United States Court of Appeals for the Federal Circuit

NOVOZYMES A/S, AND NOVOZYMES NORTH AMERICA, INC.,
Plaintiffs-Appellants,

v.

DUPONT NUTRITION BIOSCIENCES APS (formerly Danisco A/S), GENENCOR INTERNATIONAL WISCONSIN, INC., DANISCO US INC., AND DANISCO USA INC.,
Defendants-Appellees.

2012-1433

Appeal from the United States District Court for the Western District of Wisconsin in No. 10-CV-0251, Senior Judge Barbara B. Crabb.

Decided: July 22, 2013

DAVID K. TELLEKSON, Fenwick & West, LLP, of Seattle, Washington, argued for plaintiffs-appellants. With him on the brief were VIRGINIA K. DEMARCHI, MELANIE L. MAYER, JEFFREY V. LASKER, and EWA M. DAVISON. Of counsel was BRIAN D. BUCKLEY.

CHARLES E. LIPSEY, Finnegan, Henderson, Farabow, Garrett & Dunner, LLP, of Reston, Virginia, argued for defendants-appellees. With him on the brief were HOWARD W. LEVINE and LILLIAN M. ROBINSON, of Washington, DC; JENNIFER S. SWAN, of Palo Alto, California. Of counsel on the brief were TRACEY B. DAVIES, Gibson Dunn & Crutcher, LLP, of Dallas, Texas; and MICHAEL A. VALEK, Vinson & Elkins, LLP, of Austin, Texas.

Before RADER, *Chief Judge,* SCHALL and BRYSON, *Circuit Judges.*

Opinion for the court filed by *Circuit Judge* SCHALL.

Dissenting opinion filed by *Chief Judge* RADER.

SCHALL, *Circuit Judge.*

Plaintiffs-Appellants Novozymes A/S and Novozymes North America, Inc. (collectively, "Novozymes") and Defendants-Appellees DuPont Nutrition Biosciences APS, Genencor International Wisconsin, Inc., Danisco US Inc., and Danisco USA Inc. (collectively, "DuPont") are competitors in the market for enzyme preparations used in a variety of commercial applications, including ethanol production. On May 11, 2010, Novozymes brought suit against DuPont in the Western District of Wisconsin, alleging infringement of its U.S. Patent No. 7,713,723 (the "'723 patent"). The '723 patent claims particular modified enzymes that exhibit improved function and stability under certain conditions. DuPont defended on grounds of noninfringement and invalidity and filed counterclaims seeking a declaratory judgment that the claims of the '723 patent are invalid for failing to satisfy the enablement and written description requirements of 35 U.S.C. § 112.

As litigation progressed, the parties filed several motions for summary judgment. In pertinent part, the district court granted summary judgment in favor of

Novozymes on the issue of infringement and denied DuPont's motion for summary judgment of invalidity under the written description and enablement requirements. The case then went to trial before a jury, which concluded that the '723 patent's claims are not invalid on enablement or written description grounds and which awarded infringement damages to Novozymes exceeding $18 million. The district court, however, granted DuPont's post-trial motion for judgment as a matter of law that the claims of the '723 patent are invalid under § 112 for failure to satisfy the written description requirement.

Novozymes now appeals from the district court's final judgment of invalidity. For the reasons set forth below, we affirm.

BACKGROUND

I. Alpha-Amylase Enzymes

The '723 patent, entitled "Alpha-Amylase Mutants with Altered Properties," relates to recombinant enzyme technology. Enzymes are proteins that catalyze biochemical reactions, that is, they facilitate molecular processes that either would not occur or would occur much more slowly in the enzyme's absence. Living cells produce different enzymes to carry out a vast array of metabolic functions. For example, one enzyme might help to join the molecular building blocks needed to make a new DNA molecule, while another might break a complex molecule, such as a carbohydrate, into useful constituent parts.

Like all proteins, enzymes are composed of amino acid molecules linked together to form a continuous chain. An enzyme's primary structure is defined by the sequence of amino acid molecules in the chain; in general, each individual position in the amino acid sequence can consist of any one of twenty amino acids normally found in nature. In addition, the linear amino acid chains of different

enzymes will bend, fold, and loop onto themselves to assume characteristic three-dimensional conformations. Both the primary amino acid sequence and the three-dimensional structure affect an enzyme's ultimate functional properties.

