the litigation," particularly if the district court's claim construction is upheld as not clearly erroneous. *Id*. As described previously, Butamax stipulated to no literal infringement under the district court's construction, and the district court granted summary judgment of no infringement under the doctrine of equivalents under that same construction. (Pet. App. 34-35.) That makes it particularly appropriate to hold this petition pending decision in *Teva,* followed by a grant, vacate and remand.

CONCLUSION

The petition for writ of certiorari should be granted so that this case may be considered alongside the *Teva* case, and the judgment of the Court of Appeals reversed. Alternatively, this petition should be held pending review in the *Teva* case, upon which the petition should be granted, the Federal Circuit's judgment vacated, and the case remanded to the district court for further proceedings.

Respectfully submitted,

MICHELLE S. RHYU
Counsel of Record
BENJAMIN G. DAMSTEDT
LORI R. MASON
KATHRYN D. DUVALL
COOLEY LLP
Five Palo Alto Square
3000 El Camino Real
Palo Alto, CA 94306
650-843-5000
mrhyu@cooley.com

JAMES P. BROGAN
COOLEY LLP
380 Interlocken Crescent
Suite 900
Broomfield, CO 80021-8023
720-566-4000

Counsel for Petitioner
Gevo, Inc.

APPENDIX

APPENDIX

TABLE OF CONTENTS

APPENDIX A

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

2013-1342

[Filed February 18, 2014]

BUTAMAX(TM) ADVANCED BIOFUELS LLC,
Plaintiff-Appellant,

v.

GEVO, INC.,
Defendant- Appellee.

Appeal from the United States District Court for the District of Delaware in No. 11-CV-0054, Judge Sue L. Robinson.

LEORA BEN-AMI, Kirkland & Ellis, LLP, of New York, New York, argued for plaintiff-appellant. With her on the brief were THOMAS F. FLEMING, CHRISTOPHER T. JAGOE, and PETER B. SILVERMAN.

MICHELLE S. RHYU, Cooley, LLP, of Palo Alto, California, argued for defendant-appellee. With her on the brief were STEPHEN C. NEAL, BENJAMIN G. DAMSTEDT, DANIEL J. KNAUSS, of Palo Alto, California; and JAMES P. BROGAN, of Broomfield, Colorado.

Before RADER, *Chief Judge,* LINN, and WALLACH, *Circuit Judges.*

LINN, *Circuit Judge*.

Butamax™ Advanced Biofuels LLC ("Butamax") owns U.S. Pat. No. 7,851,188 ("'188 patent") and No. 7,993,889 ("'889 patent") (collectively, the "patents-in-suit") and appeals a final judgment entered against it following the district court's 1) claim construction and denial of Butamax's motion for summary judgment of literal infringement of the asserted claims of the '188 and '889 patents by Gevo, Inc. ("Gevo"), 2) grant of Gevo's motion for summary judgment of noninfringement under the doctrine of equivalents of the asserted claims of the '188 and '889 patents, 3) grant of Gevo's motion for summary judgment of invalidity of claims 12 and 13 of the '889 patent for lack of written description, and 4) judgment of invalidity of claims 12 and 13 of the '889 patent for lack of enablement. Opinion, *Butamax™ Advanced Biofuels LLC v. Gevo, Inc.*, No. 11-54-SLR, 2013 WL 3914467 (D. Del. March 19, 2013) ("*Opinion*"). Because the district court erred in its claim construction, this court vacates the district court's denial of Butamax's motion for summary judgment of infringement and its grant of Gevo's motion of noninfringement under the doctrine of equivalents. Because the district court failed to recognize the existence of genuine issues of material fact on Gevo's motion for summary judgment of invalidity as to claims 12 and 13 of the '889 patent, this court reverses the district court's grant of that motion. Finally, this court reverses the grant of summary judgment of invalidity for lack of enablement because that judgment appears to have been a scrivener's error.

App. 3

I. BACKGROUND

A. The '188 Patent

The '188 patent covers a recombinant microbial host cell that uses a particular biosynthetic pathway to produce isobutanol, which is useful as a fuel or fuel additive. *Opinion* at *3. The claimed biosynthetic pathway comprises essentially five steps. *See* '188 Patent fig. 1.

Claim 1 of the '188 patent recites the first four steps:

> 1. A recombinant microbial host cell comprising heterologous DNA molecules encoding polypeptides that catalyze substrate to product conversions for each step below:
>
> i) pyruvate to acetolactate;
>
> ii) acetolactate to 2,3-dihydroxyisovalerate;
>
> iii) 2,3-dihydroxyisovalerate to α-ketoisovalerate; and
>
> iv) α-ketoisovalerate to isobutyraldehyde;
>
> wherein said microbial host cell produces isobutanol; and wherein
>
> a) the polypeptide that catalyzes a substrate to product conversion of pyruvate to acetolactate is acetolactate synthase having the EC number 2.2.1.6;
>
> b) the polypeptide that catalyzes a substrate to product conversion of acetolactate to 2,3-

> dihydroxyisovalerate is *acetohydroxy acid isomeroreductase* having the EC number 1.1.1.86;
>
> c) the polypeptide that catalyzes a substrate to product conversion of 2,3-dihydroxyisovalerate to α-ketoisovalerate is acetohydroxy acid dehydratase having the EC number 4.2.1.9;
>
> d) the polypeptide that catalyzes a substrate to product conversion of α-ketoisovalerate to isobutyraldehyde is branched-chain α-keto acid decarboxylase having the EC number 4.1.1.72.

'188 Patent col. 335 ll. 21–44 (emphasis added). In the fifth step, isobutyraldehyde is converted into isobutanol. *See* '188 Patent col. 336 ll. 43–48 (dependent claim 18, reciting a method for producing isobutanol from the recombinant microbial host cell of claim 1).

Claim 15 depends from claim 1 and recites "[a] host cell according to claim 1 wherein the acetohydroxy acid isomeroreductase has an amino acid sequence selected from the group consisting of SEQ ID NO:43, SEQ ID NO:181, SEQ ID NO:183, and SEQ ID NO:185." '188 Patent col. 336 ll. 33–36. SEQ ID NO:183 is a sequence of *Methanococcus*.

This appeal primarily concerns step (ii): the conversion of acetolactate ("AL") to 2,3-dihydroxyisovalerate ("DHIV"), catalyzed by the polypeptide enzyme acetohydroxy acid isomeroreductase (also known as keto-acid reductoisomerase, or "KARI") "having the EC number 1.1.1.86." KARI assists reactions by rearranging (i.e.,

isomerizing) a reagent and also by "reducing" (the process of adding electrons) this rearranged molecule. To accomplish the reduction, KARI needs a source for the added electrons. This electron source is known as the "cofactor" or "coenzyme." Two such cofactors are NADH (nicotinamide adenine dinucleotide + hydrogen) and NADPH (nicotinamide adenine dinucleotide phosphate + hydrogen).

The '188 patent's specification provides "definitions . . . to be used for the interpretation of the claims," including a definition of KARI:

> an enzyme that catalyzes the conversion of acetolactate to 2,3-dihydroxyisovalerate using NADPH (reduced nicotinamide adenine dinucleotide phosphate) as an electron donor. Preferred acetohydroxy acid isomeroreductases are known by the EC number 1.1.1.86 and sequences are available from a vast array of microorganisms, including but not limited to . . . *Methanococcus maripaludis*. . . .

'188 Patent col. 7 ll. 35–47.

EC number 1.1.1.86, referenced in both this definition and claim 1, is an Enzyme Commission number for an enzyme known by the names KARI, "acetohydroxy acid isomeroreductase," and several other names. The EC enzyme classification system was developed in the 1950s to standardize enzyme nomenclature. *Opinion* at *15. Notably, Rule 18 of the EC system states that "[f]or oxidoreductases using NAD+ or NADP+ [the oxidized states of NADH and NADPH, respectively], the coenzyme should always be named as the acceptor" unless a certain exception

applies, which is irrelevant here. *Id.* However, it also appears common to assign different EC numbers to the same enzyme, where the difference between the numbers is the identity of the cofactor named. *Id.* at 15 n.8. EC number 1.1.1.86 names only NADP+ as an acceptor, and neither party calls attention to another EC number for KARI naming any other cofactor as an acceptor.

Butamax alleges that Gevo infringes claim 1 of the '188 patent and claims 2–4, 13–15, 17, and 36 dependent therefrom, as well as claim 18 and claims 19–25, and 34–35 dependent therefrom.

B. The '889 Patent

The '889 patent issued from a divisional of the application from which the '188 patent issued. The patents' specifications largely are identical, each for example including the KARI definition quoted above. *See* '889 Patent col. 7 ll. 8–20. The '889 patent focuses on a method of producing isobutanol from a recombinant yeast microorganism that expresses the five-step biosynthetic pathway described above.

Claim 1 of the '889 patent states:

> 1. A method for producing isobutanol comprising;
>
> a. providing a fermentation media comprising carbon substrate; and
>
> b. contacting said media with a recombinant yeast microorganism expressing an engineered isobutanol biosynthetic pathway wherein said

pathway comprises the following substrate to product conversions;

i. pyruvate to acetolactate (pathway step a);

ii. acetolactate to 2,3-dihydroxyisovalerate (pathway step b);

iii. 2,3-dihydroxyisovalerate to α-ketoisovalerate (pathway step c);

iv. α-ketoisovalerate to isobutyraldehyde (pathway step d); and

v. isobutyraldehyde to isobutanol (pathway step e);

and wherein

a) the substrate to product conversion of step (i) is performed by an acetolactate synthase enzyme;

b) the substrate to product conversion of step (ii) is performed by an acetohydroxy acid isomeroreductase enzyme;

c) the substrate to product conversion of step (iii) is performed by an acetohydroxy acid dehydratase enzyme;

d) the substrate to product conversion of step (iv) is performed by a decarboxylase enzyme; and

e) the substrate to product conversion of step (v) is performed by an alcohol

> dehydrogenase enzyme; whereby isobutanol is produced.

'889 Patent col. 325 ll. 14–43. As with the '188 patent, the primary issue with the '889 patent on appeal involves step (ii): the conversion of AL to DHIV using acetohydroxy acid isomeroreductase enzyme, i.e., KARI. Unlike claim 1 of the '188 patent, claim 1 of the '889 patent does not refer to any EC classification number.

Butamax alleges that Gevo has infringed claim 1 of the '889 patent and claims 2–14 and 16–19 dependent therefrom.

C. The Parties and Previous Proceedings

Butamax was formed in 2009 as a joint venture between E.I. du Pont de Nemours and Co. ("Du Pont") and BP Biofuels North America LLC. The applications that led to the patents-in-suit are part of Du Pont's previous research and development into isobutanol production. The patents-in-suit have been assigned to Butamax.

Gevo was incorporated in 2005 as Methanotech, Inc. and likewise pursues isobutanol production. Gevo uses mutant KARI enzymes that when using NADH as a cofactor exhibit significantly lower K_m (Michaelis-Menten constant) for the AL-to-DHIV conversion than when using NADPH as a cofactor. This indicates that the reaction rate with Gevo's mutant enzymes is much faster with NADH than with NADPH.

On January 14, 2011, Butamax sued Gevo in the district court and on September 22, 2011, moved for a preliminary injunction predicated on the '889 patent.

The district court construed the KARI term as "an enzyme that is solely NADPH-dependent" and denied the motion. *Butamax(TM) Advanced Biofuels LLC v. Gevo, Inc.*, 486 F. App'x 883 (Fed. Cir. 2012). This court affirmed the denial of the preliminary injunction. *Id.* However, this court noted that the district court's construction of the KARI term was "very questionable" and asked the district court "to reconsider its construction when it holds the *Markman* hearing." *Id.*

At the *Markman* hearing, the district court construed the term as "an enzyme known by the EC number 1.1.1.86 that catalyzes the conversion of acetolactate to 2,3-dihydroxyisovalerate and is NADPH-dependent." *Opinion* at *21. Additionally, adopting Butamax's proposed construction, the district court construed the '889 patent's term "pathway step (a); . . . pathway step (b); . . . pathway step (c); . . . pathway step (d); . . . pathway step (e)" to mean "the pathway steps a-e are contiguous steps such that the product of step a is the substrate for step b; the product of step b is the substrate for step c; etc." *Id.* at * 22.

At the district court, Butamax moved for summary judgment of infringement of the patents-in-suit and for a judgment of no invalidity of the '889 patent. *Opinion* at *2. Gevo moved for summary judgment of invalidity and non-infringement. *Id.* In a memorandum opinion, the district court denied Butamax's motion for summary judgment of infringement. The district court granted Gevo's motion for summary judgment of noninfringement as it related to the doctrine of equivalents, but otherwise denied the motion. Each of Butamax's motion of no invalidity and Gevo's motion

for invalidity was granted by the district court with respect to some claims and denied with respect to others. Relevant to this appeal, the district court granted Gevo's invalidity motion and denied Butamax's motion of no invalidity with respect to claims 12 and 13 of the '889 patent, finding the claims lacking in written description support. *Opinion* at *52–53. The district court issued an order reflecting the memorandum opinion and also holding claims 12 and 13 the '889 patent invalid for lack of enablement, a ground not raised in the motions of the parties.

Butamax appeals the claim construction of the KARI term, the denial of Butamax's motion for summary judgment of literal infringement, the grant of Gevo's motion for summary judgment of noninfringement under the doctrine of equivalents, the grant of Gevo's motion for summary judgment of invalidity of claims 12 and 13 of the '889 patent for inadequate written description, and the order also holding those same claims invalid for lack of enablement. This court has jurisdiction under 28 U.S.C. § 1295(a)(1).

II. DISCUSSION

A. Standards of Review

"We review claim construction de novo." *Thorner v. Sony Computer Entm't Am. LLC*, 669 F.3d 1362, 1365 (Fed. Cir. 2012).

Summary judgment is granted "if the movant shows that there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(a). "This court reviews the district court's grant or denial of summary judgment

under the law of the regional circuit." *Lexion Med., LLC v. Northgate Techs., Inc.,* 641 F.3d 1352, 1358 (Fed. Cir. 2011). The Third Circuit "review[s] an order granting summary judgment de novo, applying the same standard used by the District Court." *Azur v. Chase Bank, USA, Nat'l Ass'n,* 601 F.3d 212, 216 (3d Cir. 2010) (quotation omitted).

"[A] determination of infringement, both literal and under the doctrine of equivalents, is a question of fact." *Lockheed Martin Corp. v. Space Sys./Loral, Inc.*, 324 F.3d 1308, 1318 (Fed. Cir. 2003). "Summary judgment on the issue of infringement is proper when no reasonable jury could find that every limitation recited in a properly construed claim either is or is not found in the accused device either literally or under the doctrine of equivalents." *PC Connector Solutions LLC v. SmartDisk Corp.*, 406 F.3d 1359, 1364 (Fed. Cir. 2005).

B. Claim Construction

The primary dispute between the parties concerns whether the claimed KARI must be "NADPH-dependent." The district court considered the patents' specifications, prosecution histories, and the extrinsic evidence such as expert testimony and the EC enzyme classification system and other enzyme databases. It concluded that in the "state of the art," the "KARI enzyme known by the EC number 1.1.1.86 was generally understood to be NADPH-dependent." *Opinion* at *20. This decision is premised in large part on the district court's conclusion that the patentees acted as their own lexicographers in defining KARI by reference to EC number 1.1.1.86 and the enzyme's "use" of NADPH rather than use of NADH or both

NADPH and NADH. *Id.* at *19–20. The district court therefore construed the KARI term as "an enzyme known by the EC number 1.1.1.86 that catalyzes the conversion of acetolactate to 2,3-dihydroxyisovalerate and is NADPH-dependent." *Id.* at *21.

Butamax argues that the district court erred because KARI's plain meaning merely refers to an enzyme catalyzing the AL to DHIV conversion and because the patentees did not expressly relinquish any of that claim scope in the specification or the prosecution history. Butamax contends that the patentees in defining KARI did not clearly express an intent to redefine KARI to be NADPH-dependent. In support, Butamax points to the other claims, the embodiments provided in the specifications, and extrinsic evidence including contemporary scientific literature, a database referenced in EC number 1.1.1.86, and Gevo's use of EC number 1.1.1.86 to describe its own enzymes.

Gevo disagrees, arguing that the district court construed the term correctly. Gevo contends that the specifications' definition of KARI demonstrates that the patentees did clearly express an intent to specify KARI as NADPH-dependent, and points to other aspects of the specifications as well as the prosecution histories in support. Gevo further contends that extrinsic evidence, such as EC number 1.1.1.86 and its references, the EC rules, and Butamax's internal documents and subsequent patent applications indicate that the claimed KARI must be NADPH-dependent.

> Generally, claim terms are:
>
> > given their ordinary and customary meaning as understood by a person of ordinary skill in the art when read in the context of the specification and prosecution history. There are only two exceptions to this general rule: 1) when a patentee sets out a definition and acts as his own lexicographer, or 2) when the patentee disavows the full scope of a claim term either in the specification or during prosecution.

Thorner, 669 F.3d at 1365 (citation omitted). "To act as its own lexicographer, a patentee must 'clearly set forth a definition of the disputed claim term' other than its plain and ordinary meaning." *Id.* at 1365 (quoting *CCS Fitness, Inc. v. Brunswick Corp.*, 288 F.3d 1359, 1366 (Fed. Cir. 2002)). "It is not enough for a patentee to simply disclose a single embodiment or use a word in the same manner in all embodiments, the patentee must 'clearly express an intent' to redefine the term." *Id.* (citing *Helmsderfer v. Bobrick Washroom Equip., Inc.*, 527 F.3d 1379, 1381 (Fed. Cir. 2008)).

i. KARI's Ordinary Meaning

The initial inquiry is whether the plain meaning of KARI indicates that the enzyme is NADPH-dependent. While the district court found that "the scientific references almost exclusively characterize KARI enzymes as NADPH-dependent," *Opinion* at *19, there is nothing in the record to indicate that persons of ordinary skill in the art in 2005 understood the plain meaning to be limited to dependence on NADPH as a cofactor. Gevo conceded as much at the district court, acknowledging that under KARI's plain meaning, the

enzyme converts AL to DHIV "using NADH or NADPH as a cofactor." *See* Joint Appendix ("J.A.") 10240.

We agree that the plain meaning of KARI itself imposes no limitation on the cofactor or source of electrons for the AL to DHIV conversion. The question then becomes whether the asserted claims are limited, as Gevo contends, to the use of NADPH only based principally on the "explicit definition" set forth in the patents-in-suit. *See* J.A. 10241.

ii. The Specifications and Claims

a. The Patentees' Definition of KARI

The patents provide definitions of several terms, noting that "[t]he following definitions and abbreviations are to be used for the interpretation of the claims and specification." '188 Patent col. 7 ll. 12–14.[1] As described above, the patents subsequently define KARI as:

> an enzyme that catalyzes the conversion of acetolactate to 2,3-dihydroxyisovalerate using NADPH (reduced nicotinamide adenine dinucleotide phosphate) as an electron donor. Preferred acetohydroxy acid isomeroreductases are known by the EC number 1.1.1.86 and sequences are available from a vast array of microorganisms, including but not limited to . . . *Methanococcus maripaludis* . . . .

'188 Patent col. 7 ll. 35–47.

---

[1] Because the specifications of the patents-in-suit largely are identical, the court for brevity will cite only to the '188 patent.

It cannot be disputed that the patentees offered a definition of KARI. It is disputed, however, whether this definition "clearly expresses an intent" to redefine KARI in a way that differs from the plain and ordinary meaning identified above and, if so, the extent of any such difference. Gevo contends that the phrase "using NADPH . . . as an electron donor" is a clear expression of the patentees' intent to exclude KARI that are not "NADPH-dependent."

Butamax disagrees and asserts that the fact that an enzyme can catalyze the conversion of AL to DHIV "using NADPH" does not, on its own, indicate that the enzyme cannot *also* use other cofactors, such as NADH, to catalyze that conversion.

Gevo argues that Butamax's interpretation reads out an important aspect of the patentees' definition of KARI because all KARI are capable of using NADPH as a cofactor. Thus, Gevo argues it would have been completely unnecessary for the patents to have referred to "using NADPH" in the first instance. Gevo also argues that the phrase "using NADPH" must be understood in light of other aspects of the specifications. Gevo first contends that the specifications use the term "use(s) NADPH" interchangeably with the phrase "NADPH-dependent." Gevo points to this passage:

> [A]lcohol dehydrogenase VI (ADH6) and Ypr1p . . . use NADPH as electron donor. An NADPH dependent reductase, YqhD, . . . has also been recently identified in *E. coli* . . . .

'188 Patent col. 12 ll. 50–60. The patents further describe ADH6 as "NADPH-dependent cinnamyl

alcohol dehydrogenase." *Id.* at col. 4 ll. 60–62. However, "[i]t is not enough for a patentee to simply disclose a single embodiment or use a word in the same manner in all embodiments." *Thorner*, 669 F.3d at 1365.

