IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

BUTAMAX™ ADVANCED BIOFUELS LLC,	)	
Plaintiff/Counterclaim Defendant	)	
v.	)	Civ. No. 11-54-SLR
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

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)

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 dehydralase 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 ketol acid reductoisomerase ["KARI"] enzymes[1] known by the 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

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[1]According to Butamax, "[t]he parties agree that 'acetohydroxy acid isomeroreductase' is synonymous with ketol 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)

[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).

enzymes can use either NADPH or NADH as an electron donor (D.I. 494 at ¶ 36[4]), a construction limited 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)

1. Intrinsic record

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[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, 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)

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 BJA1484) 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 with an EC number to the fourth level is discretely and specifically classified on the basis of its function." (*Id.* at BJA1653 (emphasis added)) The patentees further disclosed a method that was "able to

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[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.

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 BJA1654) 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 BJA1656)

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 BJA1701-2) 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 BJA1702)

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 BJA1652)

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 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-

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[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.

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

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[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)

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 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).

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[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 Biophysica Acta, 380 (1965).

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

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 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:

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[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).

(1) Arfin & Umbarger (reference 639169), as described above; (2) Kiritani (reference 639171), as described above; (3) Dumas (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 data or other literature references to support it, and the other (Rane)

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

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 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

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[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.

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

[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

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 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

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IV.B.3.a.)

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 non-moving 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 SmithKline 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

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[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)

with an enzyme having KARI activity.[19] (D.I. 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-dependent, comparing the difference to Dr. Kirsh's "gray area" in cofactor usage.[22] (D.I. 648 at 31)

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

[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

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 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

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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.

[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)

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 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

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[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.

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) (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

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[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.

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

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 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

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

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 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.

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[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.

('188 patent, 1:39-40; '889 patent, 1:39-40) The patents also refer to and 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. Stephanopoulos concluded that "the scientific

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[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 *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)

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 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; 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*

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

& 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, 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. 623 at 58)

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[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:

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.

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

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- "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 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.

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

[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)

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]

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

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[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 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).

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

An appropriate order shall issue.