Alpha-amylases constitute a class of enzymes synthesized by a variety of organisms—from bacteria to fungi to humans—that break down large molecules known as polysaccharides. Polysaccharides, such as starch and glycogen, are defined as long-chain polymers made of repeating simple sugar molecules like glucose, among others. Alpha-amylases sever the bonds between adjacent sugars in a polysaccharide to yield single or short-chain simple sugars that can provide energy or be used as building blocks for other cellular processes. On average, alpha-amylase enzymes comprise approximately 500 amino acids.

Beyond a widespread role in natural systems, alpha-amylases also have important commercial applications in detergent formulations, sugar refining, and ethanol production, among other uses. Of particular note, many alpha-amylases derived from bacteria of the genus *Bacillus* exhibit exceptional enzymatic activity, which has made those bacterial enzymes attractive for commercial use. One such product is a preparation of alpha-amylase derived from *B. licheniformis* ("BLA") that Novozymes markets under the name Termamyl™.

II. Novozymes's 2000 Patent Application

Many of the most common commercial or industrial applications for alpha-amylase enzymes involve harsh conditions, including high temperatures and/or high acidity. Exposure to such conditions progressively destabilizes and deactivates natural *Bacillus* alpha-amylase enzymes, degrading the performance of the associated enzyme-based products or processes over time. In the late 1990s, Novozymes sought to improve the acid tolerance

and heat tolerance ("thermostability") of *Bacillus* alpha-amylases used in commercial processes.

Traditionally, the solution had been to add excess calcium to commercial alpha-amylase formulations intended for use under extreme temperature or pH conditions. While concentrated calcium is effective for stabilizing alpha-amylases to preserve their enzymatic activity, it represents an added cost and often imposes undesirable effects on industrial equipment. Thus, Novozymes's aim was to modify a naturally occurring "parent" *Bacillus* alpha-amylase to produce an enzyme having improved stability and thus more durable activity under harsh conditions, even without calcium supplementation.

Enzymes can often be altered at one or more positions along their amino acid chain without destroying their function. Changes (known as "mutations") in a parent enzyme can include deleting one or more amino acids, adding one or more amino acids, or substituting the original amino acid with one of the nineteen other possibilities at any given position in the sequence. An enzyme that has one or more mutations relative to its natural parent sequence is referred to as a "variant." The effects of any given mutation or combination of mutations in a variant can differ depending on the position(s) modified and the specific mutation implemented at each position. Some mutations may have no discernible effect on enzyme function, some may lead to varying degrees of instability or functional impairment, and some may actually improve enzyme activity or impart other desirable properties, such as improved stability at high temperatures.

Novozymes pursued two parallel strategies in attempting to identify promising mutation sites among the approximately 500 amino acids that make up a *Bacillus* alpha-amylase polypeptide: rational protein design and random mutagenesis. Rational protein design involves making functional inferences from the amino acid se-

quence and three-dimensional shape of a protein to predict which positions may influence a property of interest, such as thermostability, enzymatic activity, or calcium binding. In contrast, random mutagenesis involves making random mutations in a parent enzyme and then screening the resulting variants to identify those that exhibit the desired functional effects. Using rational protein design and random mutagenesis, Novozymes identified thirty-three *Bacillus* alpha-amylase amino acid positions as targets for mutation in attempting to create alpha-amylase variants with enhanced stability. Of those thirty-three positions, seventeen were predicted using rational protein design techniques, while sixteen were identified via random mutagenesis experiments.

With that information in hand, Novozymes filed U.S. Provisional Patent Application No. 60/249,104 on November 16, 2000 (the "2000 application"), relating to *Bacillus* alpha-amylase variants with enhanced stability.[1] The 2000 application disclosed seven potential parent enzymes, including an alpha-amylase isolated from BLA bacteria that Novozymes was already using in its Termamyl™ product, and another alpha-amylase produced by *B. stearothermophilus* ("BSG"). *See* '723 patent col. 3 ll. 1–38. The 2000 application also disclosed the thirty-three separate amino acid positions along the alpha-amylase chain that Novozymes identified as promising mutation targets using rational protein design or random mutagenesis. In addition, the specification indicated that one or more of those sites might be altered in any of the seven disclosed parent alpha-amylases by deletion, addi-