We agree with Butamax and find no reason to constrict the phrase "using NADPH" to mean "only use NADPH" or "NADPH-dependent." We also disagree with Gevo's argument that such an interpretation reads out an important part of the patentees' definition. The patents' definition at least excludes as-yet-undiscovered KARI enzymes that could catalyze the conversion of AL to DHIV without using NADPH at all. Moreover, the description of specific types of KARI as NADPH-dependent does not clearly express an intent to redefine all KARI "using NADPH" as KARI that must be NADPH-dependent.

Next, Gevo points to the patents' descriptions of other enzymes that use or utilize either NAD^+ or "NADH . . . and/or NADPH" as an electron donor. *Id.* at col. 8 ll. 14– 16, 25–29. Gevo contends that the patentees knew how to describe enzymes that used NADH or both NADH and NADPH and that the patentees instead chose to define KARI as using only NADPH.

Butamax counters that the patents' descriptions of other enzymes "using" or "utilizing" various cofactors merely is a reference to particular EC numbers or the assays for the enzymes in question. For example, Butamax contends that the standard assay for KARI is the Arfin-Umbarger assay, which "uses" NADPH to measure KARI activity by monitoring the consumption of NADPH in the presence of acetolactate and the enzyme in question. Appellant's Br. 14. The patents'

Example 2 expressly teaches to measure KARI activity "using the method described by Arfin and Umbarger," '188 Patent col. 33 ll. 45–47. Example 10 teaches using the same method. *Id.* at col. 39 ll. 4–5. Butamax also argues that the patents' reference to "using NADPH" merely matches the description of the enzyme in EC number 1.1.1.86, which notes the use of $NADP^+$ but is silent as to NAD^+ or NADH. Butamax notes that the other enzymes in question from the specifications have multiple EC numbers—each referring to NADH, NADPH, or both NADH and NADPH—and/or have multiple different assays for their identification—each assay using a different cofactor. Thus, Butamax argues that the patentees merely referred the other cofactors where appropriate. Appellant's Br. 45.

We agree with Butamax that the references to other enzymes as either using NAD^+ or using NADH and/or NADPH do not imply that the patentees intended to limit KARI's use of NADH. The patentees' description of KARI merely corresponds with the Arfin-Umbarger assay and the description of KARI in EC Number 1.1.1.86.

b. Reference to EC Number 1.1.1.86 in Claim 1

The '188 patent's claim 1 explicitly states that the enzyme in question is "acetohydroxy acid isomeroreductase having the EC number 1.1.1.86." '188 Patent col. 335 ll. 33–36. As described above, EC number 1.1.1.86 identifies $NADP^+$ as the cofactor, but does not itself mention NAD^+ or NADH. *See* Appellee's Br. 45. The EC rules provide that for an enzyme "using" both NADH and NADPH, the entry should "always" name both cofactors. Gevo contends that this confirms that a person of ordinary skill in the art

understood KARI having EC number 1.1.1.86 to be NADPH-dependent.

It must first be appreciated that the EC nomenclature was drafted to categorize naturally-occurring enzymes and that new EC numbers generally are not created for modified forms of enzymes that might rely on different cofactors. *See* J.A. 17810–11. The nomenclature is also not necessarily complete. In 2005, for example, it was known that some KARI, such as KARI from at least some species of *Methanococcus*, can use either cofactor effectively. Significantly, *Methanococcus* was explicitly recited in Butamax's own definition as a preferred KARI and recited in dependent claim 15. '188 Patent col. 7 ll. 40–47.

Butamax points to additional evidence showing persons of skill in the art would have understood that EC number 1.1.1.86 enzymes need not be NADPH-dependent. The EC number 1.1.1.86 entry contains a link to the BRENDA database (Braunchschweig Enzyme Database), which contains a reference to a mutated KARI enzyme in which NADH "can substitute for NADPH." Appellant's Br. 16. The district court discounted this lone reference because it was the only reference out of many indicating that NADH could be substituted and because the specific enzyme in question was a "quadruplet mutant." *Opinion* at *19–20.

However, even a single reference to mutant KARI under EC number 1.1.1.86 is particularly important here because the accused enzymes also are mutants. Butamax points to evidence that Gevo in approximately 2008—prior to the litigation—described its own mutant enzymes by reference to EC number 1.1.1.86. *See, e.g.,*

Appellant's Br. 25; J.A. 9804. And of course Gevo contends that its enzymes are not NADPH-dependent. Though this evidence identified by Butamax did not exist until years after the patents-in-suits were filed in 2005, the BRENDA entry for EC number 1.1.1.86 referred to a mutant KARI that was not NADPH-dependent and was known prior to 2005, and Gevo years later indicated that EC number 1.1.1.86 still "would have been the best way [they] knew how" to describe its own mutant enzyme. Appellant's Br. 25 (citing testimony of Gevo's former Executive Vice President of Technology). *See e.g., ASM Am., Inc. v. Genus, Inc.*, 401 F.3d 1340, 1347 (Fed. Cir. 2005) (concluding that extrinsic evidence that post-dated the patent filing date nonetheless was helpful in determining how a person of ordinary skill in the art would have understood the claim term at the time it was filed).

For the foregoing reasons, the Court cannot conclude that the reference to EC number 1.1.1.86 is an expression of a clear intent to redefine KARI to be NADPH-dependent.

c. Preferred Embodiments and Dependent Claims

Other aspects of the patents raise further doubt of any express intent to redefine KARI in the limited way adopted by the district court. As above, the patents specifically list "*Methanococcus maripaludis* . . . SEQ ID NO: 183" as a source organism for the preferred KARI. '188 patent at col. 7 ll. 35–47. Moreover, dependent claim 15 of the '188 patent claims that KARI. '188 Patent col. 336 ll. 33–36. Butamax contends that it would be wrong to conclude that KARI from this organism are NADPH-dependent, pointing to evidence

that at least some *Methanococcus* KARI are "able to utilize NADH as well as NADPH" and have "broad specificity for NADPH and NADH." Further, Butamax notes that "NADH supported 60% of the methanococcal activity obtained with NADPH." *See* R. Xing & W. Whitman, Characterization of Enzymes of the Branched-Chain Amino Acid Biosynthetic Pathway in Methanococcus spp, 173(6) J. Bacteriology 2086–92 (1991) ("Xing").

The district court discounted Xing because it provided no references or data to support these findings. *Opinion* at *19 (noting that Xing "included a single conclusory sentence with no data or other literature references to support it"). However, Xing's accuracy is not in dispute. Indeed, Gevo's 2007 Pat. App. No. 61/016,483 cites to Xing for this very proposition. Gevo does note that the patents identify the KARI of *Methanococcus maripaludis* while Xing examined the KARI of *Methanococcus aeolicus*, a different species of *Methanococcus*. However, there is no genuine dispute that *Methanococcus maripaludis* exhibits similar characteristics. *See* Appellant's Reply Br. 9.

The district court's claim construction, without justification, excludes a preferred embodiment, which in this case also is the subject of dependent claim 15, and this court "normally do[es] not interpret claim terms in a way that excludes embodiments disclosed in the specification." *Oatey Co. v. IPS Corp.*, 514 F.3d 1271, 1276 (Fed. Cir. 2008).

iii. Prosecution History

Gevo also contends that the prosecution history evinces an express intent to redefine KARI to be NADPH-dependent. The Patent Office separately rejected Butamax's claims for lack of enablement and for lack of written description, and Gevo contends that the patentees' responses demonstrated that the claimed KARI are NADPH-dependent.

In the application leading to the '188 patent, the Patent Office rejected for inadequate written description a then-pending claim which stated:

> A recombinant microbial host cell comprising at least one DNA molecule encoding a polypeptide that catalyzes a substrate to product conversion selected from the group consisting of:
>
> i) pyruvate to acetolactate (pathway step a)
>
> ii) acetolactate to 2,3-dihydroxyisQvalerate (pathway step b)
>
> iii) 2,3-dihydroxyisovalerate to aketoisovalerate (pathway step c)
>
> iv) a-ketoisovalerate to isobutyraldehyde, (pathway step d), and
>
> v) isobutyraldehyde to isobutanol; (pathway step e)
>
> wherein the at least one DNA molecule is heterologous to said microbial host cell and wherein said microbial host cell produces isobutanol.

J.A. 6906. The Patent Office concluded that "[o]ne skilled in the art would require additional guidance, such as information regarding the specific identity and structure of the polypeptides that catalyze[]" the conversions in the claim. J.A. 6927. The patentees responded, amending the claim to refer to the EC numbers of the various enzymes, submitting a copy of the EC nomenclature rules, and pointing to the specific examples of the enzymes in the specification (including SEQ ID No: 183—*Methanococcus maripaludis*—as an example of KARI). J.A. 7095. The Patent Office concluded that this sufficiently described the claimed inventions but concluded that the claim lacked enablement for its full scope. J.A. 7117. The patentees disagreed, contending that the EC numbers, together with the level of ordinary skill in the art (including knowledge reflected in the BRENDA database) did enable skilled artisans to identify appropriate enzymes, and the examiner eventually withdrew the rejection. J.A. 7209, 7251.

In the application leading to the '889 patent, a then-pending claim similarly was rejected for lack of enablement. J.A. 7572–73. The patentees again amended, this time naming the enzymes used in each claimed step without referring to any EC numbers. J.A. 7585. The patentees argued that "[t]he specific enzymes that catalyze the steps of the pathway recited in the claims are described in the application in an abundance of detail," and went on to discuss Table 2 as a particular example. J.A. 7583.

In the prosecution history, the patentees defended their claims by referring the Patent Office to the EC numbers and the examples of the enzymes provided in

the specifications. For the reasons stated above, these references do not clearly express an intent by the patentees to redefine KARI to be NADPH-dependent. Indeed, the patentees specifically named *Methanococcus maripaludis* KARI as an example during the prosecution history, a KARI that appears to "use" NADH.

Accordingly, the court does not consider the prosecution history to warrant any limitation of the claimed KARI as being NADPH-dependent.

iv. Extrinsic Evidence

Gevo also relies on extrinsic evidence to support its arguments. EC number 1.1.1.86 was discussed above. Gevo further points to Butamax's internal documents and subsequent patent applications. For example, based on its research, Butamax filed a patent application in 2008 which stated that "discovery of a KARI enzyme that can use NADH as a cofactor as opposed to NADPH would be an advance in the art." J.A. 8794. Gevo contends that this application and the related evidence demonstrate that Butamax itself recognized that the earlier-filed patents-in-suit did not encompass KARI that use NADH.

However, as discussed above, the ordinary meaning of KARI is not cofactor dependent, and this subsequent extrinsic evidence does not clearly express an intent *at the time of the invention* to redefine KARI to use one cofactor over another. The subsequent discovery of the beneficial results obtained by the use of NADH does not support the conclusion that it was understood to be excluded as a cofactor at the time the patents-in-suit were filed.

v. Claim Construction

For all of the foregoing reasons, the term "acetohydroxy acid reductoisomerase" is construed as "an enzyme, whether naturally occurring or otherwise, known by the EC number 1.1.1.86 that catalyzes the conversion of acetolactate to 2,3-dihydroxyisovalerate."

C. Infringement

Butamax contends that this court, under the more accurate claim construction, should reverse the district court's ruling that denied Butamax's motion for summary judgment of literal infringement. Gevo disagrees, contending that 1) there remains a dispute concerning the "contiguous" pathway term and 2) there remains a dispute as to the accused enzymes' "use" of NADPH.

The continuous pathway term relates only to the '889 patent and does not present a genuine issue of material fact on this record. Butamax provided expert testimony, and Gevo failed to present any contention, interrogatory, or expert testimony challenging Butamax's contention that the limitation was met.

As to the dispute over whether Gevo's enzymes use detectable levels of NADPH, Gevo argues on appeal that there is a distinction between *in vivo* and *in vitro* use that gives rise to a genuine issue of material dispute. However, Gevo does not appear to have argued at any point before the district court that the construction of KARI requires focusing on use of a specific cofactor *in vivo* as opposed to *in vitro*. This court declines to consider what appears to be a new claim construction argument raised for the first time on appeal.

Gevo further contends that Butamax's *in vitro* testing of Gevo's enzymes, showing them to use NADPH, may be unreliable. Appellee's Br. 61. Gevo's argument however, is not that the results of the testing were inaccurate, but rather that a person of ordinary skill in the art would not draw the same conclusions from the experiments as the conclusions drawn by Butamax's expert. Whether Gevo's arguments create a genuine issue of material fact under the claim construction set forth in this opinion is best left to the district court on remand.

The court accordingly vacates the district court's denial of Butamax's motion for summary judgment of infringement of claims 1, 2–4, 13–15, 17–25, and 34–36 of the '188 patent and claims 1, 2–14, and 16–19 of the '889 patent and directs the district court to reconsider the question under this court's new claim construction.

D. Invalidity

i. Written Description of Claims 12 and 13 of the '889 Patent

Claim 12 of the '889 patent states:

> 12. The recombinant yeast microorganism of claim 1 wherein the said microorganism further comprises inactivated genes thereby reducing yield loss from competing pathways for carbon flow.

Claim 13 of the '889 patent states:

> 13. The recombinant yeast microorganism of claim 12, wherein said inactivated genes reduce pyruvate decarboxylase activity.

The district court found that both claims were inadequately described and thus invalid because the specification does not sufficiently describe how to inactivate genes to disable the competing synthetic pathway.

> When determining whether a specification contains adequate written description, one must make an "objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art." [Citation.] Because the specification is viewed from the perspective of one of skill, in some circumstances, a patentee may rely on information that is "well-known in the art" for purposes of meeting the written description requirement.

Boston Scientific Corp. v. Johnson & Johnson, 647 F.3d 1353, 1366 (Fed. Cir. 2011) (citation omitted).

The district court concluded that while the patent's specification "may be interpreted as identifying both the [ ] problem and the solution, it does not even begin to describe how to put into practice the solution." *Opinion* at *52. Butamax disagrees, but its evidence in support of its arguments is weak. First, Butamax contends that the patent does teach how to deactivate the pathway in question. In support, Butamax cites to multiple aspects of the specification, but each describes only a desire to deactivate the genes rather than how to actually do it. *See, e.g.,* '889 Patent col. 1 ll. 63–65 ("[t]here is a *need* . . . for an environmentally responsible, cost-effective process for the production of isobutanol as a single product"), col. 16 ll. 55–57 ("[t]he microbial host *has to be* manipulated in order to

inactivate competing pathways for carbon flow by deleting various genes"), col. 12 ll. 12–17 ("[t]o prevent misdirection of pyruvate away from isobutanol production, a decarboxylase with decreased affinity for pyruvate *is desired*") (all emphasis added).

Next, Butamax contends that irrespective of what is explicitly taught in the specification itself, it was well-known in the art how to deactivate the genes that express the pathway. Butamax points to the testimony of Gevo's own experts, Dr. Stephanopolous and Dr. Kirsch, contending that they agreed that it was "conventional" in 2005 to deactivate the pathway. However, the expert testimony on which Butamax relies merely agrees that, in light of the specification, it would have been understood that such deactivation was desirable. *See, e.g.,* Appellant's Br. 68 (Dr. Stephanopolous agreeing that "the concept" of deactivating the pathway was conventional by 2005, that it was "nothing new" to "want to get rid of competing pathways," that the patents "tell you [you] want to delete" the competing pathway, and that the patent "tells you you're knocking out" that pathway); s*ee also, e.g.,* Appellant's Br. 69 (Dr. Kirsch agreeing that the patents teach that "you *want* to knock out" the competing pathway) (emphasis added).

Butamax also relies on extrinsic evidence purportedly teaching how to deactivate the pathway. Butamax submitted the declaration of Alexander M. Klibanov, who opined that it would have been well-known to a person of ordinary skill in the art how to deactivate the genes, citing to seven references that purportedly describe organisms with reduced or inactivated pyruvate decarboxylase activity.

Appellant's Br. 67; J.A. 3141. The district court does not appear to have addressed Mr. Klibanov's testimony or six of the references he cited. The seventh reference, Dickinson, was addressed by the district court, which agreed that Dickinson discloses yeast with deactivated genes associated with pyruvate decarboxylase activity as described in claim 13. *Opinion* at *53. However, the district court concluded that Dickinson was not appropriately incorporated by reference into the '889 patent for this point and even if it had been, that Dickinson effectively teaches away from claim 13 because in deactivating those genes responsible for expressing the pathway, isobutanol production was "virtually abolished." *Id.*

Notwithstanding the shortcomings of the foregoing, Butamax has identified sufficient evidence that at least creates a genuine dispute of material fact. Gevo makes much of the fact that Dickinson, though cited in the '889 patent, was not cited in connection with the deactivation of this pathway and was not incorporated by reference into the patent. Nonetheless, Dickinson's teachings still reflect what was known in the art. *See Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1368 (Fed. Cir. 2006) (holding that where "accessible literature sources clearly provided" a description of the teachings at issue, the written description requirement does not require their incorporation by reference). Dickinson does show that persons of ordinary skill in the art could deactivate the pathway in question, and though it appears that according to Dickinson the claimed invention would not have worked particularly well (isobutanol production would be "virtually abolished"), the evidence at least creates a genuine dispute as to whether a person of ordinary skill in the

art would have understood the patentees to have possessed the invention on some level (isobutanol production would not necessarily have been completely abolished). Further, Mr. Klibanov opined that deactivation of the genes associated with the pathway was well-known in the art, and cited Dickinson as well as six other references in support. Gevo's experts disagree with Mr. Klibanov and his interpretation of these references, but this merely indicates the existence of a genuine dispute of material fact.

Though not addressed by the district court, Gevo raises an argument that there can be no genuine dispute of material fact because a subsequent Butamax patent application demonstrates conclusively that the '889 patent lacks an adequate written description of these claims. Butamax filed a continuation-in-part of the applications leading to the '188 and '889 patents, this time providing additional detail on the deactivation of certain genes. *See* U.S. Pat. App. No. 12/966,333. The Patent Office concluded that the '889 patent was not—on its own—invalidating prior art to this application because the '889 patent "do[es] not teach the disruption of endogenous pyruvate decarboxylase genes." J.A. 17353. However, the issue here is not just whether the '889 patent itself teaches the disruption such that the patent itself would be invalidating prior art on that point. There is a genuine dispute with respect to whether in 2005 it was generally well-known in the art how to deactivate the genetic pathway such that a person of ordinary skill in the art reading the '889 patent would understand the patentees to have possessed the invention claimed in claims 12 and 13.

For these reasons, the district court's grant of Gevo's motion for summary judgment of invalidity of claims 12 and 13 for lack of adequate written description is reversed.

ii. Enablement of the '889 Patent's Claims 12 and 13

In its order, the district court summarily concluded that claims 12 and 13 were invalid for lack of enablement. However, its memorandum opinion does not reflect that judgment, nor did Gevo move for invalidity of those claims on this basis. On appeal, Gevo does not defend the judgment. It thus appears that the judgment was a scrivener's error, and this court reverses the judgment that the claims are invalid for lack of enablement.

III. CONCLUSION

For the forgoing reasons, this court vacates the district court's denial of Butamax's motion for summary judgment of literal infringement of the asserted claims of the '188 and '889 patents and remands the question of infringement to the district court for reconsideration under the claim construction set forth herein. Further, this court likewise vacates and remands the district court's grant of Gevo's motion for summary judgment of noninfringement under the doctrine of equivalents. The court further reverses the district court's grant of Gevo's motion for summary judgment of invalidity for lack of written description of claims 12 and 13 of the '889 patent and the district court's order that those same claims are invalid for lack of enablement.

REVERSED-IN-PART, VACATED-IN-PART, AND REMANDED

IV. COSTS

Costs are awarded to Butamax.

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

NOTICE OF ENTRY OF JUDGMENT
ACCOMPANIED BY OPINION

OPINION FILED AND JUDGMENT ENTERED:
02/18/2014

The attached opinion announcing the judgment of the court in your case was filed and judgment was entered on the date indicated above. The mandate will be issued in due course.

Information is also provided about petitions for rehearing and suggestions for rehearing en banc. The questions and answers are those frequently asked and answered by the Clerk's Office.

Costs are taxed against the appellee in favor of the appellant under Rule 39. The party entitled to costs is provided a bill of costs form and an instruction sheet with this notice.

The parties are encouraged to stipulate to the costs. A bill of costs will be presumed correct in the absence of a timely filed objection.

Costs are payable to the party awarded costs. If costs are awarded to the government, they should be paid to the Treasurer of the United States. Where costs are awarded against the government, payment should be made to the person(s) designated under the governing statutes, the court's orders, and the parties' written settlement agreements. In cases between private parties, payment should be made to counsel for the party awarded costs or, if the party is not

represented by counsel, to the party pro se. Payment of costs should not be sent to the court. Costs should be paid promptly.

If the court also imposed monetary sanctions, they are payable to the opposing party unless the court's opinion provides otherwise. Sanctions should be paid in the same way as costs.

Regarding exhibits and visual aids: Your attention is directed Fed. R. App. P. 34(g) which states that the clerk may destroy or dispose of the exhibits if counsel does not reclaim them within a reasonable time after the clerk gives notice to remove them. (The clerk deems a reasonable time to be 15 days from the date the final mandate is issued.)

FOR THE COURT
/s/ Daniel E. O'Toole
Daniel E. O'Toole
Clerk of Court

cc: Leora Ben-Ami
James P. Brogan
Benjamin G. Damstedt
Thomas F. Fleming
Christopher T. Jagoe
Daniel Jedediah Knauss
Stephen C. Neal
Michelle S. Rhyu
Peter B. Silverman

13-1342 - Butamax(TM) Advanced Biofuels v. Gevo, Inc.
United States District Court for the District of Delaware, Case No. 11-CV-0054

APPENDIX B

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

C.A. No. 11-54-SLR

[Filed April 10, 2013]

BUTAMAX(TM) ADVANCED BIOFUELS LLC,	)
Plaintiff,	)
v.	)
GEVO, INC.,	)
Defendant,	)

AMENDED FINAL JUDGMENT

WHEREAS on March 19, 2013, the Court entered a Memorandum Order (D.I. 707, 708) regarding, among other things, motions for summary judgment and claim construction concerning disputed limitations of the asserted claims of the United States Patent Nos. 7,851,188 ("the '188 patent") and 7,993,889 ("the '889 patent"); and held a Final Pretrial Conference on March 20, 2013.

WHEREAS the Court granted-in-part Defendant's Motion for Summary Judgment of invalidity, holding that claims 12 and 13 of the '889 patent are invalid. (D.I. 708 at 1-2).

WHEREAS the Court granted Defendant's Motion for Summary Judgment of no infringement under the doctrine of equivalents. (D.I. 708 at 2).

WHEREAS Plaintiff has stipulated that, subject to its right to appeal all appealable issues, and based on the Court's construction of the disputed limitations "acetohydroxy acid isomeroreductase" of the asserted claims of the '188 and '889 patents, the accused products—Defendant's strains 6293, 7046, 7529, 10557, 11071, 11245—have not literally infringed and do not literally infringe, these patents.

WHEREAS the Court has expressly determined that there is no just reason for delay in entering final judgment on the claims relating to the '188 and '889 patents until final determination of the claims remaining in C.A. No. 11-54-SLR—which relate to the separate claims concerning Gevo's 8,017,375 and 8,017,376 patents—and therefore, in the interest of judicial efficiency, pursuant to Fed. R. Civ. P. 21 the Court severed the claims and defenses relating to the '375 and '376 patents from the above-captioned action.

IT IS HEREBY ORDERED and ADJUDGED this 10th day of April, 2013 that final judgment be and hereby is entered in favor of Defendant Gevo, Inc. and against Plaintiff Butamax™ Advanced Biofuels LLC with respect to the Butamax claims relating to '188 and '889 patents.

/s/
United States District Judge

APPENDIX C

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

Civ. No. 11-54-SLR

[Filed March 19, 2013]

BUTAMAX™ ADVANCED BIOFUELS LLC,

Plaintiff/Counterclaim Defendant

v.

GEVO, INC.,

Defendant/Counterclaim Plaintiff

v.

E.I. DUPONT DE NEMOURS AND COMPANY,

Counterclaim Defendant

Richard L. Horwitz, Esquire and David E. Moore, Esquire of Potter, Anderson & Corroon LLP, Wilmington, Delaware. Counsel for Plaintiff. Of Counsel: Leora Ben-Ami, Esquire, Thomas F. Fleming, Esquire, Christopher T. Jagoe, Esquire and Patricia A.

Carson, Esquire, Daniel Forchheimer, Esquire, and Peter B. Silverman, Esquire of Kirkland & Ellis LLP.

Thomas C. Grimm, Esquire and Jeremy A. Tigan, Esquire of Morris, Nichols, Arsht & Tunnell LLP, Wilmington, Delaware. Counsel for Defendant. Of Counsel: Stephen C. Neal, Esquire, Michelle S. Rhyu, Esquire, Benjamin G. Damstedt, Esquire, Daniel J. Knauss, Esquire of Cooley LLP.

MEMORANDUM OPINION

Dated: March 19, 2013
Wilmington, Delaware

/s/
ROBINSON, District Judge

I. INTRODUCTION

On January 14, 2011, plaintiff Butamax™ Advanced Biofuels LLC ("Butamax") filed suit in this district against defendant Gevo, Inc. ("Gevo") alleging infringement of U.S. Patent No. 7,851,188 ("the '188 patent"). (D.I. 1) The '188 patent discloses and claims "a recombinant microorganism having an engineered isobutanol biosynthetic pathway" that "may be used for the commercial production of isobutanol." ('188 patent, 2:3-6) Gevo answered the complaint on March 25, 2011. (D.I. 10) On August 11, 2011, Butamax filed an amended complaint, alleging that Gevo also infringed U.S. Patent No. 7,993,889 ("the '889 patent"). (D.I. 41) The '889 patent was filed as a divisional application from the '188 patent and claims a method for isobutanol production using recombinant microorganisms with an engineered biosynthetic pathway. ('889 patent, 2:3-6)

Gevo answered the amended complaint on September 13, 2011 and counterclaimed against Butamax and E.I. DuPont De Nemours and Company ("DuPont") alleging infringement of U.S. Patent Nos. 8,017,375 ("the '375 patent") and 8,017,376 ("the '376 patent"), also related to the production of isobutanol from recombinant microorganisms. (D.I. 52) Butamax and DuPont answered the counterclaims on November 18, 2011 and counter-counterclaimed against Gevo seeking a declaratory judgment on non-infringement and invalidity of the '375 patent and the '376 patent. (D.I. 117) On December 9, 2011, Gevo answered the counter-counterclaims. (D.I. 130) On February 24, 2012, Butamax and DuPont filed a motion to sever Gevo's counterclaims, which was granted. (D.I. 213, D.I. 371) On June 21, 2012, upon the grant of its timely motion to amend, Butamax and DuPont amended its answer to the counterclaims and the counter-counterclaims adding affirmative defenses and counter-counterclaims of inequitable conduct. (D. I. 372) Gevo's untimely motion, filed June 29, 2012, seeking to amend its answer and counterclaims to include an affirmative defense and counterclaim of inequitable conduct was denied. (D.I. 388; D.I. 693)

On September 22, 2011, Butamax filed a motion for preliminary injunction which sought to enjoin Gevo from infringing the '889 patent. (D.I. 61) After an evidentiary hearing on the matter, March 1-2, 2012, the court denied Butamax's motion for preliminary injunction on June 19, 2012. (D.I. 370) On June 25, 2012, Butamax appealed this decision. (D.I. 376) On December 26, 2012, the Federal Circuit affirmed this court's denial of the preliminary injunction. *Butamax*

Advanced Biofuels LLC v. Gevo, Inc., No. 12-1490 (Fed. Cir. Nov 16, 2012).

Presently before the court are several motions for summary judgment: Butamax's summary judgment motion of infringement of the '188 and '889 patents (D.I. 595) and cross-motion of no invalidity of the '889 patent (D.I. 622), as well as Gevo's motions for summary judgment of invalidity and non-infringement of the '188 and '889 patents. (D.I. 598; D.I. 610) Butamax and DuPont also filed a motion to exclude testimony by Gevo's experts with respect to the '188 patent and '376 patent. (D.I. 640) The court herein addresses this motion as it relates to the '188 patent and reserves its decision as it relates to the '376 patent. The court has jurisdiction pursuant to 28 U.S.C. §§ 1331 and 1338(a).

II. BACKGROUND

A. The Parties

Butamax is a limited liability corporation organized and existing under the laws of the State of Delaware, with its principal place of business in Wilmington, Delaware. (D.I. 41 at ¶ 1) Butamax develops methods of making biofuels such as biobutanol, a product which may be used as a fuel or as a feed-stock chemical in the production of various plastics, fibers and other products. (*Id*.) In particular, Butamax has developed a biological method of producing isobutanol, a type of biobutanol. *(Id*.)

Gevo is a corporation organized and existing under the laws of the State of Delaware, with its principal place of business in Englewood, Colorado. (D.I. 52 at 5 ¶ 1) Gevo is also involved in the commercial-scale

production of isobutanol using biological methods. (*Id*. at ¶ 11; D.I. 154 at 3)

DuPont is a corporation organized and existing under the laws of the State of Delaware, with its principle place of business in Wilmington, Delaware. (D.I. 470 at 9 ¶ 2) DuPont is engaged in research and development relating to the production of isobutanol. (*Id.* at 1 ¶ 5)

B. Technology

Isobutanol is an industrial chemical that may be blended with gasoline-based fuels as an alternative to ethanol, the current dominant biofuel in gasoline blends. ('889 patent, 6:38-40) Isobutanol is preferred over ethanol because it has a higher energy content and is less corrosive. ('889 patent, 6:33-40) Butamax proposes a method of producing isobutanol using genetically-engineered yeast microorganisms that promises to facilitate the transition to renewable transportation fuels and reduce greenhouse gas emissions. (D.I. 41 at 1 ¶ 1)

This improved method for producing isobutanol is achieved by introducing engineered deoxyribonucleic acid ("DNA") into microorganisms in order to stimulate isobutanol production. (*Id.* at ¶ 12; '889 patent, 17:9-19) Microorganisms such as yeast and bacteria are capable of producing isobutanol through a five-step pathway consisting of the following five chemical conversions: (1) pyruvate to acetolactate; (2) acetolactate to 2,3-dihydroxyisovalerate; (3) 2,3-dihydroxyisovalerate to α-ketoisovalerate; (4) α-ketoisovalerate to isobutyraldehyde; and (5) isobutyraldehyde to isobutanol. (D.I. 41 at ¶ 12; '889 patent, 325:19-30) The

engineered DNA constructs encode enzymes that catalyze, or increase the chemical reaction rate, of the five steps in the isobutanol biosynthesis pathway. (D.I. 41 at ¶ 12; '889 patent, 325:32-42) Introducing these enzyme-coding DNA constructs into the microorganism stimulates the biosynthetic pathway and increases overall isobutanol production. (D.I. 41 at ¶ 12; '889 patent, 44:28-32)

C. The Patents

The '188 patent, entitled "Fermentive Production of Four Carbon Alcohols," was filed on October 25, 2006 and issued on December 14, 2010. It claims priority from provisional application No. 60/730,290 which was filed on October 26, 2005. The '889 patent was filed on January 23, 2008 and issued on August 9, 2011. The '889 patent is a divisional application of the '188 patent. Both the '889 patent and the '188 patent are assigned to Butamax. (D.I. 41 at ¶¶ 6, 9)

The specifications of the '188 and '889 patents admit that isobutanol may be chemically synthesized from starting materials derived from petrochemicals, but this method of synthesis is expensive and bad for the environment. ('889 patent, 1:33-35; '188 patent, 1:33-35) The inventors assert that using yeast or other comparable microorganisms to produce isobutanol would reduce greenhouse gas emissions and, therefore, would be a desirable alternative to chemical synthesis. ('889 patent, 1:36-38; '188 patent, 1:36-38)

Yeast naturally produce low levels of isobutanol as a by-product of fermentation. ('889 patent, 1:39-49; '188 patent, 1:39-49) More specifically, isobutanol is produced from the catabolism, or metabolic breakdown,

of the amino acid L-valine. ('889 patent, 1:39-49; '188 patent, 1:39-49) However, use of L-valine on an industrial scale as a feed-stock for yeast fermentation is prohibitively expensive. ('889 patent, 1:57-59; '188 patent, 1:57-59) The inventors claim a more cost-efficient method of producing isobutanol directly from pyruvate, a product of sugar digestion, in lieu of L-valine. ('889 patent, 325:15-23; '188 patent, 335:20-23) The transformation of pyruvate to isobutanol is achieved through one of four multi-step biosynthetic pathways. ('889 patent, 11 :40-43; '188 patent, 12:1-4)

In the claimed biosynthetic pathway, all of the necessary reaction substrates are components of "well-characterized pathways" that are naturally present in yeast. ('889 patent, 11:57-61; '188 patent, 12:19-21) The inventors assert that stimulating this pathway through the introduction of DNA constructs coding for one or more enzymes specific to pathway steps yields increased isobutanol production. ('889 patent, 17:9-19, 44:28-32; '188 patent, 19:45-55, 49:46-51) Although the enzymes are introduced via genetic manipulation, the enzymes also exist in yeast or other microorganisms as naturally-occurring components of the "well-characterized" enzymatic pathways. ('889 patent, 11:58-12:32; '188 patent, 12:19-60)

Independent claim 1 of the '889 patent, reproduced below, describes the preferred biosynthetic pathway and identifies which enzymes catalyze each step of the claimed pathway:

> 1. A method for producing isobutanol comprising;
> a. providing a fermentation media comprising carbon substrate; and

b. contacting said media with a recombinant yeast microorganism expressing an engineered isobutanol biosynthetic pathway wherein said pathway comprises the following substrate to product conversions;
i. pyruvate to acetolactate (pathway step a);
ii acetolactate to 2,3-dihydroxyisovalerate (pathway step b);
iii. 2,3-dihydroxyisovalerate to α-ketoisovalerate (pathway step c);
iv. α-ketoisovalerate to isobutyraldehyde (pathway step d); and
v. isobutyraldehyde to isobutanol (pathway step e); and wherein
a) the substrate to product conversion of step (i) is performed by an acetolactate synthase enzyme;
b) the substrate to product conversion of step (ii) is performed by an acetohydroxy acid isomeroreductase enzyme;
c) the substrate to product conversion of step (iii) is performed by an acetohydroxy acid dehydratase enzyme;
d) the substrate to product conversion of step (iv) is performed by a decarboxylase enzyme; and
e) the substrate to product conversion of step (v) is performed by an alcohol dehydrogenase enzyme; whereby isobutanol is produced.

('889 patent, 325:15-44) Independent claim 1 of the '188 patent, reproduced below, is directed at the recombinant microbial host cell:

1. A recombinant microbial host cell comprising heterologous DNA molecules

encoding polypeptides that catalyze substrate to product conversions for each step below:

i) pyruvate to acetolactate;

ii) acetolactate to 2,3-dihydroxyisovalerate;

iii. 2,3-dihydroxyisovalerate to α-ketoisovalerate;

iv. α-ketoisovalerate to isobutyraldehyde; wherein said microbial host cell produces isobutanol; and wherein

a) the polypeptide that catalyzes a substrate to product conversion of pyruvate to acetolactate is acetolactate synthase having the EC number 2.2.1.6;

b) the polypeptide that catalyzes a substrate to product conversion of acetolactate to 2,3-dihydroxyisovalerate is acetohydroxy acid isomeroreductase having the EC number 1.1.1.86;

c) the polypeptide that catalyzes a substrate to product conversion of 2,3-dihydroxyisovalerate to α-ketoisovalerate is acetohydroxy acid dehydralase having the EC number 4.2.1.9;

d) the polypeptide that catalyzes a substrate to product conversion of α-ketoisovalerate to isobutyraldehyde is branched-chain α-keto acid decarboxylase having the EC number 4.1.1.72.

('188 patent, 335:19-44) Butamax alleges that Gevo's lead strains infringe certain claims of the '188 patent. (D.I. 41 ¶¶ 17 -20) Butamax further alleges that Gevo's processes infringe certain claims of the '889 patent. (D.I. 41 ¶¶ 21-23)

III. CLAIM CONSTRUCTION

A. Legal Principles

Claim construction is a matter of law. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1330 (Fed. Cir. 2005) (en banc). Claim construction focuses on intrinsic evidence - the claims, specification and prosecution history - because intrinsic evidence is "the most significant source of the legally operative meaning of disputed claim language." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996); *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). Claims must be interpreted from the perspective of one of ordinary skill in the relevant art at the time of the invention. *Phillips*, 415 F.3d at 1313.

Claim construction starts with the claims, *id.* at 1312, and remains centered on the words of the claims throughout. *Interactive Gift Express, Inc. v. Compuserve, Inc.*, 256 F.3d 1323, 1331 (Fed. Cir. 2001). In the absence of an express intent to impart different meaning to claim terms, the terms are presumed to have their ordinary meaning. *Id.* Claims, however, must be read in view of the specification and prosecution history. Indeed, the specification is often "the single best guide to the meaning of a disputed term." *Phillips,* 415 F.3d at 1315.

B. "Acetohydroxy Acid Isomeroreductase Enzyme"

The above identified enzyme is recited in the engineered isobutanol biosynthetic pathway ("the pathway") claimed by Butamax. The patentees of the '188 and '889 patents offered a definition of this

enzyme, *inter alia*, "to be used for the interpretation of the claims and the specification," to wit:

> The terms "acetohydroxy acid isomeroreductase" and "acetohydroxy acid reductoisomerace" are used interchangeably herein to refer to an enzyme that catalyzes the conversion of acetolactate to 2,3-dihydroxy- isovalerate using NADPH (reduced nicotinamide adenine dinucleotide phosphate) as an electron donor. Preferred acetohydroxy acid isomeroreductases are known by the EC number 1.1.1.86 and sequences are available from a vast array of microorganisms . . . .

('188 patent, 7:12-13, 35-42; '889 patent, 6:52-53, 7:8-15) Despite being a defined term, the parties dispute how persons of skill in the art would interpret the language used by the patentees, more specifically, whether those of skill in the art would include within the scope of this definition enzymes that use either NADH or NADPH or both as a cofactor in the recited catalytic conversion.

Butamax suggests that a broad construction is most consistent with the intrinsic evidence and skill in the art, namely, "an enzyme that is structurally similar to acetohydroxy acid isomeroreductase or ketal acid reductoisomerase ["KARI"] enzymes[1] known by the

---

[1] According to Butamax, "[t]he parties agree that 'acetohydroxy acid isomeroreductase' is synonymous with ketal acid isomeroreductase (KARI) and describes a class of enzymes that catalyzes the conversion of acetolactate (AL) to 2,3-dihydroxyisovalerate (DHIV)." (D.I. 492 at 9)

EC number 1.1.1.86[2] and that converts acetolactate to 2,3-dihydroxyisovalerate." (D.I. 492 at 9) Under this construction, to determine whether an enzyme literally meets the claim term, a skilled artisan would: (1) compare the enzyme's amino acid sequence to the sequences of known KARI enzymes having EC number 1.1.1.86 (D.I. 492 at 10; D.I. 494 at ¶ 45); and (2) test the enzyme for activity using a standard KARI assay, e.g., the assay described in a 1969 reference by Arfin & Umbarger[3] (D.I. 492 at 10; D.I. 495 at ¶¶ 41-43). According to Butamax, "[t]his two prong analysis, consistent with the intrinsic evidence, allows a skilled artisan to come to a conclusion that an enzyme literally meets the KARI claim element." (D.I. 492 at 10) With respect to the characterization in the specification relating to cofactor NADPH, Butamax explains that, because it was well known in 2005 and 2006 that KARI enzymes can use either NADPH or NADH as an electron donor (D.I. 494 at ¶ 36[4]), a construction limited

---

[2] The parties also agree that "EC number 1.1.1.86" refers to an "Enzyme Commission" number. (D.I. 492 at 9)

[3] "Arfin & Umbarger" is Stuart M. Arfin and H. Edwin Umbarger, *Purification and Properties of the Acetohydroxy Acid Isomeroreductase of* Salmonella typhimurium, 244(5) J. Biological Chemistry, 1118 (1969).

[4] Dr. Rabinowitz, one of Butamax's experts, avers that,

> [w]here the only cofactor in the environment is NADPH, such as in the Arfin & Umbarger assay, a KARI will use that cofactor exclusively because it is the only one present. Likewise, in a system where the only cofactor in the environment is NADH, that cofactor will be used exclusively. In environments like living yeast cells, both cofactors are present in varying concentrations. Therefore,

to enzymes that will use solely NADPH is inappropriate without strong evidence of a clear intent to redefine the term narrowly, or an unambiguous disavowal of the full scope of the claim term.

Gevo's proposed construction is more narrow, that is, "an enzyme which catalyzes the conversion of acetolactate to 2,3-dihydroxyisovalerate and that is solely NADPH-dependent (as opposed to NADH-dependent or NADH and NADPH-dependent), having the EC number 1.1.1.86." (D.I. 535 at 7) According to Gevo, its construction is most consistent with the intrinsic record, given that the patentees specifically included within its definition of "acetoydroxy acid isomeroreductase," EC nomenclature and the use of NADPH as an electron donor, and clearly knew how to describe the use of both NADH and NADPH as cofactors, as they did elsewhere in the specification. (D.I. 535)

> in such an environment, after each catalytic cycle, when the enzyme needs to bind another cofactor molecule, it will bind either NADPH or NADH. Which cofactor becomes bound at any one instance is random, but statistically both the concentration of the cofactor and the K_m for the cofactor will determine the aggregate cofactor binding.