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[1] The written descriptions of the 2000 application and the '723 patent are nearly identical. For convenience, we will cite portions of the '723 patent when referencing identical, corresponding disclosures in the 2000 application.

tion, or substitution. *See id.* col. 7 ll. 36–57. The 2000 application further indicated that the disclosed variants would exhibit improved stability at "high temperatures (i.e., 70-120°C.) and/or extreme pH (i.e., low or high pH, i.e., pH 4-6 or pH 8-11), in particular at free (i.e., unbound, therefore in solution) calcium concentrations below 60 ppm." *See id.* col. 16 ll. 42–47.

Given the number of parent enzymes (7), the number of target positions in each of those parent enzymes (33), and the number of possible mutations at each of those target positions (at least 40),[2] the disclosure in the 2000 application spans a potentially wide range of alpha-amylase variants. For example, one of the seventeen positions identified by rational protein design was position 239, occupied by the amino acid serine (abbreviated as "S") in the disclosed parent alpha-amylase proteins. Many mutations would be possible at position 239, such as an enumerated variant that would require replacing the original serine with the amino acid tryptophan (abbreviated as "W")—a substitution mutation that can be expressed as "S239W." *See id.* col. 8 l. 12. The 2000 application includes pages of similar exemplary substitutions, presented alone and in double, triple, or larger combinations, but the application does not state that any one of the thirty-three disclosed mutations sites is preferred over any other and does not state whether single or combined mutations are preferred. *See id.* col. 8 l. 25 – col. 16 l. 37.

Finally, the 2000 application provided two examples with empirical data confirming the enhanced stability of

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[2] According to the 2000 application, the possible mutations at any amino acid position would include a single deletion, a substitution with any of the 19 other amino acids, and a single downstream addition of any of the 20 amino acids. *See* '723 patent col. 7 ll. 45–52.

selected variants harboring mutations at the sixteen positions that were identified through random mutagenesis. *See id.* col. 25 l. 1 – col. 26 l. 65. No such data were disclosed regarding the activity or thermostability of any of the seventeen positions that had been identified through rational protein design, however. Indeed, later experiments revealed that some of the seventeen predicted positions did not yield *any* thermostable variants, and even for many of those that did, only a minority of substitutions actually had the desired effect. For example, no substitutions at predicted positions 179 or 180 actually led to increased thermostability, and thirteen of the nineteen possible substitutions at position 239 proved similarly ineffective, including the disclosed S239W mutation.

Novozymes filed its first non-provisional patent application claiming priority from the 2000 application on July 31, 2001. After the examiner issued a restriction requirement directing Novozymes to elect a single disclosed species, i.e., a single specific parent alpha-amylase with a single specific amino acid substitution, Novozymes elected a BLA parent modified at position 49. In addition, Novozymes filed a continuation application on July 29, 2003, electing a BLA parent modified at position 170. Neither of those applications resulted in an issued patent.

III. DuPont's Accused Products and the '723 Patent

In 2006, while Novozymes's patent prosecution efforts remained ongoing, DuPont began work to develop an alpha-amylase having increased stability at high temperatures and low calcium concentrations for use in corn ethanol production. Starting from a BSG parent enzyme that corresponded to one of its own existing alpha-amylase products, DuPont produced approximately 1,500 alpha-amylase variants with substitutions covering 150 of the 515 amino acid positions in the parent BSG enzyme. Of those 150 positions, six also appeared in the list of

thirty-three candidate positions disclosed in Novozymes's 2000 application. DuPont then screened its panel of 1,500 variants for increased thermostability under low-calcium conditions and identified a variant substituted at position 239 as the best performer. As described, position 239 was also among the thirty-three positions disclosed in Novozymes's 2000 application, though the particular substitution DuPont chose—replacing serine 239 with glutamine ("Q"), denoted "S239Q"—was not. In November 2008, DuPont filed a patent application and developed a new thermostable alpha-amylase product based on the BSG S239Q variant. DuPont's patent application issued as U.S. Patent No. 7,541,026 in June 2009.