(D.I. 494 at ¶ 36)

1. Intrinsic record

a. Prosecution history[5]

Claims 1, 4-8, 15-31 and 38 of the '188 patent were rejected by the examiner as failing to comply with the written description requirement, 35 U.S.C. § 112, first paragraph. (D.I. 508 at BJA 1482) It was the examiner's position that, while the specification described a genus of polypeptides catalyzing the reactions described in the pathway, the specification did not describe "any structural features, amino acid sequences, and/or biological functions that are commonly possessed by members of each claimed genus." (*Id.* at BJA 1484) The specification also failed to disclose "a representative number of species of each claimed genus, which includes many members with widely differing structural, chemical, and biological functions. There is no recognized correlation between any structure and catalytic activity of conversion of the substrates to products as recited in parts i) - v)." (*Id.*)

The patentees responded by amending claim 1 "to an isobutanol producing host cell comprising at least one nucleic acid molecule that encodes the enzymes listed in claim 1 **as now further limited to those enzymes possessing a specific Enzyme Commission (EC) number to the fourth level.** It is well known in the art that the Enzyme Commission numbering system categorizes enzymes based on the reactions they are able to perform. An enzyme classed

---

[5] The prosecution history for the '188 and '889 patents (D.I. 505-511) substantially track each other vis a vis the term in dispute. Therefore, the court will limit its references to the prosecution history of the '188 patent.

with an EC number to the fourth level is discretely and specifically classified on the basis of its function." (*Id.* at BJA 1653 (emphasis added)) The patentees further disclosed a method that was "able to discriminate between enzymes assigned to different EC numbers exhibiting distinct functions," thus "indicating a correlation between structural elements of enzyme binding pockets and their functional classification by EC number." (*Id.* at BJA 1654) In sum, the patentees submitted that "the specific guidance relating to the structure and physiochemical properties of enzymes that may be used in the invention [were] provided in the EC number of each enzyme." (*Id.* at BJA 1656)

The examiner also rejected the application on enablement grounds. In this regard, the patentees responded that "[a] patent need not teach, and preferably omits, what is well known in the art. . . Thus a claim is enabled if the specification **in combination** with what is well known in the art permits the skilled person to make and use the invention without undue experimentation." (*Id.* at BJA 1701-2) To illustrate their point, the patentees referred the examiner to a publicly available database and explained that, "[u]sing the BRENDA database, the skilled person, searching for the EC number for[, e.g.,] acetolactate synthase . . . would find corresponding enzymes catalyzing the conversion of pyruvate to acetolactate from 39 organisms. These polypeptides and the genes encoding them can be obtained from the recited organisms by methods well known in the art and without any excessive screening or additional guidance and used in the present invention." (*Id.* at BJA 1702)

The '188 patent ultimately issued on December 14, 2010. As noted by the patentees in the prosecution history, claim 1 was amended to "limit the enzyme terms to their corresponding EC numbers." (*Id.* at BJA 1652)

b. Specification

In addition to defining the enzymes of the pathway by their known EC numbers, the patentees added cofactor information to some of the definitions, including the one in dispute. For example, in defining the term "branched-chain alcohol dehydrogenase," the patentees instructed that "[p]referred branched-chain alcohol dehydrogenases are known by the EC number 1.1.1.265, but may also be classified under other alcohol dehydrogenases (specifically, EC 1.1.1.1 or 1.1.1.2)," and then noted that "[t]hese enzymes utilize NADH . . . and/or NADPH as electron donor." ('188 patent, 8:9-16; '889 patent, 7:49-56) Likewise, in defining the term "acylating aldehyde dehydrogenase," the patentees referred to an enzyme that "catalyzes the conversion of isobutyryl-CcA to isobutyraldehyde, using either NADH or NADPH as electron donor," with "preferred" enzymes "known by the EC numbers 1.2.1.10 and 1.2.1.57." ('188 patent, 8:44-48; '889 patent, 8:17-21) In addition, in defining the term "valine dehydrogenase," the patentees referred "to an enzyme that catalyzes the conversion of α-ketoisovalerate to L-valine using NAD(P)H as electron donor," instructing that "preferred" enzymes "are known by the EC numbers 1.4.1.8 and 1.4.1.9." ('188 patent, 9:9-11; '889 patent, 8:49-51) Finally, the patentees defined the term "branched-chain keto acid dehydrogenase" as "an enzyme that catalyzes the

conversion of α-ketoisovalerate to isobutyryl-CoA (isobutrl-coenzyme A), using NAD^+ (nicotinamide adenine dinucleotide) as electron acceptor," instructing that "preferred" enzymes are "known by the EC number 1.2.4.4." ('188 patent, 8:25-29; '889 patent, 7:65-8:3)

Claim 1 of the '188 patent includes the EC nomenclature for the enzymes of the pathway; claim 1 of the '889 patent does not. ('188 patent, 335:21-45; '889 patent, 325:16-42) Dependent claim 14 of the '889 patent refers to the method of claim 1, with the further limitation that "one or more enzymes of said engineered isobutanol biosynthetic pathway uses NADH as an electron donor." ('889 patent, 326:37-39)

2. Extrinsic evidence[6]

The term "cofactor" is generally understood to refer to an organic molecule that is required for certain enzymatically catalyzed reactions to proceed. Cofactors bind to enzymes as substrates of the enzymes that rely on them and are converted to products of the enzymatic reaction after it is completed. NADH and NADPH are two important and distinct cofactors that are also substrates. These cofactors act as electron donors and, in their oxidized forms (NAD^+ and $NADP^+$), as electron acceptors, respectively, in oxidation or reduction

[6] The court recognizes that extrinsic evidence generally is not considered in the claim construction exercise. Under the circumstances at bar, however, where the parties are disputing how those of skill in the art would interpret the definition provided by the patentees, the court finds it instructive, if not imperative, to consider expert testimony and the scientific literature referenced in the patent to illuminate the disputed language.

reactions. Enzymes that depend on them for catalytic activity are frequently termed NADH- or NADPH-dependent. (D.I. 537 at ¶¶ 8, 9)

NADH and NADPH have distinct chemical structures, with NADPH containing an additional phosphate group. This extra phosphate group allows NADPH "to be recognized selectively by the enzymes involved in biosynthesis;" thus, "'despite their close chemical resemblance,' NADH and NADPH are 'not metabolically interchangeable.'" (*Id.* at ¶¶ 4, 12 (citations omitted)) To put the point another way, "[t]he difference between NADH and NADPH is trivial in chemical terms, but it is crucial for their distinctive functions." (*Id.* at ¶ 11 (citation omitted))

"As of October 26, 2005, all natural KARI enzymes were known to be NADPH-dependent." (D.I. 537 at ¶ 40) Although "the limits of biology virtually guarantee that all KARI enzymes will have at least some ancillary activity with both cofactors," a person of ordinary skill in the art would understand that an enzyme that "uses NADPH" or that "uses NADH" is "NADPH-dependent" or "NADH-dependent", respectively. (*Id.* at ¶ 58)

The EC enzyme classification system was developed in the 1950s to provide international standards of nomenclature. According to the "second general principle" of the EC classification system, "enzymes are principally classified and named according to the reaction they catalyse. The chemical reaction catalysed is the specific property that distinguishes one enzyme from another, and it is logical to use it as the basis for the classification and naming of enzymes." (D.I. 496, ex. A at 5) Relevant to the dispute at bar is Rule 18 of

the EC nomenclature, which states that, "[f]or oxidoreductases using NAD^+ or $NADP^+$, the coenzyme should always be named as the acceptor[7] . . . Where the enzyme can use either coenzyme, this should be indicated by writing $NAD(P)^+$." (D.I. 496, ex. A at 18) Although some enzymes are classified based on their cofactor selectivity,[8] no unique EC numbers have been assigned to EC 1.1.1.86 to reflect this feature.

Examining EC 1.1.1.86, the chemical reaction that distinguishes this class of enzymes is described as "(*R*)-2,3-dihydroxy-3-methylbutanoate + $NADP^+$ = (*S*)-2-hydroxy-2-methyl-3-oxobutanoate + NADPH + H^+." (D.I. 496, ex. C) The IUBMB[9] Enzyme Nomenclature also includes four references[10] and links to other

---

[7] With an exception apparently not applicable here.

[8] *See, e.g.*, the EC nomenclature for some of the enzymes defined in the patents-in-suit, to wit: "EC 1.1.1.1 - alcohol dehydrogenase" (which only describes reactions using NAD+) compared with "EC 1.1.1.2 - alcohol dehydrogenase (NADP+)" (which only describes reactions using NADP+); and "EC 1.4.1.8 - valine dehydrogenase (NADP+)" (which only describes reactions using NADPH) compared with "EC 1.4.1.9 - leucine dehydrogenase" (which only describes reactions using NADH). (http://www.brenda-enzymes.info)

[9] The International Union of Biochemistry and Molecular Biology. (D.I. 495 at ¶ 17)

[10] "Hill" is Richard K. Hill and Seiji Sawada, *Stereochemistry of Valine and Isoleucine Biosynthesis*, 8 Bioorganic Chemistry, 175 (1979). "Kiritani" is Kiritani, et al., *The Reductoisomerase of* Neurospora crassa, 241(9) J. Biological Chemistry, 2047 (1966). "Satyanarayana" is T. Satyanarayana and A. N. Radhakrishnan, *Biosynthesis of Valine and Isoleucine in plants*, 110 Biochimica et

databases. With respect to the listed references: (1) Arfin & Umbarger, which describes a standard assay to identify a KARI enzyme in an environment where AL and NADPH are present (*id.*, ex. E; D.I. 492 at 10-11); (2) Hill, which studied the synthesis, configuration and enzymatic specificity of intermediates involved in the biosynthesis of isoleucine and valine, notes that "[a]ssays were performed by measuring the rate at which NADPH was oxidized, as described previously by Arfin & Umbarger" (D.I. 496, ex. F at 175-76, 181); (3) Kiritani, which sought to characterize the reductoisomerase involved in the isoleucine-valine pathway of *Neurospora crassa*, includes the observation that "NADPH is required for enzymatic activity, and NADH does not substitute" (D.I. 496, ex. G at 2047-48); and (4) Satyanarayana, which studied the properties of a reductoisomerase involved in the synthesis of valine and isoleucine in plants, used TPNH,[11] and states that no α-keto-β-hydroxy acids could be detected when "TPNH was omitted from the standard assay mixture" (*id.*, ex. H at 380-81, 387).

In looking at the enzyme entries for EC 1.1.1.86 found in the listed databases, one finds the following: (1) the ExPASy database entry describes the reaction catalyzed as one using NADPH (D.I. 497, ex. FF); (2) the KEGG database entry describes the reaction, the substrate, and the product in relation to NADPH or NADP+ (*id.*, ex. GG); (3) the PDB database entry

---

Biophysica Acta, 380 (1965).

[11] TPNH is an older notation form of NADPH. *See e.g.* http://pubchem.ncbi.nlm.nih.gov/.

describes reactions involving NADPH and NADP(+)[12] (*id.*, ex. HH); and (4) the BRENDA database entry likewise describes the reaction in relation to NADPH (*id.*, ex. D at 1).

Unlike the other databases identified in the IUBMB Enzyme Nomenclature, the BRENDA database includes information about specific activity, substrates, products, and organisms, with commentaries and multiple references to literature. In the 43 pages of information contained on the BRENDA database for EC 1.1.1.86, NADH is mentioned in only 16 entries, all of which refer to one or more of only five literature references.[13] (*Id.*, ex. D at 13-14, 22, 25, 28, 39-40) The five literature references are: (1) Arfin & Umbarger (reference 639169), as described above; (2) Kiritani (reference 639171), as described above; (3) Dumas

---

[12] The PDB database also includes the following diagram:

EC 1.-.-.- Oxidoreductases.

EC 1.1.-.- Acting on the CH-OH group of donors.

EC 1.1.1.- With NAD(+) or NADP(+) as acceptor.

EC 1.1 .1.86 Ketol-acid reductoisomerase.

[13] "Dumas (1989)" is Renaud Dumas et al., *Purification and Characterization of Acetohydroxyacid Reductoisomerase from Spinach Chloroplasts*, 262 Biochem. J., 971 (1989). "Dumas (1992)" is Renaud Dumas et al., *Isolation and Kinetic Properties of Acetohydroxy Acid Isomeroreductase from Spinach* (Spinacia oleracea) *Chloroplasts Overexpressed in* Escherichia coli, 288 Biochem. J., 865 (1992). "Rane" is Madhavi J. Rane and K. C. Calvo, *Reversal of the Nucleotide Specificity of Ketol Acid Reductoisomerase by Site-Directed Mutagenesis Identifies the NADPH Binding Site*, 338(1) Archives Biochemistry and Biophysics, 83 (1997).

(1989) (reference 639176), which includes the observation that "[t]he enzyme also utilized NADH as electron donor," but describes the reaction as an "NADPH-dependent reduction" and goes on to analyze how the enzyme was regulated by the NADPH/$NADP^+$ ratio (D.I. 497, ex. AA at 971, 974-975); (4) Dumas (1992) (reference 639176), which reiterates the earlier observation that "the over-expressed enzyme was able to use NADH as an electron donor," nevertheless, "the plant enzyme displays a very high selectivity for NADPH" (D. I. 538, ex. X at 870, 873); and (5) Rane (reference 639183), which started with the stated goal of "identify[ing] the positively charged amino acid(s) that confer NADPH specificity on KARI," and found that by altering four amino acids and constructing a "quadruplet mutant," "the specificity constants for NADH and NADPH are almost exactly reversed in the mutant relative to the wild type," i.e., the "mutant was changed from being a NADPH-specific dehydrogenase into a NADH specific enzyme" (D.I. 497, ex. BB).

In connection with the argument posed by Butamax that the specification "lists 'preferred' KARIs, denoted by EC 1.1.1.86, that have **significant activity with NADH,**" (D.I. 492 at 11 (emphasis added)), the one KARI enzyme identified in this regard is the *Methanococcus maripaludis* KARI ('188 patent, 7:46-47; '889 patent, 7:19-20) and the analysis of such KARI enzyme in a single reference, R. Xing. & W. Whitman, *Characterization of Enzymes of the Branched-Chain Amino Acid Biosynthetic Pathway in* Methanococcus *spp*, 173(6) J. Bacteriology 2086-2092 (1991). (D.I. 496, ex. K; *see* D.I. 492 at 11; D.I. 493 at ¶ 34; D.I. 494 at ¶¶ 39-40; D.I. 495 at ¶ 48) The authors of the reference observe that, "[w]hile the eubacterial and eucaryotic

AAIRs are NADPH specific, NADH supported 60% of the methanococcal activity obtained with NADPH." (D.I.496, ex. K at 2089) There is neither a reference nor data noted to support this assertion.

3. Analysis

The court starts with the premise that the claims and specification of a patent serve a public notice function, and that patentees who choose to provide definitions should be especially mindful of being their own lexicographers. *See, e.g., Johnson & Johnston Associates Inc. v. R.E. Service Co., Inc.*, 285 F.3d 1046, 1052 (Fed. Cir. 2002) (citing *Mahn v. Harwood*, 112 U.S. 354, 361 (1884)) (claims give notice to the public of the scope of the patent); *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994) (patentee choosing to define terms must do so "with reasonable clarity, deliberateness, and precision"). In this case, the patentees choose to define the KARI enzyme not only by reference to its EC classification, but by its "use" of NADPH. Having reviewed the scientific literature referenced through the patent's definitional language, the court finds the expert opinions proffered by Gevo (and, therefore, Gevo's proposed construction) to be more consistent with the intrinsic record.

In this regard, the scientific references almost exclusively characterize KARI enzymes as NADPH-dependent. Of the two references relied on by Butamax to support the use of NADH by KARI enzymes,[14] one (Xing) included a single conclusory sentence with no

[14] By "use," the court refers not to ancillary activity, but that the enzyme is NADH- or NADPH-dependent.

data or other literature references to support it, and the other (Rane) described having to construct a "quadruplet mutant" in order to change a KARI enzyme from being NADPH-dependent to being NADH-dependent.

Even if the court were to accept the proposition that those of skill in the art recognized in 2005 that the KARI enzyme known by EC number 1.1.1.86 could use NADH and/or NADPH as an electron donor, consistent with Butamax's position in this dispute, the question remains why the patentees choose then to include more limiting language in their definition. Butamax responds by arguing that NADPH was simply a known tool for identifying a KARI enzyme (referencing the Arfin & Umbarger standard assay), and co-factor usage was not meant to be a limiting physiochemical property of the enzyme.

The court declines, however, to make superfluous the patentees' description of the very reaction that is the defining characteristic of the KARI enzyme. In light of the record,[15] the patentees' definition of "acethydroxy acid isomeroreductase enzyme" simply reflects the state of the art, that is, that the KARI enzyme known by the EC number 1.1.1.86 was generally understood to be NADPH-dependent. That dependent claim 14 of the '889 patent calls out use of NADH is of no moment in this analysis, given that more than one of the enzymes

---

[15] Including, but not limited to, the fact that NADH and NADPH are different in terms of structure and function and, even if (or especially if) it was well known in the art that KARI enzymes could "use" either NADH or NADPH or both, the patentees knew how to describe that and choose not to.

of the claimed pathway were defined by the patentees as using NADH as an electron donor. ('889 patent, 7:54-56, 7:67-8:1, 8:19, 51)

4. Conclusion

For the reasons stated above, the court concludes that a person of ordinary skill in the art would understand "acetohydroxy acid isomeroreductase" to be "an enzyme known by the EC number 1.1.1.86 that catalyzes the conversion of acetolactate to 2,3-dihydroxyisovalerate and is NADPH-dependent."

C. Other Terms of the '889 Patent

1. "[A] recombinant yeast micoorganism expressing an engineered isobutanol biosynthetic pathway"

The court construes this term to mean "a recombinant yeast microorganism that is genetically transformed such that it expresses the five enzymes that form the biosynthetic pathway described hereafter for the production of isobutanol, wherein one or more of those enzymes is recombinantly expressed."

Butamax does not contend that all five enzymes in the "engineered isobutanol biosynthetic pathway" must be recombinantly expressed and Gevo asserts that "the patent contemplates engineered pathways where only one or more of the enzymes are recombinantly expressed." (D.I. 492 at 26; D.I. 535 at 27) The court's construction resolves any ambiguity in this regards. According to Butamax, "[t]he parties' only apparent substantive dispute regarding this term is whether it should be construed to require carbon flow through pathway steps a-e recited later in the claim." (D.I. 552

at 12) Gevo argues that Butamax's construction is ambiguous and that "the patent recites several different pathways for isobutanol production." (D.I. 535 at 28) The court finds that the remaining language of the claim resolves this dispute. In other words, the entire phrase "a recombinant yeast micoorganism expressing an engineered isobutanol biosynthetic pathway . . . **wherein said pathway comprises the following substrate to product conversions"** instructs that the "engineered isobutanol biosynthetic pathway" is in fact the pathway described in the following steps a-e. ('889 patent, 325:19-22 (emphasis added))

2. "([P]athway step a); . . . (pathway step b); . . . ," etc.

The court construes this term to mean "the pathway steps a-e are contiguous steps such that the product of step a is the substrate for step b; the product of step b is the substrate for step c; etc." The court recognizes that the term "comprising" recited in the introductory language "raises a presumption that the list of elements is nonexclusive." *Dippin' Dots, Inc. v. Mosey*, 476 F.3d 1337, 1343 (Fed. Cir. 2007). However, the court agrees with Butamax that the intrinsic evidence demonstrates the patentees' intent that the addition of intermediate steps to the preferred claim 1 pathway forms a different pathway that is outside the scope of the claim and that the claim's use of "comprising" reflects that the claimed pathway can be used as part of a larger process, and additional steps might be performed before or after without avoiding infringement. (D.I. 492 at 28-29) This construction is not inconsistent with *Dippin' Dots*, wherein the Federal

Circuit declares that the enumerated steps "must . . . all be practiced as recited in the claim for a process to infringe." *Id.*

3. "The microorganism produces isobutanol as a single product"

The parties agree that any fermentation process produces more than one single product.[16] (D.I. 552 at 15) Butamax reasons that one skilled in the art would understand this term to mean producing "predominantly one product." (D.I. 552 at 15) This reasoning is consistent with distinguishing the production of isobutanol as a primary product with production of by-products or as part of a mixture. The court construes this term to mean "[t]he microorganism produces isobutanol without substantial amounts of other fermentation products."

IV. STANDARDS OF REVIEW

A. Summary Judgment

"The court shall grant summary judgment if the movant shows that there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(a). The moving party bears the burden of demonstrating the absence of a genuine issue of material fact. *Matsushita Elec. Indus. Co. v. Zenith Radio Corp.*, 415 U.S. 574, 586 n.10 (1986). A party asserting that a fact cannot be—or, alternatively, is—genuinely disputed must

---

[16] The court notes that Gevo acknowledges that any fermentation process produces more than one single product in its later filings. (D.I. 623 at 54; *see infra* part IV.B.3.a.)

support the assertion either by citing to "particular parts of materials in the record, including depositions, documents, electronically stored information, affidavits or declarations, stipulations (including those made for the purposes of the motions only), admissions, interrogatory answers, or other materials," or by "showing that the materials cited do not establish the absence or presence of a genuine dispute, or that an adverse party cannot produce admissible evidence to support the fact." Fed. R. Civ. P. 56(c)(1)(A) & (B). If the moving party has carried its burden, the nonmovant must then "come forward with specific facts showing that there is a genuine issue for trial." *Matsushita*, 415 U.S. at 587 (internal quotation marks omitted). The court will "draw all reasonable inferences in favor of the nonmoving party, and it may not make credibility determinations or weigh the evidence." *Reeves v. Sanderson Plumbing Prods., Inc.*, 530 U.S. 133, 150 (2000).

To defeat a motion for summary judgment, the nonmoving party must "do more than simply show that there is some metaphysical doubt as to the material facts." *Matsushita*, 475 U.S. at 586-87; *see also Podohnik v. U.S. Postal Service*, 409 F.3d 584, 594 (3d Cir. 2005) (stating party opposing summary judgment "must present more than just bare assertions, conclusory allegations or suspicions to show the existence of a genuine issue") (internal quotation marks omitted). Although the "mere existence of some alleged factual dispute between the parties will not defeat an otherwise properly supported motion for summary judgment," a factual dispute is genuine where "the evidence is such that a reasonable jury could return a verdict for the nonmoving party."

Anderson v. Liberty Lobby, Inc., 411 U.S. 242, 247-48 (1986). "If the evidence is merely colorable, or is not significantly probative, summary judgment may be granted." *Id.* at 249-50 (internal citations omitted); *see also Celotex Corp. v. Catrett*, 411 U.S. 317, 322 (1986) (stating entry of summary judgment is mandated "against a party who fails to make a showing sufficient to establish the existence of an element essential to that party's case, and on which that party will bear the burden of proof at trial").

B. Infringement

A patent is infringed when a person "without authority makes, uses or sells any patented invention, within the United States . . . during the term of the patent." 35 U.S.C. § 271 (a). A two-step analysis is employed in making an infringement determination. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995). First, the court must construe the asserted claims to ascertain their meaning and scope. *See id.* Construction of the claims is a question of law subject to de novo review. *See Cybor Corp. v. FAS Techs.*, 138 F.3d 1448, 1454 (Fed. Cir. 1998). The trier of fact must then compare the properly construed claims with the accused infringing product. *See Markman*, 52 F.3d at 976. This second step is a question of fact. *See Bai v. L & L Wings, Inc.*, 160 F.3d 1350, 1353 (Fed. Cir. 1998).

"Direct infringement requires a party to perform each and every step or element of a claimed method or product." *BMC Res., Inc. v. Paymentech, L.P.*, 498 F.3d 1373, 1378 (Fed. Cir. 2007), *overruled on other grounds by* 692 F.3d 1301 (Fed. Cir. 2012). "If any claim limitation is absent from the accused device, there is no

literal infringement as a matter of law." *Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241, 1247 (Fed. Cir. 2000). If an accused product does not infringe an independent claim, it also does not infringe any claim depending thereon. *See Wahpeton Canvas Co. v. Frontier, Inc.*, 870 F.2d 1546, 1553 (Fed. Cir. 1989). However, "[o]ne may infringe an independent claim and not infringe a claim dependent on that claim." *Monsanto Co. v. Syngenta Seeds, Inc.*, 503 F.3d 1352, 1359 (Fed. Cir. 2007) (quoting *Wahpeton Canvas*, 870 F.2d at 1552) (internal quotations omitted). A product that does not literally infringe a patent claim may still infringe under the doctrine of equivalents if the differences between an individual limitation of the claimed invention and an element of the accused product are insubstantial. *See Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 24, 117 S. Ct. 1040, 137 L. Ed. 2d 146 (1997). The patent owner has the burden of proving infringement and must meet its burden by a preponderance of the evidence. *See Smith Kline Diagnostics, Inc. v. Helena Lab. Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988) (citations omitted).

When an accused infringer moves for summary judgment of non-infringement, such relief may be granted only if one or more limitations of the claim in question does not read on an element of the accused product, either literally or under the doctrine of equivalents. *See Chimie v. PPG Indus., Inc.*, 402 F.3d 1371, 1376 (Fed. Cir. 2005); *see also TechSearch, L.L.C. v. Intel Corp.*, 286 F.3d 1360, 1369 (Fed. Cir. 2002) ("Summary judgment of noninfringement is . . . appropriate where the patent owner's proof is deficient in meeting an essential part of the legal standard for infringement, because such failure will render all other

facts immaterial."). Thus, summary judgment of non-infringement can only be granted if, after viewing the facts in the light most favorable to the non-movant, there is no genuine issue as to whether the accused product is covered by the claims (as construed by the court). *See Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1304 (Fed. Cir. 1999).

For there to be infringement under the doctrine of equivalents, the accused product or process must embody every limitation of a claim, either literally or by an equivalent. *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 41 (1997). An element is equivalent if the differences between the element and the claim limitation are "insubstantial." *Zelinski v. Brunswick Corp.*, 185 F.3d 1311, 1316 (Fed. Cir. 1999). One test used to determine "insubstantiality" is whether the element performs substantially the same function in substantially the same way to obtain substantially the same result as the claim limitation. *See Graver Tank & Mfg. Co. v. Linde Air Products Co.*, 339 U.S. 605, 608 (1950). This test is commonly referred to as the "function-way-result" test. The mere showing that an accused device is equivalent overall to the claimed invention is insufficient to establish infringement under the doctrine of equivalents. The patent owner has the burden of proving infringement under the doctrine of equivalents and must meet its burden by a preponderance of the evidence. *See SmithKline Diagnostics, Inc. v. Helena Lab. Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988) (citations omitted).

The doctrine of equivalents is limited by the doctrine of prosecution history estoppel. In *Festo Corp.*

v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd., 535 U.S. 722 (2002), the Supreme Court stated:

> Prosecution history estoppel ensures that the doctrine of equivalents remains tied to its underlying purpose. Where the original application once embraced the purported equivalent but the patentee narrowed his claims to obtain the patent or to protect its validity, the patentee cannot assert that he lacked the words to describe the subject matter in question. The doctrine of equivalents is premised on language's inability to capture the essence of innovation, but a prior application describing the precise element at issue undercuts that premise. In that instance the prosecution history has established that the inventor turned his attention to the subject matter in question, knew the words for both the broader and narrower claim, and affirmatively chose the latter.

Id. at 734-735. In other words, the prosecution history of a patent, as the public record of the patent proceedings, serves the important function of identifying the boundaries of the patentee's property rights. Once a patentee has narrowed the scope of a patent claim as a condition of receiving a patent, the patentee may not recapture the subject matter surrendered. In order for prosecution history estoppel to apply, however, there must be a deliberate and express surrender of subject matter. *See Southwall Tech., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1580 (Fed. Cir. 1995).

Once a court has determined that prosecution history estoppel applies, it must determine the scope of

the estoppel. *See id.* at 1580. This requires an objective examination into the reason for and nature of the surrendered subject matter. *Id.*; *see also Augustine Med., Inc. v. Gaymar Indus., Inc.*, 181 F.3d 1291, 1299 (Fed. Cir. 1999). If one of ordinary skill in the art would consider the accused product to be surrendered subject matter, then the doctrine of equivalents cannot be used to claim infringement by the accused product; i.e., prosecution history estoppel necessarily applies. *Augustine Med.*, 181 F.3d at 1298. In addition, a "patentee may not assert coverage of a 'trivial' variation of the distinguished prior art feature as an equivalent." *Id.* at 1299 (quoting *Litton Sys., Inc. v. Honeywell, Inc.*, 140 F.3d 1449, 1454 (Fed. Cir. 1998)).

C. Invalidity

1. Anticipation

An anticipation inquiry involves two steps. First, the court must construe the claims of the patent in suit as a matter of law. *Key Pharms. v. Hercon Labs Corp.*, 161 F.3d 709, 714 (Fed. Cir. 1998). Second, the finder of fact must compare the construed claims against the prior art. *Id.* A finding of anticipation will invalidate the patent. *Applied Med. Res. Corp. v. U.S. Surgical Corp.*, 147 F.3d 1374, 1378 (Fed. Cir. 1998).

Under 35 U.S.C. § 102(b), "[a] person shall be entitled to a patent unless the invention was patented or described in a printed publication in this or a foreign country . . . more than one year prior to the date of the application for patent in the United States." The Federal Circuit has stated that "[t]here must be no difference between the claimed invention and the referenced disclosure, as viewed by a person of ordinary

skill in the field of the invention." *Scripps Clinic & Research Found. v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991). In determining whether a patented invention is explicitly anticipated, the claims are read in the context of the patent specification in which they arise and in which the invention is described. *Glaverbel Societe Anonyme v. Northlake Mktg. & Supply, Inc.*, 45 F.3d 1550, 1554 (Fed. Cir. 1995). The prosecution history and the prior art may be consulted if needed to impart clarity or to avoid ambiguity in ascertaining whether the invention is novel or was previously known in the art. *Id.* The prior art need not be ipsissimis verbis (i.e., use identical words as those recited in the claims) to be anticipating. *Structural Rubber Prods. Co. v. Park Rubber Co.*, 749 F.2d 707, 716 (Fed. Cir. 1984).

A prior art reference also may anticipate without explicitly disclosing a feature of the claimed invention if that missing characteristic is inherently present in the single anticipating reference. *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991). The Federal Circuit has explained that an inherent limitation is one that is necessarily present and not one that may be established by probabilities or possibilities. *Id.* That is, "[t]he mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id.* The Federal Circuit also has observed that "[i]nherency operates to anticipate entire inventions as well as single limitations within an invention." *Schering Corp. V. Geneva Pharms. Inc.*, 339 F.3d 1373, 1380 (Fed. Cir. 2003). Moreover, recognition of an inherent limitation by a person of ordinary skill in the art before the critical date is not required to establish inherent anticipation. *Id.* at 1377.

2. Obviousness

"A patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a). Obviousness is a question of law, which depends on underlying factual inquiries.

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.

KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 406 (2007) (quoting *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)).

"[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 550 U.S. at 418. Likewise, a defendant asserting obviousness in view of a combination of references has the burden to show that a person of ordinary skill in the relevant field had a reason to combine the elements in the manner claimed. *Id.* at

418-19. The Supreme Court has emphasized the need for courts to value "common sense" over "rigid preventative rules" in determining whether a motivation to combine existed. *Id.* at 419-20. "[A]ny need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420. In addition to showing that a person of ordinary skill in the art would have had reason to attempt to make the composition or device, or carry out the claimed process, a defendant must also demonstrate that "such a person would have had a reasonable expectation of success in doing so." *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007).

A combination of prior art elements may have been "obvious to try" where there existed "a design need or market pressure to solve a problem and there [were] a finite number of identified, predictable solutions" to it, and the pursuit of the "known options within [a person of ordinary skill in the art's] technical grasp" leads to the anticipated success. *Id.* at 421. In this circumstance, "the fact that a combination was obvious to try might show that it was obvious under § 103." *Id.* Federal Circuit precedent has also established that "[s]tructural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds," and that particular types of structural similarity can give rise to a case of prima facie obviousness. *Genetics Institute, LLC v. Novartis Vaccines and Diagnostics, Inc.*, 655 F.3d 1291, 1312 (Fed. Cir. 2011) (citing *In re Deuel*, 51 F.3d 1552,1558 (Fed. Cir. 1995)).

A court is required to consider secondary considerations, or objective indicia of nonobviousness, before reaching an obviousness determination, as a "check against hindsight bias." *See In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1079 (Fed. Cir. 2012). "Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1966).

"Because patents are presumed to be valid, *see* 35 U.S.C. § 282, an alleged infringer seeking to invalidate a patent on obviousness grounds must establish its obviousness by facts supported by clear and convincing evidence." *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 968 (Fed. Cir. 2006) (citation omitted). In conjunction with this burden, the Federal Circuit has explained that,

> [w]hen no prior art other than that which was considered by the PTO examiner is relied on by the attacker, he has the added burden of overcoming the deference that is due to a qualified government agency presumed to have properly done its job, which includes one or more examiners who are assumed to have some expertise in interpreting the references and to be familiar from their work with the level of skill in the art and whose duty it is to issue only valid patents.

PowerOasis, Inc. v. T-Mobile USA, Inc., 522 F.3d 1299, 1304 (Fed. Cir. 2008) (quoting *Am. Hoist & Derrick Co. v. Sowa & Sons*, 725 F.2d 1350, 1359 (Fed. Cir. 1984)).

3. Written description

a. Indefiniteness

The definiteness requirement is rooted in § 112, ¶ 2, which provides that "the specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." "A determination of claim indefiniteness is a legal conclusion that is drawn from the court's performance of its duty as the construer of patent claims." *Personalized Media Comm., LLC v. Int'l Trade Com'n*, 161 F.3d 696, 705 (Fed. Cir. 1998).

> Determining whether a claim is definite requires an analysis of whether one skilled in the art would understand the bounds of the claim when read in light of the specification . . . If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more.

Id. (citing *Miles Lab., Inc. v. Shandon, Inc.*, 997 F.2d 870, 875 (Fed. Cir. 1993)).

b. Enablement and written description

The statutory basis for the enablement and written description requirements, § 112 ¶ 1, provides in relevant part:

> 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 is met where one skilled in the art, having read the specification, could practice the invention without 'undue experimentation.'" *Streck, Inc. v. Research & Diagnostic Systems, Inc.*, 665 F.3d 1269, 1288 (Fed. Cir. 2012) (citation omitted). "While every aspect of a generic claim certainly need not have been carried out by the inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997). The specification need not teach what is well known in the art. *Id.* (citing *Hybritech v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986)). A reasonable amount of experimentation may be required, so long as such experimentation is not "undue." *ALZA Corp. v. Andrx Pharms., Inc.*, 603 F.3d 935, 940 (Fed. Cir. 2010).

"Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." *Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1378 (Fed. Cir. 2009) (citing *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). The Federal Circuit has provided several factors that may be utilized in determining whether a disclosure would

require undue experimentation: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance disclosed in the patent; (3) the presence or absence of working examples in the patent; (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 of the art; and (8) the breadth of the claims. *In re Wands*, 858 F.2d at 737. These factors are sometimes referred to as the "*Wands* factors." A court need not consider every one of the *Wands* factors in its analysis, rather, a court is only required to consider those factors relevant to the facts of the case. *See Streck, Inc.*, 655 F.3d at 1288 (citing *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991)).

The enablement requirement is a question of law based on underlying factual inquiries. *See Green Edge Enters., LLC v. Rubber Mulch Etc., LLC*, 620 F.3d 1287, 1298-99 (Fed. Cir. 2010) (citation omitted); *Wands*, 858 F.2d at 737. Enablement is determined as of the filing date of the patent application. *In re '318 Patent Infringement Litigation*, 583 F.3d 1317, 1323 (Fed. Cir. 2009) (citation omitted). The burden is on one challenging validity to show, by clear and convincing evidence, that the specification is not enabling. *See Streck, Inc.*, 665 F.3d at 1288 (citation omitted).

A patent must also contain a written description of the invention. 35 U.S.C. § 112, ¶ 1. The written description requirement is separate and distinct from the enablement requirement. *See Ariad Pharms., Inc. v. Eli Lilly and Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2011). It ensures that "the patentee had possession of the claimed invention at the time of the application,

i.e., that the patentee invented what is claimed." *LizardTech, Inc. v. Earth Resource Mapping, Inc.*, 424 F.3d 1336, 1344-45 (Fed. Cir. 2005). The Federal Circuit has stated that the relevant inquiry – "possession as shown in the disclosure" – is an "objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art. Based on that inquiry, the specification must describe an invention understandable to that skilled artisan and show that the inventor actually invented the invention claimed." *Ariad*, 598 F.3d at 1351.

This inquiry is a question of fact: "the level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology." *Id.* (citation omitted). In this regard, Gevo must provide clear and convincing evidence that persons skilled in the art would not recognize in the disclosure a description of the claimed invention. *See PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1306-17 (Fed. Cir. 2008) (citation omitted). While compliance with the written description requirement is a question of fact, the issue is "amenable to summary judgment in cases where no reasonable fact finder could return a verdict for the non-moving party." *Id.* at 1307 (citing *Invitrogen Corp. v. Clontech Labs., Inc.*, 429 F.3d 1052, 1072-73 (Fed. Cir. 2005)).

V. DISCUSSION

A. Infringement

The court starts its infringement analysis of claim 1 of both patents-in-suit with the term "acetohydroxy

acid isomeroreductase," construed by the court as "NADPH-dependent." Butamax contends that Gevo's lead strains are similar to KARIs having E.C. number 1.1.1.86 and catalyze the AL to DHIV conversion.[17] (D.I. 596 at 18, 20) Butamax makes the following usage arguments in light of its alternative claim construction, which includes "using NADPH as an electron donor."[18] (D.I. 596 at 31; D.I. 648 at 30) Gevo's lead strains "use NADPH at values similar to or greater than several wild-type KARIs from other bacteria." (D.I. 596 at 20 (emphasis omitted); D.I. 648 at 30) For instance, the patents-in-suit identify a specific activity of 0.026 units/mg with an enzyme having KARI activity.[19] (D.I.

---

[17] Butamax specifically references Gevo's strains P2D1A and SE26E6. (D.I. 596 at 17) Butamax's experts analyzed the P2D1A1 enzyme and found that the "sequence is 99% identical to several . . . KARI enzymes . . . having E.C. number 1.1.1.86." (*Id.* at 19)

[18] Although the court is most interested in Butamax's arguments under a "NADH-dependent" construction, Butamax's usage arguments are considered for completeness. In its opening brief, Butamax does not address infringement under Gevo's proposed construction. (D.I. 596) Butamax responded to Gevo's summary judgment motion of non-infringement, argued primarily from a standpoint that Gevo's claim construction of acetohydroxy acid reductoisomerase as "solely NADPH dependent" is correct (D.I. 611), by arguing for its proposed claim construction (D.I. 648). Butamax chooses to offer the following unsupported argument if Gevo's claim construction is adopted: "Even under Gevo's claim construction, there are genuine issues of material fact precluding summary judgment of non-infringement, as both parties' experts agree a KARI's use of NADPH is insubstantially different than use of NADH." (D.I. 648 at 32)

[19] For this proposition, Butamax cites to example 10, which describes a method for cloning and expression of acetohydroxy acid

648 at 30 (citing '889 patent, 35:2-9 and '188 patent, 39:5-10)) Butamax then compares this specific activity to several values disclosed in Gevo's patents and published data, concluding that the data "prove[s the] activity with NADPH exceeds the 0.026 units/mg disclosed in the Butamax patents."[20] (D.I. 648 at 30 (emphasis omitted)) Butamax asserts "that P2D1A1 and SE26E6 have statistically significant activity with NADPH, which follows a dose response," based on its expert's experiments.[21] (D.I. 596 at 21) Butamax further argues that Gevo's KARI enzymes "can use NADH or NADPH, as they have roughly equivalent specific activity with use of either cofactor." (D.I. 648 at 31) To support this statement, Butamax cites to Gevo's published data showing a 6 to 1 and 8 to 1 preference for NADH to NADPH for SE26E6 and P2D1A1 strains, respectively, determined using specific activities. (D.I. 648 at 31) Butamax concludes that this difference is not enough to define Gevo's KARIs as NADH-

---

reductoisomerase in *E. coli*. The activity of enzyme was then measured in the cell free extracts. ('889 patent, 34:45-35:9 and '188 patent, 38:45-39:10) 'Three hours after induction with IPTG, an acetohydroxy acid reductoisomerase activity of 0.026 units/mg was detected." ('889 patent, 35:2-9 and '188 patent, 39:5-10)

[20] Butamax cites a Gevo patent indicating specific activities of 0.15 U/mg and 0.1 U/mg for P2D1A1 and SE26E6 respectively. (D.I. 648 at 30)

[21] Butamax's expert, Dr. Brown, used assays as described by Arfin & Umbarger. (D.I. 596 at 21; D.I. 648 at 31 & n.16; D.I. 649, ex. MMMM at ¶¶ 13-19 and NNNN at 166-71)

dependent, comparing the difference to Dr. Kirsh's "gray area" in cofactor usage.[22] (D.I. 648 at 31)

In response, Gevo asserts that its strains are NADH-dependent and do not infringe Butamax's patents. (D.I. 611 at 34-39) Citing to the same set of published data as Butamax, but relying on kinetic data,[23] Gevo asserts that the SE26E6 "enzyme has a catalytic efficiency for NADH that is 172-fold higher than its catalytic efficiency for NADPH." (D.I. 611 at 38) Gevo maintains that its strains show some ancillary usage of NADPH, but disputes Butamax's characterization and testing of the usage of NADPH by its strains. (D.I. 611 at 47-48) To refute Dr. Brown's

---

[22] Gevo's expert, Dr. Kirsh, testified that an enzyme that "use[d] exclusively or nearly exclusively NADH as opposed to NADPH" would show usage "at some level between 50 percent and 100 percent." He further testified that "70/30" would be "fairly interchangeable" and there would be a "gray area" that "[w]ell, the gray area might be between discriminations of 3 to 1 and 10 to 1, perhaps." (D.I. 648 at 31; D.I. 597, ex. A at 380:18-381:25) Importantly, Dr. Kirsh was contemplating a competitive binding experiment when describing enzymes using nearly exclusively NADPH. (D.I. 597, ex. A at 386)

[23] Gevo supports the statement that its strains are NADH dependent with data and measurements "of K_{cat}/K_m, referred to as the 'catalytic efficiency' of an enzyme." (D.I. 611 at 34-39; D.I. 612 at ¶¶ 49, 89) This measurement and the use of K_m is present in many of the references cited by both parties. *See, e.g.,* Carol Larroy et al., *Characterization of the* Saccharomyces cerevisiae *YMR318C (ADH6) gene product as a broad specificity NADPH-dependent alcohol dehydrogenase: relevance in aldehyde reduction,* 361(1) Biochemical J., 163 (2002) ("Larroy 2002"); Kiritani; Dumas (1992 and 1989); Xing; and, BRENDA database. Butamax's expert, Dr. Rabinowitz, used K_m. *See supra* note 4.

conclusions from his experiments, Gevo argues that Dr. Brown used different parameters to run the Arfin & Umbarger assay and engineered the parameters to "force the assay to produce his desired results."[24] (D.I. 611 at 47-48)

As is often the case, the parties to this dispute rely on different data obtained by different means to illustrate their respective infringement arguments. Butamax supports its infringement position with three sources of data: (1) the 0.026 units/mg value taken from a single experiment in *E. coli,* the purpose of which was not related to determining NADH/NADPH dependency; (2) Dr. Brown's assay showing statistically significant activity with NADPH; and (3) Gevo's published data showing a 6 to 1 (for strain SE26E6) and 8 to 1 (for strain P2D1A1) preference for NADH to NADPH, using specific activities. In contrast, Gevo's expert disputes both the design of Dr. Brown's assay and the interpretation of the results. Further, using the same published data, Gevo has compared the catalytic efficiencies of its lead strains as between NADH and NADPH, demonstrating a 172-fold difference in efficiency for NADH.