Upon learning that DuPont had introduced a thermostable BSG alpha-amylase variant substituted at position 239, Novozymes filed a new continuation application on December 22, 2009, (the "2009 application") that claimed priority from its original 2000 application. The written descriptions of the 2009 application and the 2000 application were nearly identical, but Novozymes for the first time sought claims drawn specifically to BSG alpha-amylase variants substituted at position 239. The '723 patent issued from the 2009 application on May 11, 2010, with seventeen claims. Claim 1 is representative:

> 1. An isolated variant of a parent alpha-amylase, wherein:
>
> (a) the variant has at least 90% sequence identity to SEQ ID NO: 6 [BSG alpha-amylase],
>
> (b) the variant *comprises a substitution of serine at position 239* relative to the parent alpha-amylase, using the amino acid sequence of SEQ ID NO: 8 [BLA alpha-amylase] for determining position numbering, and
>
> (c) the variant has increased thermostability relative to the parent alpha-amylase, wherein

> thermostability is determined at pH 4.5, 90° C. and 5 ppm calcium and has alpha-amylase activity.

'723 patent col. 87 ll. 40–51 (emphasis added). Like claim 1, all claims of the '723 patent require an alpha-amylase variant with at least the following three features: (1) a parent sequence having at least 90% homology with BSG alpha-amylase; (2) a substitution at position S239; and (3) increased thermostability at 90°C, pH 4.5, and 5 ppm calcium. Each of those limitations can be found at points within the underlying 2000 application, but, outside of the '723 patent's claims, Novozymes never presented them together in any particular embodiment and did not highlight the BSG parent or position 239 among the other disclosed options.

IV. District Court Proceedings

On May 11, 2010, the same day the '723 patent issued, Novozymes filed a complaint in the Western District of Wisconsin accusing DuPont of infringing claims 1–5, 8–13, and 15–16 of the '723 patent. DuPont's answer included noninfringement and invalidity defenses, as well as counterclaims for invalidity under the enablement and written description requirements of § 112, ¶ 1.[3] Shortly thereafter, the district court denied Novozymes's motion for a preliminary injunction, in part because, in its view, DuPont's written description challenge had raised a substantial question regarding the validity of the '723 patent's claims. *Novozymes A/S v. Danisco A/S*, No. 10-cv-251, 2010 WL 3783682, at *5 (W.D. Wis. Sept. 24,

[3] Paragraph 1 of 35 U.S.C. § 112 was replaced with newly designated § 112(a) when § 4(c) of the Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112-29, took effect on September 16, 2012. Because this case was filed before that date, we will refer to the pre-AIA version of § 112.

2010) ("[A] substantial question remains whether [the] '723 patent will survive defendants' challenge to the patent's validity.").

On February 4, 2011, the district court denied DuPont's motion for summary judgment that the '723 patent was invalid for lack of written description. *Novozymes A/S v. Danisco A/S*, No. 10-cv-251 (W.D. Wis. Feb. 4, 2011), ECF No. 185 ("*Written Description Summary Judgment Order*"). The district court indicated that it "still [had] doubts that the specification of the '723 patent provides an adequate written description for the claims," *id.* at 2, but the court concluded that the parties' conflicting positions reflected at least a genuine issue of material fact. The district court later granted summary judgment in favor of Novozymes on the issue of infringement, holding that DuPont's products literally infringed the asserted claims of the '723 patent. *Novozymes A/S v. Danisco A/S*, No. 10-cv-251, slip op. at 4–30 (W.D. Wis. July 7, 2011), ECF No. 399.

The case then went to trial before a jury. DuPont maintained its validity challenges, asserting that the claimed subject matter was neither enabled nor sufficiently described in the 2000 application. At the trial's conclusion, the jury was provided a special verdict form that asked whether DuPont had "proven by clear and convincing evidence that any one or more of the ['723 patent's] claims are invalid because the application filed on November 16, 2000 . . . does *not* contain an adequate written description," and, similarly, whether DuPont had established that the claims were not enabled. The jury answered "No" as to each claim. The jury further concluded that DuPont's adjudged infringement was willful and awarded Novozymes $18,219,500 in damages. Accordingly, the district court entered judgment for Novozymes on October 27, 2011.