While Butamax's evidence of infringement is less than compelling, nonetheless, the court finds it sufficient to withstand Gevo's motion for summary judgment, as it raises genuine issues of material fact as to how a person of ordinary skill in the art at the time

---

[24] Dr. Brown testified that he used higher amounts of enzyme and lower temperatures to perform his assay than as described in the Arfin & Umbarger assay. (D.I. 611 at 47-48; D.I. 613 at ex. 73 at 148: 2-4; 148:19-149: 9; 130:19-25)

the invention was made would determine NADH-dependency.[25] Therefore, the parties' motions for summary judgment are denied in this regard.

Gevo also moves for summary judgment of no infringement under the doctrine of equivalents, asserting that its NADH-dependent enzyme is not equivalent to an NADPH-dependent enzyme. (D.I. 610; D.I. 611 at 43-44) Butamax alleges that the doctrine of equivalents should apply because "the use of NADH as an electron donor is insubstantially different from the use of NADPH." (D.I 648 at 33) For the reasons discussed above in claim construction, the court does not agree that NADH and NADPH are insubstantially different.[26] *See supra* part III.B; *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 955-56 (Fed. Cir. 2006)

---

[25] The court notes that metabolic engineering, including cofactor engineering, is a recognized area of research. (*See, eg.*, D.I. 603 ex. 17, Stephanopoulos et al, *Metabolic Engineering: Principles and Methodologies* (1998)); *see also*, Sonia Cortassa et al., *An Introduction To Metabolic And Cellular Engineering* (2d ed. 2012); *The Metabolic Pathway Engineering Handbook: Fundamentals* (Christina Smolke, ed., 1st ed. 2010). In this research area, cofactor dependency is extensively analyzed. The term of art, cofactor-dependent (i.e., NADPH-dependent and NADH-dependent), is replete in the scientific literature, the EC databases, and in the parties' references. (*See, e.g.*, Larroy (2002 and 2003); Dumas (1989 and 1992); Xing; and BRENDA database) However, the court does not find a quantification for this term in the parties' documents and, therefore, does not define it herein, but leaves the explanation of this term of art at trial to the parties' scientific experts.

[26] For example, a quadruple mutant was needed in order to change an enzyme from NADPH-dependent to NADH-dependent. *See supra* part III.B.2.

(holding that a patented device claiming a particular part with a convex shape was not infringed under the doctrine of equivalents by a similar device using a part with a concave shape, even though the device could function with either a convex or concave portion); *Novartis Pharms. Corp. v. Eon Labs Mfg., Inc.*, 363 F.3d 1306, 1312 (Fed. Cir. 2004) (affirming summary judgment of no infringement under the doctrine of equivalents because this would vitiate one of the claimed requirements of the patent); *Zelinski v. Brunswick Corp.*, 185 F.3d 1311, 1317 (Fed. Cir. 1999) (finding that the district court's grant of summary judgment was proper where the only evidence on infringement under the doctrine of equivalents was a conclusory statement of plaintiff's expert). The court grants Gevo's summary judgment of no infringement under the doctrine of equivalents.[27]

B. Invalidity

1. Anticipation

Gevo contends that the '889 patent is invalid as anticipated. (D.I. 598) More specifically, claim 1 is expressly and inherently anticipated by Larroy (2003) and inherently anticipated by Yocum and Elischweski.[28] (D.I. 599 at 11) Gevo begins with the

---

[27] The court declines to address prosecution history estoppel, having found that there is no plausible doctrine of equivalents argument.

[28] Larroy (2003)" is Carol Larroy et al., *Properties and functional significance of* Saccharomyces cerevisiae *ADHVI*, 143-144 Chemico-Biological Interactions, 229-238 (2003). "Elischweski" is Elischweski et al., U.S. Patent No. 6,787,334, issued September 7,

assertion that "[t]he existence and operation of the five-step isobutanol biosynthetic pathway recited in [claim 1] was known in yeast . . . for decades." (D.I. 599 at 3) Production of isobutanol is an inherent property of the recombinant yeast, as evidenced by references showing isobutanol production in non-recombinant yeast. (D.I. 9-10) Further, Gevo argues that "the prior art included many references that disclosed yeast microorganisms that recombinantly expressed one or more enzymes of the claimed five-step pyruvate-to-isobutanol pathway." (D.I. 599 at 11) Larroy (2003) expressly discloses the production of isobutanol by a recombinantly engineered enzyme. (D.I. 599 at 12-13) Yocum and Elischweski also disclose the construction of recombinant yeast, which overexpress certain of the five enzymes. (D.I. 599 at 15-16) Gevo contends that the references do not have to demonstrate isobutanol production, as anticipation requires only an enabling disclosure. (D.I. 650 at 12, 16) Gevo asserts that even under the court's construction that the pathway is contiguous, these three references inherently anticipate claim 1. (D.I. 599 at 17-18)

Butamax responds that none of these references describes expression of all five enzymes identified in the five-step biosynthetic pathway disclosed in claim 1. (D.I. 623 at 32) Moreover, there is no evidence that yeast in general, or in the prior art references, "necessarily" produce isobutanol, let alone through the five-step pathway. (D.I. 623 at 33-34) Butamax asserts that Gevo's evidence through three references regarding natural, nonrecombinant yeast cannot be

---

2004. "Yocum" is Yocum et al., U.S. Patent Application Publication No. 2004/0146996 A1, published July 29, 2004.

used to show that genetically engineered yeast in the prior art would inherently produce isobutanol through the five-step pathway, thus defeating inherency. (D.I. 623 at 36-37) Butamax's expert explains that even if all the enzymes have been characterized in native yeast, this does not establish that they work together in a five-step biosynthetic pathway in recombinant yeast because the enzymes must be expressed properly at the same time and in the same place for this to occur. (D.I. 623 at 39, 45) Similarly, Butamax argues that Yocum and Elischweski teach the genetic manipulation of microorganisms for the production of pantothenate, not isobutanol. (D.I. 623 at 45-50) For both of these references, Butamax argues that Gevo improperly seeks to rely on post-filing references as another layer to complete its theory. (D.I. 623 at 48-49)

The court recognizes that the prior art discloses that isobutanol is produced during fermentation. Indeed, Larroy (2003) expressly discloses isobutanol production as a product of recombinant yeast fermentation. The court has construed the term "engineered isobutanol pathway" to require that one or more enzymes in the pathway be engineered. The prior art references disclose genetically engineering one or more enzymes in the pathway. Butamax's argument that the references do not specifically disclose isobutanol production is of no consequence as inherency does not require recognition of the inherent element before the critical date. *Crown Packaging Tech., Inc. v. Ball Metal Beverage Container Corp.*, 635 F.2d 1373, 1383 (Fed. Cir. 2011) (citations omitted); *accord Schering Corp. v. Geneva Pharms. Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003). The court finds that Gevo has raised a substantial question regarding whether claim 1 is

inherently anticipated by the prior art. There remain factual disagreements between the parties, however, as to whether the references disclose each and every claim limitation sufficient to find inherent anticipation. As the court must draw all reasonable inferences in favor of Butamax, the court denies Gevo's motion for summary judgment of invalidity as to claim 1 of the '889 patent. For the same reasons, the court also denies Butamax's summary judgment motion of no anticipation.

2. Obviousness

Gevo contends that claims 1-4, 13-15, 17-25, and 34-36 of the '188 patent and claims 1-7, 9-11, 12, 14-19 of the '889 patent are invalid for obviousness in view of the combination of Boulton[29] with other prior art references.[30] Butamax asserts that Gevo's obviousness arguments do not rest on "analogous art." (D.I. 623 at 14) The court disagrees. Analogous art encompasses references "not within the field of the inventor's endeavor, . . . [if it] is reasonably pertinent to the particular problem with which the inventor is involved. *In re Klein*, 647 F.3d 1343, 1348 (Fed Cir. 2011) (citation omitted). The patents-in-suit state that "[i]sobutanol is produced biologically as a by-product of yeast fermentation," acknowledging that yeast fermentation is related and relevant. ('188 patent, 1:39-40; '889 patent, 1:39-40) The patents also refer to and

---

[29] "Boulton" is Chris Boulton & David Quain, *Brewing Yeast & Fermentation*, 113-21 (Blackwell Science Ltd. 2001).

[30] The combination references will be introduced as needed for the court's analysis.

discuses "fusel oil" in the context of "beverage fermentation." ('188 patent, 1:39-62; '889 patent, 1:39-62) The patents-in- suit cite to at least one article from the applied brewing and fermentation arts. ('188 patent, 1:51-52; '889 patent, 1:51-52)

Butamax next argues that "nothing would lead a [person of ordinary skill in the art] to combine a reference about trace amounts of flavor components in beer with knowledge about genetic engineering to make isobutanol." (D.I. 623 at 14) This argument is contrary to the references to beverage fermentation in the patents and to Butamax's expert's research.[31] Statements in the cited references, such as "manipulation of the concentrations of individual higher alcohols is possible via genetic modification of yeasts," also refute this argument. (D.I. 650 at 25 (citing Boulton, at 121))

Gevo contends that the five-step pyruvate to isobutanol pathway is described in the prior art. (D.I. 599 at 3-4) Specifically, Gevo's expert, Dr. Stephanopoulos, refers to Boulton as a prior art reference disclosing the pathway and each of the enzymes.[32] (D.I. 599 at 4; D.I. 683 at ¶¶ 41-44) Dr.

---

[31] Butamax's expert, Dr. Henry, cites to beverage fermentation in an article she co-authored on research directed at the ethanol fuel industry. (D.I. 650 at 26; D.I. 651, ex. 130, Erin L. Krause, et al., *Determining the effects of inositol supplementation and the* opi1 *mutation on ethanol tolerance of* Saccharomyces cerevisiae, 3 Industrial Biotechnology, 260-68, ref. 12, 22 (2007), at 10)

[32] Gevo also points to several other references including A. Dinsmoor Webb & John L. Ingraham, *Fusel Oil, in*, 5 *Advances in Applied Microbiology* 317 (1963); C. Rainbow, *Brewers' Yeast*, in 3

Stephanopoulos concluded that "the scientific literature concerning the natural production of higher alcohols such as isobutanol from yeast demonstrates that these products are produced from the α-keto acid intermediate that is derived from two sources: amino acid catabolism and biosynthesis from pyruvate." (*Id.* at ¶ 49) Butamax's expert, Dr. Henry, opines that "Boulton does not provide any data confirming or tracing the intermediates in the purported pathway or show that the identified enzymes are expressed in such a manner to form an actual functional pathway." (D.I. 623 at 18; D.I. 625, ex. LLL at ¶¶ 53-56, 84-89) Instead, Dr. Henry avers that "Boulton expressly acknowledges that the purported metabolic pathways are not entirely understood . . . ." *Id.* at ¶ 54) Butamax alleges that the addition of other references does not illuminate the issue. Dr. Henry does not agree that the other references show that the five-step pathway occurs naturally in yeast. (D.I. 625, ex. LLL at ¶¶ 84) In particular, Dr. Henry questions whether the references show each step and the enzyme involved. (*Id.*) As each expert interprets the scientific literature differently, there is a factual disagreement on whether the prior art renders the independent claims of the '188 and '889 patent obvious.

Setting aside Butamax's general argument that there is no motivation to combine the beverage fermentation references with recombinant engineering references, the experts next disagree on whether the references teach recombinantly overexpressing one or

---

The Yeasts, 147 (A. H. Rose and J. S. Harrison, eds, 1970); E. Chen, *Formation and Analysis of Fusel Alcohols in Beer*, (1977) (Doctoral Thesis, McGill University, Montreal: Canada)

all of the enzymes in the five-step pathway to increase isobutanol production. Dr. Henry opines that Yocum teaches away from the engineered pathway in claim 1 of the '188 patent. (D.I. 625, ex. LLL at ¶¶ 91) Dr. Stephanopoulos opines that recombinant engineering techniques existed and, "because it was also known that increasing expression of a component of a pathway would enhance production of the end product above background levels, expressing genes encoding pathway enzymes to increase levels of the end product above background levels would have been obvious to those of ordinary skill in metabolic engineering." (D.I. 683 at ¶¶ 80-82) Whether or not it was obvious to combine the recombinant references with Boulton is a question of fact, not appropriate for decision on summary judgment. For these reasons and in light of the clear and convincing burden needed to find invalidity, the court denies Gevo's motion for summary judgment of invalidity as to the obviousness of the asserted claims of the '188 and '889 patents and Butamax's motion for partial summary judgment of no invalidity.

3. Written description

a. Indefiniteness

Gevo contends that claim 8 of the '889 patent is indefinite. (D.I. 599 at 31) Butamax filed a cross-motion for summary judgment that claim 8 is not indefinite as a matter of law. (D.I. 623 at 20) Claim 8 limits independent claim 1, adding that "the microorganism produces isobutanol as a single product." ('889 patent, 326:21-22) Butamax argues that, as both parties have agreed that the term "single product" is capable of being construed, Gevo cannot contend that the term and claim are indefinite. At this

stage of the proceedings, Gevo's proffer of a claim construction does not foreclose its argument that the claim is indefinite.

Both parties agree that in fermentation, an organism would not produce a single product to the exclusion of all others. (D.I. 599 at 32; D.I. 623 at 54) Butamax argues that "single product" is measurable as different from a "by-product" or as distinguishing the patent from "the traditional processes whereby isobutanol was produced as a component of 'fusel oil' or as part of a mixture with acetone and ethanol." (D.I. 623 at 53-54) Gevo frames the question as "how much non-isobutanol fermentation product does a microorganism need to produce in order for the isobutanol production to no longer be considered a 'single product' of the microorganism?" (D.I. 599 at 32) Butamax avers that "substantial" is sufficiently clear to one skilled in the art to render the claim term definite. *See Exxon Research & Eng'g Co. V. United States*, 265 F.3d 1371, 1375 (Fed. Cir. 2001). As the court adopted Butamax's construction, the court denies Gevo's motion for summary judgment that claim 8 is indefinite and grants Butamax's motion for partial summary judgment that claim 8 is not indefinite.

b. Enablement and written description

Gevo contends that claim 8 of the '889 patent is invalid for lack of written description and lack of enablement under 35 U.S.C. §112. (D.I. 599 at 33) As discussed above, claim 8 contains the added limitation of "single product." The court determined that the term "single product" could be construed and adopted Butamax's claim construction, that is, "[t]he

microorganism produces isobutanol without substantial amounts of other fermentation products." *See supra* part III.C.3.

Gevo argues that the specification does not demonstrate to a person of ordinary skill in the art that Butamax was in possession of a microorganism capable of producing isobutanol as a "single product." (D.I. 599 at 35) In this regard, Dr. Stephanopoulos points out that the highest yield disclosed in the '889 patent was 0.6% according to example 18. (D.I. 599 at 35 (citing '889 patent, tbl.9)) Dr. Stephanopoulos concludes that this yield indicates that other products were being produced in large quantities by the yeast. (D.I. 599 at 35; D.I. 601 at ¶ 189) Finally, Gevo avers that Butamax could only produce isobutanol at background levels using the methods of the '889 patent and "did not accomplish its own target laboratory yields for at least three years after the '889 application was filed." (D.I. 650 at 31)

Butamax's expert contends that the recombinant yeast cells producing more isobutanol than the control strains shows that claim 8 is "sufficiently enabled and supported by the written description."[33] (D.I. 623 at 57;

---

[33] Butamax's expert, Dr. Henry, explains that the specification of the '889 patent "shows that recombinant yeast cells expressing an engineered isobutanol biosynthetic pathway produced substantially more isobutanol than the control strains." (D.I. 625, ex. LLL at ¶ 206 (citing '889 patent, example 18, 42:60-44:33)) The concentration of isobutanol recovered from the experiments shown in the examples varies widely - from 0.4 mM to 1.2 mM of isobutanol produced from *E. Coli* strains grown on glucose versus no detected isobutanol in the control strains (*see* '889 patent, example 15 & tbl.5) and from 0.20 mM to 0.97 mM, for isobutanol

D.I. 625, ex. LLL at ¶ 206) Further, Dr. Klibanov opines that any additional experimentation for "refining and optimizing yields" would be routine. (D.I. 623 at 57; D.I. 625, ex. OOO at ¶ 216) Butamax's experts do not respond to Dr. Stephanopoulos' contentions that Butamax could not produce "commercial levels" of isobutanol or that it had not achieved its own production goals. (D.I. 650 at 39; D.I. 652 ¶ 208)

"Enablement does not require an inventor to meet lofty standards for success in the commercial marketplace. Title 35 does not require that a patent disclosure enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect." *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1338 (Fed. Cir.2003); *cf. Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1577 (Fed. Cir. 1984) (patentee's experiments designated as "failures" because they were "not optimal under all conditions" did not establish nonenablement; "such optimality is not required for a valid patent"). As Butamax did not claim a commercially viable product, it is of no consequence whether the patent enables such a product.

The question of undue experimentation is a matter of degree and the amount of experimentation may not be "unduly extensive." *Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247, 1253 (Fed. Cir. 2004) *(quoting PPG Indus., Inc. v. Guardian Indus., Corp.*, 75 F.3d 1558,

---

produced by *Saccharomyces cervisiae* on glucose versus 0.11-0.12 mM for the control (*see* example 18, tbl.9).

1564 (Fed. Cir. 1996)). Experiments involving repetition of known or commonly used techniques do not necessarily render the experimentation "undue". *See Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 1360 (Fed. Cir. 1998) (finding that the difficulty in experimentation was not due to shortcomings in the patent disclosure, but due to the difficulty in producing certain antibodies using techniques commonly requiring repetition). It is important to note that the "test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance . . . ." *PPG Indus., Inc.*, 75 F.3d at 1564 (citation and quotation omitted).

"Permissible experimentation is, nevertheless, not without bounds." *Cephalon, Inc. v. Watson Pharmaceuticals, Inc.*, --- F.3d ----, 2013 WL 538507 at *6-7, (Fed. Cir. 2013); *AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244 (Fed. Cir. 2003) (finding the amount of experimentation excessive where the specification taught away from the claimed subject matter and there was evidence of the patentee's own failures to make and use the later claimed invention at the time of the application); *White Consol. Indus., Inc. v. Vega Servo-Control, Inc.*, 713 F.2d 788, 791 (Fed. Cir. 1983) (holding experimentation was unreasonable, where one and a half to two years' work was required to practice the patented invention).

There is a genuine issue of material fact about whether a showing of increased isobutanol production in recombinant yeast over controls is sufficient to enable a claim of producing isobutanol as a "single

product;" i.e., when a yield for a product is low, there are necessarily other products present. The parties' experts disagree on the amount of product necessary to meet the "single product" claim term and how much isobutanol could be produced by the methods of the '889 patent. Butamax argues that refining the yields for isobutanol would involve routine additional experiments. Gevo has not proffered evidence that the specification would not allow a person of ordinary skill in the art to understand the claimed invention. As Gevo's burden is one of clear and convincing evidence, the court denies Gevo's motion for summary judgment of invalidity of claim 8 for lack of enablement and written description, and also denies Butamax's cross-motion for partial summary judgment of no invalidity of claim 8 for lack of enablement and written description.

Gevo next contends that claims 12 and 13 of the '889 patent are invalid for lack of written description under 35 U.S.C. §112. (D.I. 599 at 35) Claim 12 and 13 read:

> 12. The recombinant yeast microorganism of claim 1 wherein the said microorganism further comprises inactivated genes thereby reducing yield loss from competing pathways for carbon flow.
>
> 13. The recombinant yeast microorganism of claim 12, wherein said inactivated genes reduce pyruvate decarboxylase activity.

('889 patent, 326:29-36) The '889 patent does not contain a description or examples of a recombinant yeast microorganism with inactivated genes to reduce yield loss from competing pathways for carbon flow or

to reduce pyruvate decarboxylase activity ("PDC"). (D.I. 599 at 36) The '889 mentions inactivation of genes only once: "The microbial host also has to be manipulated in order to inactivate competing pathways for carbon flow by deleting various genes. This requires the availability of either transposons to direct inactivation or chromosomal integration vectors." ('889 patent, 16:55-59) Gevo argues that the '889 "patent does not identify any microbial host, any examples, any pathways, or any specific genes that could be inactivated in order to achieve" the goals of claims 12 and 13. (D.I 599 at 37-38) Gevo also asserts that Butamax may not rely on the citation to Dickinson[34] in the specification as support for these claims as it (1) was not incorporated by reference; (2) was cited in the invention's background section as support for increasing isobutanol production in yeast using L-valine; and (3) does not teach reducing PDC activity to achieve increased isobutanol production. (D.I. 599 at 38-39)

Butamax responds that the patent specification, combined with the knowledge of those of skill in the art, renders these claims sufficiently described.[35] (D.I.

---

[34] "Dickinson" is Dickinson et al., *An Investigation of the Metabolism of Valine to Isobutyl Alcohol in* Saccharomyces cerevisiae, 273(40) J. Biological Chemistry, 25752-25756 (1998).

[35] Butamax's expert, Dr. Klibanov cites to three portions of the specification:

- "α-Ketoisovalerate can be converted to isobutyraldehyde by a number of keto acid decarboxylase enzymes, such as for example pyruvate decarboxylase. To prevent misdirection of

623 at 58) The specification identifies both the problem and the solution. (D.I 623 at 59) Butamax also avers that "the art contained numerous teachings regarding the deletion of PDC genes, including Dickinson." (D.I. 623 at 60)

The dispute at bar lies in whether the portions of the specification cited by Butamax satisfy the written description requirement of § 112 ¶ 1, that is, are so "full, clear, concise, and exact" that one of skill in the art would be able to use the same. None of the cited portions of the specification provide a description to one of skill in the art on how to construct a recombinant yeast microorganism with "inactivated genes" to reduce "yield loss from competing pathways." Although the specification may be interpreted as identifying both the the problem and the solution, it does not even begin to describe how to put into practice the solution.[36] The court finds that the written description for claim 12 is insufficient.

---

pyruvate away from isobutanol production, a decarboxylase with decreased affinity for pyruvate is desired. ('889 patent, 12:12-17)

- The microbial host also has to be manipulated in order to inactivate competing pathways for carbon flow by deleting various genes. This requires the availability of either transposons to direct inactivation or chromosomal integration vectors. ('889 patent, 16:55-59)
- Citation to Dickinson, explaining the Ehrlich pathway. ('889 patent, 1:46-47)

[36] Butamax attempts to rescue this argument stating, "brevity should be lauded, not punished." (D.I. 623 at 59) The information as to how to construct the claimed recombinant yeast microorganism is not brief; it is non-existent.

With respect to claim 13, there is no dispute that the specification of the '889 patent does not specifically disclose "inactivated genes" that "reduce pyruvate decarboxylase activity." ('889 patent, 326: 35-36) Again, the dispute is whether the portions of the specification cited by Butamax nevertheless satisfy the written description requirement. The specification identifies two enzymes which have "decreased affinity for pyruvate," but there is no discussion about gene inactivation or about PDC in that context. ('889 patent, 12:17-23) The generic suggestion to inactivate competing pathways does not teach anything specific about reducing PDC activity by inactivating those genes. ('889 patent, 16:55-57) The citation to Dickinson ('889 patent, 1:46-47) does not provide adequate written description. Said reference is neither incorporated by reference, nor is it cited in the '889 patent in the context of deleting PDC genes. Instead it is used to support the specification's description of the Ehrlich pathway in the background section. ('889 patent, 1:39-47) Further, this reference analyzes the metabolism of valine to isobutyl alcohol and describes yeast strains that have three PDC genes deleted. It states that the "route, via pyruvate decarboxylase, is the one that is used because elimination of pyruvate decarboxylase activity in a . . . triple mutant virtually abolished isobutyl alcohol production" and "a single pyruvate decarboxylase isozyme is all that is required for isobutyl alcohol formation from valine," effectively teaching away from the meaning of claim 13. (D.I. 603, ex. 35 at 25751, 25755) Even if Butamax had incorporated this reference to support claim 13, it does not supplement the specification in such a way as to provide a sufficient written description.

The court concludes that the specification of the '889 patent does not provide a sufficient written description of claim 13. For these reasons, the court grants Gevo's motion for summary judgment of invalidity of claims 12 and 13 for lack of written description and denies Butamax's cross-motion of no invalidity.

C. Excluding Expert Testimony

Rule 702 of the Federal Rules of Civil Procedure allows a qualified witness to testify in the form of an opinion if the witness' "scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue" and if his/her testimony is the product of reliable principles and methods which have been reliably applied to the facts of the case.

Butamax moves to exclude the testimony and reports of Gevo's expert, Dr. Stephanopoulos, on inherent anticipation of the '889 patent. (D.I. 641) Butamax contends that Dr. Stephanopoulos based his analysis on "the incorrect legal construct that inherent anticipation can be found when the prior art 'possibly' practices the claimed invention." (D.I. 641 at 2) Gevo argues that the "prior art reference need not practice the claims all the time under every conceivable condition." (D.I. 683 at 6) The court concludes that, at most, the standard for finding inherent anticipation was not eloquently articulated in Dr. Stephanopoulos' expert report. Reading the articulated standard as a whole, Dr. Stephanopoulos applied the correct

standard.[37] (D.I. 683, ex. A at ¶ 18); *Glaxo Group Ltd. v. Teva Pharms.*, Civ. No. 02-219, 2004 WL 1875017, at *19 (D. Del. Aug. 20, 2004) ("Although inherent anticipation does not require the element to be present each and every time, it does require the result to be a necessary and inevitable consequence of practicing the invention claimed in the prior art under normal conditions.").

Butamax's repeated arguments that Dr. Stephanopoulos did not independently conduct experiments as part of his analysis are of no consequence. (D.I. 641 at 4) By analogy, "[a] patentee may prove . . . infringement by either direct or circumstantial evidence. There is no requirement that direct evidence be introduced." *Liquid Dynamics Corp. v. Vaughan Co.*, 449 F.3d 1209, 1219 (Fed. Cir. 2006) (citing *Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 1272 (Fed. Cir. 1986) (abrogated on other grounds)). Dr. Stephanopoulos formed his opinions based on scientific literature and was not required to retest the results and methods detailed therein.[38]

---

[37] In part, he explained that, "[w]hat matters for anticipation is that all elements of a patent claim are present at the same time, at any time, in the prior art. If this requirement is satisfied, I understand that the prior art anticipates the claim even if, under some conditions, the same article described in the prior art sometimes does not have all the elements of the claim." (D.I. 683, ex. A at ¶ 18)

[38] To put Butamax's protests to rest, expert testimony was excluded in *Izumi*, when the theory advanced was not based on testing, literature references or any other scientifically recognized

Butamax also argues that "Dr. Stephanopoulos extrapolates from statements made in references alleging that isobutanol is sometimes produced in non-recombinant yeast to conclude that the recombinant yeast in the prior art would necessarily produce isobutanol." (D.I. 641 at 10-11) According to Butamax, this "sometimes" production renders Dr. Stephanopoulos' opinions improper as a matter of law and would be misleading and confusing to a jury. (D.I. 641 at 10-11) Gevo responds that the fact that yeast naturally produce isobutanol is a known and well characterized property of yeast. (D.I. 683 at 8) Gevo avers that extrapolating from natural yeast to recombinant yeast is proper under normal fermentation conditions, identifying "several references In which the claimed isobutanol pathway was genetically engineered to overexpress one of the enzymes in the pathway." (D.I 683 at 10) The court denies Butamax's motion to exclude Gevo's expert, Dr. Stephanopoulos's opinions on inherent anticipation.

V. Conclusion

For the foregoing reasons, the court denies Butamax's summary judgment motion of infringement and grants Gevo's cross-motion for summary judgement of no infringement. The court denies in part and grants in part the parties motions regarding validity. The court denies Butamax's motion to exclude Gevo's expert's testimony with regards to the '188

---

data. The court found that the expert's theory was "based solely on his subjective belief." *Izumi Prods. Co. v. Koninklijke Philips Elecs. N.V.*, 315 Fr. Supp. 2d 589, 602 (D. Del. 2004).

patent. The court reserves its decision on Butamax's motion to exclude expert testimony on the '376 patent.

An appropriate order shall issue.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

Civ. No. 11-54-SLR

[Filed March 19, 2013]

BUTAMAX™ ADVANCED BIOFUELS LLC,	)
Plaintiff/Counterclaim Defendant	)
v.	)
GEVO, INC.,	)
Defendant/Counterclaim Plaintiff	)
v.	)
E.I. DU PONT DE NEMOURS AND COMPANY,	)
Counterclaim Defendant	)

ORDER

At Wilmington this 19th day of March, 2013, consistent with the memorandum opinion issued this same date;

IT IS ORDERED that

1. Butamax's summary judgment motion of infringement of the '188 and '889 patents (D.I. 595) is denied.

2. Gevo's motion for summary judgment of non-infringement of the '188 and '889 patents (D.I. 610) is granted in part and denied in part. The motion is granted as to no infringement under the doctrine of equivalents.

3. Gevo's motion for summary judgment of invalidity (D.I. 598) is granted in part and denied in part. The motion is granted as to the invalidity of claim 12 and 13 of the '889 patent for lack of written description and enablement.

4. Butamax's cross-motion of no invalidity of the ''889 patent (D.I. 622) is granted in part and denied in part. The motion is granted as to no invalidity of claim 8 for indefiniteness.

5. Butamax and DuPont's motion to exclude testimony by Gevo's experts with respect to the '188 patent and '376 patent is denied as it relates to the '188 patent. (D.I. 640) The court reserves its decision as it relates to the '376 patent.

/s/
United States District Judge

APPENDIX D

[p.1]

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

No. 2012-1490, -1508

[November 9, 2012]

In the Matter of:

BUTAMAX (TM) ADVANCED BIOFUELS, LLC,
Plaintiff/Counterclaim Defendant-Appellant,

and

E.I. DUPONT DE NEMOURS AND CO.,
Counterclaim Defendant,

v.

GEVO, INC.,
Defendant/Counter-claimant-Cross Appellant.

On Appeal from the United States District Court
for the District of Delaware in
Case No. 11-cv-54-SLR,
The Honorable Sue L. Robinson

[p.2]

Proceedings before Judges Randall A. Rader, Timothy B. Dyk, and Evan Wallach, Washington, D.C.

[p.3]

APPEARANCES:

On behalf of the Plaintiff/Counterclaim Defendant-Appellant:

LEORA BEN-AMI, ESQ.
Kirkland & Ellis, LLP
601 Lexington Avenue
New York, New York 10022
212-446-4800

On behalf of the Defendant/Counterclaimant-Cross Appellant:

GERALD J. FLATTMANN JR., ESQ.
Paul Hastings, LLP
75 East 55th Street
New York, New York 10022
212-318-6000

[p.4]

PROCEEDINGS

JUDGE RADER: Our last case this morning is a patent case, Butamax Advanced Biofuels v. --

(Pause.)

JUDGE RADER: Ms. Ben-Ami?

MS. BEN-AMI: May it please the court, counsel, good morning.

Your Honors have read the material. So I'd like to get to what is really --

JUDGE RADER: Many times.

(Laughter.)

MS. BEN-AMI: Get to the key issue, which is claim construction within this case because that's where the fundamental abuse of discretion came from that's in error. And we do have a Markman in this case in January, a Markman hearing in January.

So I'd like to actually just walk Your Honors through the fundamental issue here in this error. The District --

JUDGE DYK: Well, let me just ask you a question here. I think you make a good point that the District Court's claim construction is problematic, that the use

[p.5]

of the word "solely," it's difficult to read the definition as that way, if for no other reason because it excludes some of the preferred embodiments that are listed there. Okay?

So I think you made a good point about that. But why isn't the correct construction of that definitional provision that it's NADPH-dependent or that it prefers NADPH, which is a construction which would make the definition consistent with the preferred embodiments and which, I understand, would still exclude the accused product here?

So could you help me with that?

MS. BEN-AMI: Certainly, Your Honor. We start with what the specification says. And there, the specification in column 7 says that a KARI, as that's the abbreviation everyone uses, is an enzyme that uses NADPH. So the question is what does that mean? That it "uses NADPH."

JUDGE DYK: It doesn't mean solely, okay?

MS. BEN-AMI: It doesn't mean solely. It doesn't mean exclusively. And there's nothing in the specification or the prosecution history that says

[p.6]

NADPH-dependent. So that's a new term, as it is applied to KARI. That's not in the specification.

There is another enzyme on column 12, for example, around line 30 where they're giving an example, and they say that enzyme is NADPH-dependent. So wherein the applicants wanted to limit themselves in that manner, they knew how to do it.

Now, when you read --

JUDGE DYK: Do you read "dependent" as meaning the same thing as "preferring"?

MS. BEN-AMI: That hasn't actually been argued yet in this case because Gevo brought up this concept of dependency.

JUDGE DYK: Well, I thought that expert said that it was the same thing?

MS. BEN-AMI: Expert said?

JUDGE DYK: That it was the same thing.

MS. BEN-AMI: As using?

JUDGE DYK: No, no, no. As -- maybe you misunderstood my question. That NADPH-dependent means the same thing as preferred.

MS. BEN-AMI: Well, actually, Dr. Kirsch used that

[p.7]

term, and in his deposition, he said he had not defined it in his expert report. And so, the concept of preference is not actually in the specification when it goes to the concept of KARI.

JUDGE DYK: No, but -- but my question is can we agree that NADPH-dependent means the same thing as preferring NADPH?

MS. BEN-AMI: No, we can't.

JUDGE DYK: We can't? Why not?

MS. BEN-AMI: Okay. Because as we're approaching Markman, Gevo is using a different definition, which is one of efficiency. The patent doesn't talk about efficiency at all. The only thing that the patent talks about is activity.

And this paragraph is talking about what was a standard assay at that time for a KARI. If we look at example two, it talks about a KARI and it says how do we assess it? This is on column 29.

And it says that the activity is measured using a certain assay. This is at approximately line 46. And so, when you look at that, what is that assay? And that's where, I think, there's -- this breaks down, and

[p.8]

it may become clearer when we understand the assay. And the assay is in the record.

What the assay does is it says I'm taking this proposed enzyme. I want to see if it's a KARI. I put the substrate in. I put NADPH in. And I measure whether any of the NADPH has converted to NADP+. If any of that occurs, that means electrons have been donated and that the KARI enzyme has that reduction. It's a reductase and an isomerase. And that's the reductase part.

So this is the test, the normal characterization of a KARI. That assay, which is what is called out in this patent, doesn't tell you anything about what it prefers because it doesn't say I put NADH in and I put NADPH in. It simply says how do I know it's got this electron-donating function? It says I put that in, and I see that it has gone ahead and used some of the NADPH.

So preference is not in the assay at all. It's a "does it use it or not?" test. And the specification and the file history -- and I would point Your Honors to the file history at 8194 and 8201, and it says in

[p.9]

characterizing the enzyme, you use the assay of example two. And that assay has nothing to do with --

JUDGE DYK: What do you understand the definition to mean here?

MS. BEN-AMI: Of preference?

JUDGE DYK: No.

MS. BEN-AMI: Of NADPH-dependent?

JUDGE DYK: Yes.

MS. BEN-AMI: My current understanding of NADPH-dependent is that the turnover rate -- so we have an enzyme, right? The enzyme, how many times does it do the reaction in a certain amount of time? And that if it is NADPH-dependent, that by a certain order of magnitude, it will act faster than an NADPH-dependent enzyme.

But under that analysis, the methanococcus enzyme is excluded because the prior art reference with a methanococcus enzyme says that it will work 60 percent as fast, if you will, using NADH. So when we're talking about that, that's not even --

JUDGE DYK: But if dependent means the same thing as preferred, that enzyme would be within the

[p.10]

definition, right?

MS. BEN-AMI: But enzymes don't prefer. It's a question of activity rate. And if you put -- we'll take this patent. There is claim 2. Claim 2 says you're using anaerobic conditions.

JUDGE DYK: Do we have expert testimony on this? I appreciate --

MS. BEN-AMI: We do.

JUDGE DYK: And where do we find the expert testimony saying what you're saying? Where in this record do we find the expert testimony that says the same thing that you're saying now?

MS. BEN-AMI: That the anaerobic --

JUDGE DYK: That dependent means the rate rather than preference?

MS. BEN-AMI: That's in the specification of the patent. The only assay that --

JUDGE DYK: So there's no expert testimony?

MS. BEN-AMI: Expert testimony. The only expert who talked about dependence was Dr. Kirsch, and he did not define it. So --

JUDGE DYK: So I guess you guys are going to be

[p.11]

getting into these questions at the Markman hearing?

MS. BEN-AMI: I think that's certainly correct. But I think it's also correct that we need to read a patent specification for what it teaches.

JUDGE RADER: What about claim 13 --

MS. BEN-AMI: Yes.

JUDGE RADER: -- the written description?

MS. BEN-AMI: Claim 13, the expert testimony in this case on claim 13 was from Dr. Kirsch, Gevo's expert. And Dr. Kirsch said, "When I read this patent, right away I know it's telling me to knock out the PDC." And that is his testimony.

JUDGE RADER: Well, and you've got column 12, lines 15 through 18 that discuss prior art enzymes that reduce pyruvate --

MS. BEN-AMI: That's right, decarboxylase.

JUDGE RADER: Yes. Thanks for helping --

MS. BEN-AMI: So --

(Laughter.)

JUDGE RADER: I didn't want to say it.

MS. BEN-AMI: One of the few times.

JUDGE RADER: I was seeing the "d" and stopping.

[p.12]

MS. BEN-AMI: Your Honors will note that when I do ANDA cases and there are small molecules, I have much more difficulty actually saying the word. So that's my biotech background maybe. But --

JUDGE RADER: Isn't that written description support?

MS. BEN-AMI: I believe it is written description support because the patent tells you what you want to do is knock out a side reaction so you get more going straight to where you want it to go. And it says this pyruvate decarboxylase is a big thing that takes off as a side reaction.

So if you put two sentences together, and it clearly says that, and the examiner obviously found that there was sufficient description.

JUDGE RADER: Could we talk about the substantial question of validity?

MS. BEN-AMI: Yes, Your Honor.

JUDGE RADER: You've got Boulton and Chen talking about this natural pathway and setting it forth with great detail. You've got Bekkaoui and Yocum talking about adding the --

[p.13]

MS. BEN-AMI: Recombinant.

JUDGE RADER: -- yeast that's recombined to that. Why isn't -- I recognize that there might be some difficulties with absolute anticipation, but isn't there enough there for at least obviousness?

MS. BEN-AMI: Well, first of all, Your Honor, the District Court did not find obviousness.

JUDGE RADER: I understand that.

MS. BEN-AMI: And --

JUDGE RADER: But is -- but we're talking about a substantial question of invalidity.

MS. BEN-AMI: Yes, we are.

JUDGE RADER: I'm suggesting there's an awful lot of prior art that is all over the area here. Is there enough for a substantial question?

MS. BEN-AMI: No, Your Honor. Let's -- if you'd like me to address obviousness, I will do that in my short time, rather than anticipation.

JUDGE RADER: Anticipate -- give me the -- both.

MS. BEN-AMI: Okay. So what the District Court said as the anticipation was she said I find -- let's remember what the claim is. We start with the claim

[p.14]

always. The claim is a method claim. You're contacting the media with a recombinant yeast.

So step 1 is does a reference have a recombinant yeast? Step 2 is does it have the engineered pathway? And step 3 is does it have the right reactions? Four is the right enzymes, and 5 is whereby that pathway produces isobutanol.

There are no references with recombinant yeast where it shows that there is isobutanol produced. The District Court --

JUDGE RADER: Well, but Boulton is teaching the pathway and the enzymes.

MS. BEN-AMI: Boulton --

JUDGE RADER: Chen is kind of reinforcing that. And then you've got Yocum and Bekkaoui, and we've been over this.

MS. BEN-AMI: So none of those references are to recombinant enzymes, but to recombinant --

JUDGE RADER: But then that's where the Yocum, Bekkaoui, those people come in.

MS. BEN-AMI: Ah, but let's look at those references. Two of those references were to engineer a

[p.15]

different pathway for vitamin B5. So they say I'm going to engineer, and I'm going to make the pathway vitamin B5. That doesn't make making isobutanol obvious.

Two of the other references were to go ahead --

JUDGE RADER: But does it suggest to one of skill in the art that you can certainly use recombinant yeast in this kind of a setting?

MS. BEN-AMI: That one could use recombinant yeast to engineer something? I think --

JUDGE RADER: Well, in the particular pathway, of course, we've got to look at the pathway of Boulton and Chen.

MS. BEN-AMI: Now Boulton and Chen are speculation. Those are not proven pathways. And the evidence that we have in the record here --

JUDGE RADER: But they're right on.

MS. BEN-AMI: Their evidence is saying I know that there's this valine pathway. That's called the Ehrlich pathway. Is it possible that there's another pathway?

JUDGE RADER: The pyruvate.

MS. BEN-AMI: And they -- and they -- they say,

[p.16]

well, I could guess that this is the pathway. They don't show that there is a pathway, and the evidence of record also is -- and this is from Dr. Stephanopoulis, Gevo's expert, Gevo's expert. He says --

JUDGE RADER: Are you saying this prior art is not enabling?

MS. BEN-AMI: No, what I was about to say was Gevo's expert said prior to Butamax doing this, there

was no motivation for anyone to go ahead and do isobutanol production. That motivation, nobody was looking for it. Nobody thought about it. Butamax came up with it. DuPont came up with it.

But what I am also saying is those references, Boulton, those are beer references. And respectfully, that is non-analogous art. But looking at --

JUDGE DYK: Okay. But those are interesting arguments, but there's pretty substantial arguments the other way, too, right?

MS. BEN-AMI: Well, I think if there's no motivation to go ahead and do this, I think on the face, look, we take our standard law of obviousness. We say what's the prior art, assuming it's analogous.

[p.17]

I would say to Your Honor that there is no evidence in this record that it is analogous. But you say let's take the closest prior art. Let's say what changes need to be made? Where is the motivation to combine? And that motivation to combine, whether it's testimony or a piece of prior art, there has to be some motivation.

And what the evidence from Dr. Stephanopoulos was is prior to DuPont and Butamax doing this, nobody even thought about it.

JUDGE RADER: But, counsel, I'm reading into what Judge Dyk asked, and maybe I shouldn't. But you're appealing from the denial of a motion for preliminary injunction. And you got a balancing test and discretion on the part of the court.

MS. BEN-AMI: That is correct, Your Honor. But we have to do that based on the record and what the District Court found because we are now looking to see whether the District Court abused its discretion. And so, when the District Court found invalidity, the likelihood of invalidity, she did it on a reference, the Larroy reference, which I have now lost, where if

[p.18]

you look at the very first page of the Larroy reference, I believe you will see that -- here's Larroy.

He's saying the yeast genome has now been mapped. I want to find out what this DNA part does. Don't know what it does. Figures out it codes for an enzyme. And then he says right in the beginning, and "I want to speculate," and he uses the word -- they use the word "speculate" about what this enzyme might do. And points to the Ehrlich pathway, this what I'll call Boulton pathway, for want of a better word, and a third pathway.

So there's nothing in that evidence that says that that is the pathway that's working. And he's only saying that's how it would work in nature. I would remind the court that when you engage in recombinant engineering, you can be turning off enzymes.

These things, the way this works is you have DNA, but for this pathway to work, you need the enzymes. And for the enzymes, you have to have the DNA turned on for all five enzymes. They need to be transcribed. They need to be translated.

[p.19]

And as Dr. Stephanopoulos -- Gevo's expert -- said, under some conditions it might work, and under some conditions it won't work. That is not necessarily there.

JUDGE RADER: Thank you, Ms. Ben-Ami.

Let's restore your rebuttal time.

MS. BEN-AMI: Thank you, Your Honor.

JUDGE RADER: And would you give Mr. Flattmann 20 minutes? That will be her rebuttal time and a little more. If you need to use that, it's yours, Mr. Flattmann.

MR. FLATTMANN: Thank you very much, Your Honor.

Good morning. Now may it please the court, Your Honor correctly addressed the relevant standard here, which is abuse of discretion on an appeal of a denial of PI. And essentially, to overturn that judgment of the District Court on the PI --

JUDGE RADER: But don't we have a legal error of reading in a term that wasn't in the claim, "solely"?

MR. FLATTMANN: Well, I don't think we have an error, Your Honor.

JUDGE DYK: You didn't argue "solely" to the

[p.20]

District Court, did you?

MR. FLATTMANN: I don't think we did, Your Honor.

JUDGE DYK: I can understand why.

MR. FLATTMANN: Well --

(Laughter.)

MR. FLATTMANN: But I don't think we need the term "solely." I think we can understand the term, as Your Honor suggested.

JUDGE RADER: Well, then aren't you stuck with that? That's what's on review here.

MR. FLATTMANN: This court can now -- can look at claim construction de novo and reach a different construction if it so wishes, even on the appeal of the PI. And if we take out the word "solely," I think we're still in the same place in terms of finding the infringement here.

JUDGE DYK: But your argument was that it meant NADPH-dependent, right?

MR. FLATTMANN: That's absolutely correct.

JUDGE DYK: And by that, your experts meant "prefer," right?

MR. FLATTMANN: Indeed. And Your Honor asked --

[p.21]

JUDGE RADER: We heard that that really refers to a process rather than a dependency.

MR. FLATTMANN: I can explain that. There essentially is --

JUDGE RADER: It's a rate I think is what Ms. Ben-Ami said.

MR. FLATTMANN: Yes, I don't think that's correct, Your Honor. There are three classes of KARI enzymes. There are those that are NADPH-dependent and prefer NADPH. There are those that are NADH-dependent that prefer NADH. And there are those that are NADPH- or NADH-dependent. And these are three separate classes, Your Honor, and this is structural really because what you have is formation of a complex, Your Honor, where the coenzyme, the NADPH, let's say, is actually bound to a part of the KARI enzyme of a specific class. So we have a structure.

The District Court correctly read the lexicography in the specification where there was an explicit definitional section as calling for an NADPH-dependent KARI enzyme, and it did so for a number of reasons. One, there was explicit lexicography. There was a

[p.22]

definition. And under this court's precedent in cases like Synorgchem, that is very compelling evidence concerning the claim construction.

It also did so because the patentee knew how to define other classes of KARI when it wanted to, other classes of enzymes when it wanted to. There are at least three other portions of the specification which we have pointed out in our brief where the patentee pointed to NADH- and/or NADPH-dependent enzymes.

So when it wanted to characterize an enzyme in that fashion and call out a specific class of enzymes, it knew how to do so. It did not do so here. It didn't need to define as KARI with reference necessarily to any class.

JUDGE RADER: But it does list in the patent as one of the KARI enzymes NADH and suggests its use in prior art. Why isn't that sufficient to suggest that it wasn't limiting itself to NADPH?

MR. FLATTMANN: Well, Your Honor, it does not call out the KARI enzyme as NADH-dependent anywhere in the specification. It talks about other enzymes as being NADH-dependent. But it never discusses KARI enzyme.

[p.23]

And in fact, in related application that was filed as a CIP -- so it's relevant to claim construction here -- it redefined KARI as NADH- or NADPH-dependent.

So it realized that it had a restricted definition to a single class of KARIs in the patent at issue, and later on, it expanded the definition. And that's relevant as well under this court's precedent in cases like Kao, in cases like Abbott v. Sandoz. It knew how to claim this when it wanted to, and it didn't claim it here. It didn't describe it here, and it put in an explicit narrowing definition to a separate class.

Now Your Honors asked whether there was testimony, expert testimony at the hearing concerning dependency? And yes, there was. I found one just quickly in reference to Your Honors' question. The Kirsch testimony at A16568, page 207, he discusses what was explicit to him about the use of NADH- and NADPH- dependent enzymes, and it is discussed as a matter of a strong preference for that coenzyme for that particular class of KARIs.

So while the word "solely" may or may not be the best choice of words in the District Court's

[p.24]

construction, what it clearly means is dependency. Strong preference and dependency. And that is a correct definition, as we see in the patent specification.

Your Honors, in terms of other reasons why we know this claim construction is correct, we can look at claim 14. It's a dependent claim from claim 1. And it adds limitation that says "uses an NADH cofactor, essentially." Well, that language would have been entirely superfluous if claim 1 included the use of NADH or the preference for NADH in terms of the court's claim construction.

The existence of that claim tells us we know that --

JUDGE RADER: Wouldn't that cut against you by if it read the "or more" out of the claim, that step 2 is only using NADPH as the electron donor, then the term "or more" would be out of the claim.

MR. FLATTMANN: Well, Your Honor, if you see in claim 14, the NADH-dependent enzyme can be any enzyme. It doesn't have to be the KARI. There are five enzymes in this pathway, and as it turns out, if we

[p.25]

look at the prior art, we see that the last enzyme in the pathway is actually NADH-dependent.

So the KARI enzyme, there's no inconsistency. The KARI enzyme could be NADPH-dependent, as described in the specification, and then the last step in

the pathway can be NADH-dependent. The other enzyme can be NADH-dependent. So it's no inconsistency, Your Honor.

And the claim allows for one or more of those enzymes to be NADH-dependent because NADH could operate on any of the other enzymes in that five-step pathway. So the claims are entirely internally consistent, and they lead us towards the District Court's claim construction.

Now, Your Honor, there was reference to the exclusion of an embodiment. First of all, if one embodiment is excluded out of a vast array of embodiments, it can't trump clear lexicography under this court's case law. But as a factual matter, this was not proven on the record below that there was any excluded embodiment.

JUDGE DYK: Well, and I thought that if dependent means prefer and if that's the construction, then all

[p.26]

of the listed enzymes are within the claim.

MR. FLATTMANN: Absolutely, Your Honor. Even under their interpretation of the facts. That's correct. But their facts are actually wrong. They say that this one bacterial enzyme from methanococcus maripaludis -- I think I got that right -- is excluded because they looked to a paper, the Xing article, which says that it has a 60 percent preference for one enzyme over the other.

And that's not the case. The enzyme that was actually tested in that paper, which is A14751 at 2089,

was from a different bacteria, methanococcus aeolicus. So it's a different bacteria. So their facts are wrong anyway. But on the law, that would not warrant running from the lexicography anyway.

Now --

JUDGE DYK: Now address the invalidity question.

MR. FLATTMANN: Very happy to, Your Honor. The District Court found in inherent anticipation, and on the facts and on our consideration of the evidence and the expert testimony, she was certainly not abusing her discretion in doing so. As Your Honors noted, there

[p.27]

are a multitude of references, each of which independently shows the pathway that we're talking about in these claims.

And Boulton, in particular, shows us each and every enzyme that inherently operates along that pathway. She focused in her opinion on the Larroy reference, as well as some others. But if we look at Larroy in particular, Your Honors, which is A10095, there's a beautiful chart there.

Larroy engineered a recombinant yeast, put in a hyper-expressed enzyme for the last part of the pathway, an ADH6 enzyme, which is a dehydrogenase enzyme, in that pathway, and that enzyme which was put in had a preference for NADH. It's not the KARI enzyme.

And Larroy mapped out the exact pathway that's in the patent with this recombinant yeast and says isobutanol at the end of the path. And discusses --

JUDGE RADER: Was Larroy the beer reference?

MR. FLATTMANN: Yes. Larroy, I'm sorry, Your Honor. Larroy --

JUDGE RADER: Can you address the analogous art

[p.28]

question?

MR. FLATTMANN: I'm very happy to.

JUDGE RADER: And then address as well Ms. Ben-Ami says when you start recombining these enzymes, you can turn them off as well as turn them on.

MR. FLATTMANN: Right.

JUDGE RADER: Can you address that as well?

MR. FLATTMANN: I certainly can. Can I go in that order?

JUDGE RADER: Please. Whatever.

MR. FLATTMANN: Well, Larroy tells us explicitly that he turned on the enzyme by doing this recombinant work. He tells us that he got over-expression of the dehydrogenase enzyme, and he explicitly says that in his paper at -- which begins at A10087. So we know that work. We don't have to guess.

And he says he made isobutanol. We don't have to guess here. And isobutanol production would have been inherent anyway in this pathway.

JUDGE RADER: Now Larroy tested this outside the cell, right?

MR. FLATTMANN: No, this is -- he describes the

[p.29]

recombinant engineering of a cell. So this is something that he is saying happens in a cell, and he draws all the various pathways by which you can get to higher

alcohols like isobutanol and explicitly discloses those pathways.

And then this ties into the beer reference. Larroy itself is not about beer. But he -- in his chart, he references the Boulton article, which is about beer and biochemistry of beer, as the reference for his pathways and his explanations of the enzymes.

So the beer arts are the most analogous arts. We're talking about making isobutanol with yeast. We're talking about the fermentation arts. That's what biofuels are all about. And the best evidence is that Larroy himself referenced the beer article, the Boulton article, in his own paper in the chart that we're relying on.

So, Your Honor, this is just one of the many separate and independent reasons why the District Court was right in finding the claim, that there was a substantial question of validity. She could have combined other references and looked at obviousness.

[p.30]

She declined to do so because she found anticipation on several different bases in light of a number of the different pieces of art that Your Honor alluded to.

Should I --

JUDGE RADER: But there's no single reference that includes all the steps?

MR. FLATTMANN: There is.

JUDGE RADER: What's that?

MR. FLATTMANN: At least Larroy, because Larroy has a recombinant yeast. We know that.

JUDGE RADER: Yes, but it doesn't have the pathway, the claimed pathway.

MR. FLATTMANN: It does. It does, Your Honor. That pathway --

JUDGE RADER: Where does it recite the claimed pathway with all the five enzymes and the --

MR. FLATTMANN: Very happy to explain. It's at A10095, and there's a chart, Your Honor. I'll just show you so you can reference it. And it shows four of the steps of the pathway. It has a dotted line for one of the steps, and it refers you to Boulton. It incorporates Boulton.

[p.31]

It says taken from 21, which is Boulton, in modified form. If we look at Boulton, Your Honors, which is directly referenced here, Boulton lays it out chapter and verse. The entire pathway is at Boulton A09980. And all the enzymes are described at A09997.

The District Court was within its rights to credit that evidence and the testimony about that evidence from Dr. Stephanopoulos at page 80 in particular of the transcript.

Shall I move to written description, Your Honor?

JUDGE RADER: Please.

MR. FLATTMANN: Okay. The District Court was right to credit the testimony of the expert, the expert Dr. Kirsch, on this point. It's a question of fact and

reviewed for clear error. And Dr. Kirsch went through each of the three sections of the specification that plaintiff relied on to try to show written description, found that it did not describe a PDC deletion.

The testimony that was referred to by counsel had to do with Dr. Kirsch saying that one would want to do a PDC deletion. He did not testify that there was any written description of such in the specification or any

[p.32]

indication that the inventors possessed that sort of invention as planned. And that's a very different thing.

A mere wish, a suggestion, even obviousness is not proof of written description. Here, we don't have any, and I'd like to take Your Honors first to column 12, which was alluded to in the earlier part of the argument. There is a discussion of preventing misdirection of pyruvate at column 12, line 15.

JUDGE RADER: Two enzymes in the prior art reduced the pyruvate decarbo -- et cetera.

MR. FLATTMANN: Exactly. Exactly. Well, this isn't talking about a gene deletion. This says a decarboxylase with decreased affinity for pyruvate is desired. It's talking about substitution. That's very different. And it says let's get an enzyme in here that has less affinity. It doesn't say knock out the gene. And that wasn't part of their invention at the time.

The other sections that we talk about in our brief also don't discuss deletion of PDC. There's a general section that says you might want to delete genes here

[p.33]

or there. Doesn't say which ones. Then there's a reference to an article that's not even incorporated by reference, which doesn't deal with PDC deletion in this context at all. And the District Court was right to credit Dr. Kirsch's testimony on this point, and her opinion is very careful along these lines.

We have another reason for knowing that they didn't possess the invention which is outside the four corners of the patent but still very relevant. Years later, in a related application that was incorporated by reference into a CIP of the present application, the plaintiff claimed PDC deletion explicitly and described it explicitly.

So when they ultimately came into possession of that invention, we believe after reading a Gevo published application, as I think we referenced in our briefs on this subject, they included it in their specification, and that has a detailed -- with written description. That's the same application in which they said that it would be very, very helpful to have an NADH-dependent variant because none are known yet.

So, Your Honors, there is just no written

[p.34]

description here of PDC deletion whatsoever.

In terms of the harm factors, if we even get that far, Your Honor, there's no evidence that -- the evidence is that Butamax isn't even going to launch a product until late 2014. There's no real harm here. The quantities that are produced by Gevo today are minimal, easily

compensable in damages if necessary, if we go all the way through trial and don't prevail. The trial is in April.

May I address any other questions that the court may have?

JUDGE DYK: I don't have any other questions, but I do have a comment. And that is it strikes me that you were not as careful as you should have been in the confidentiality markings in the red brief. There are legal citations, descriptions of cases that are marked confidential.

The Kirsch declaration, parts of that are marked confidential, and it's a public document. Legal argument is marked is confidential. I do think you should be more careful about that.

MR. FLATTMANN: Oh, I apologize for that, Your

[p.35]

Honor. I didn't notice that, and I will take a look at that and will be careful.

Your Honors?

JUDGE RADER: All right.

JUDGE WALLACH: That was a great argument.

MR. FLATTMANN: Thank you, Your Honor.

JUDGE RADER: Ms. Ben-Ami?

MS. BEN-AMI: Your Honor, if you would look at the appendix, page 11350. It's a miniscript. So it's really page 265. You will see that Dr. Stephanopoulos, Gevo's

expert, says that Larroy is not being cited for the production of isobutanol. Larroy does not show the production of isobutanol.

That was argument, but the evidence of the witness was that it does not. And that is the first point I would like to make.

The simple fact of the matter is, just as counsel said, well, when they wanted to say NADH-dependent, they said so. In the patent, when they described the KARI, they did not say NADPH-dependent. Elsewhere in the patent, where they want to say NADPH-dependent, they do so.

[p.36]

So if you take the definition in the patent and just use the words that are in the definition, all you need to show is that this is an enzyme that uses NADPH. So we are adding preference or dependence or whatever you would like into this claim language, into this specification. This is a case where if you look at the specification, when they want it to say dependent, they did know how. And they did. And they did not say that for a KARI enzyme, Your Honor.

So we are reading dependence into the definition where it does not exist. That is what the District Court did. And you don't go ahead and construe this patent in light of what Gevo does. The fact of the matter is the evidence showed, the public evidence, that Gevo's enzyme does use NADPH.

I'd like to consider claim 14 for a second because claim 14 does show that these -- that this KARI was intended to be using NADH. Claim 14 says one or more

enzymes, and the evidence of record is that there are only two enzymes that can use NADH, and one of them is the KARI. So the support for "or more" must be the KARI enzyme.

[p.37]

Similarly, claim 2 says that the method is being used under anaerobic conditions. Anaerobic conditions, testimony of Gevo's witness, Dr. Glassner, is when you have a lot of NADH. So there you're saying I can do this anaerobically, where you're going to use a lot of NADH.

You have claim 14 that says you're going to use -- one or more of the enzymes is going to be using NADH. That has to include the KARI or else you can't say "or more."

And you have a specification where it has a definition and a section where it says it uses NADPH with no statement of preference, NADPH preference, where when it wanted to say NADPH preference for another enzyme, it used that language. So we are changing the definition that's in the patent.

As to Larroy, Dr. Stephanopoulos -- and I can't go through the whole record, it is all cited for you -- repeatedly said it depends on the conditions that in even in his view of the natural pathway, which has never been proven, he says sometimes it might work. Sometimes it might not work. It might be all turned

[p.38]

on. It might not be all turned on.

What we know from Dr. Klibanov is in the actual yeast, some of the enzymes are only being made in this organelle called mitochondria. Some of them are being made in the cytosol. So it's as if I have two different factories. One's in New York. One's in California. How did you get a pathway out of that? They're not together, and that's what the evidence of record is.

So, Your Honors, it's nice to go ahead and look at what Gevo does and say, boy, maybe it should be NADH-dependent, NADPH-dependent. Three years later, five years later, what do people want to call these things? But the fact of the matter is that in this patent, in this specification for KARI, it does not say that.

It says uses NADPH. It describes an assay. That assay does nothing, says nothing about dependence. It's a yes or no. Can it use the NADPH?

JUDGE RADER: Thank you. That concludes our morning.

(Whereupon, the proceedings were concluded.)

CERTIFICATE OF TRANSCRIBER

I, Stephanie Johns, do hereby certify that, to the best of my knowledge and belief, the attached transcript is a true and accurate transcription of the indicated audio recording.

I further certify that I am neither attorney nor counsel for nor related nor employed by any of the parties to the action; further, that I am not a relative or employee of any attorney or counsel employed by the parties hereto or financially interested in this action.

11/21/12	/s/ Stephanie Johns
DATE	Stephanie Johns
	TRANSCRIBER