After the entry of judgment, Novozymes sought a permanent injunction, fees, enhanced damages, and pre- and post-judgment interest, while DuPont filed motions for judgment as a matter of law on various issues, including willfulness, damages, and invalidity for lack of enablement and written description. In an order dated May 4, 2012, the district court granted DuPont's motion for judgment as a matter of law under Federal Rule of Civil Procedure 50(b), holding that the claims of the '723 patent were invalid under § 112 for lack of adequate written description in the 2000 application. *Novozymes A/S v. Danisco A/S*, No. 10-cv-251 (W.D. Wis. May 4, 2012), ECF No. 966 ("*JMOL Order*").

Addressing the written description requirement, the district court stated that "[t]he concern is that a patentee may attempt to use later filed claims, relying on more recently discovered data, to expand the scope of his invention or to complete an idea." *Id.* at 6 (citing *Billups-Rothenberg, Inc. v. Associated Reg'l & Univ. Pathologists, Inc.*, 642 F.3d 1031, 1036 (Fed. Cir. 2011)). Turning to the '723 patent, the court noted that the 2000 application disclosed a potentially enormous number of alpha-amylase variants, encompassing all possible combinations among the seven disclosed parent enzymes, the thirty-three disclosed positions for mutation, the numerous different mutations possible at each position, and the various possible combinations of individual mutations. The court also noted that the 2000 application did not point out the specific variants later claimed in the '723 patent. *Id.* at 6–7.

In its analysis, the district court analyzed precedents in which patent claims had been held invalid due to an underlying written description that set forth a broad, generic group of structures without specifically identifying the later-claimed species among many possible options. *Id.* at 9–12 (citing *Boston Scientific Corp. v. Johnson & Johnson*, 647 F.3d 1353 (Fed. Cir. 2011);

Billups-Rothenberg, 642 F.3d at 1036; *Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341 (Fed. Cir. 2011); *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916 (Fed. Cir. 2004); *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320 (Fed. Cir. 2000); *In re Ruschig*, 379 F.2d 990 (CCPA 1967)). Acknowledging that the '723 patent was "superficially different" from the patents at issue in those cases, in that the 2000 application expressly named the individual limitations recited in the claims, *id.* at 9–10, the district court nonetheless concluded that "there is no meaningful difference between identifying a generic group in which a limitation of a claim may be found (as in many of the prior cases) and individually listing each member of that group without directing the reader to a particular member (as in the '723 patent)." *Id.* at 11. In the district court's view, the problem in either situation was that "the specification failed to inform the reader which member of that group was the right one." *Id.* Accordingly, because "[t]he actual inventive work of producing a [working variant] was left for subsequent inventors to complete," the district court held that the 2000 application provided insufficient written description for the claims of the '723 patent and that those claims were therefore invalid under § 112. *Id.* at 17–18 (alterations in original) (quoting *Centocor*, 636 F.3d at 1353) (internal quotation marks omitted).

The district court thus granted DuPont's motion for judgment as a matter of law. *JMOL Order*, slip op. at 19. On May 11, 2012, the court entered an amended judgment in favor of DuPont, holding the claims of the '723 patent invalid for lack of sufficient written description under § 112, ¶ 1.[4]

[4] Having invalidated the claims of the '723 patent for lack of adequate written description, the district court dismissed the parties' other post-trial motions, including

Novozymes filed a timely notice of appeal on May 29, 2012. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

DISCUSSION

I. Standard of Review

When reviewing a district court's grant of judgment as a matter of law, we apply the law of the governing regional circuit. *Uniloc USA, Inc. v. Microsoft Corp.*, 632 F.3d 1292, 1301 (Fed. Cir. 2011). "The Seventh Circuit reviews a district court's grant of a JMOL motion without deference, while viewing all the evidence in the light most favorable to the nonmoving party." *Trading Techs. Int'l v. eSpeed, Inc.*, 595 F.3d 1340, 1357 (Fed. Cir 2010) (citing *Harper v. Albert*, 400 F.3d 1052, 1061 (7th Cir. 2005)). Judgment as a matter of law "is proper when 'a party has been fully heard on an issue and there is no legally sufficient evidentiary basis for a reasonable jury to find for that party on that issue.'" *Harper*, 400 F.3d at 1061 (quoting Fed. R. Civ. P. 50(a)(1)).

II. Issues Presented

A. The Written Description Requirement

The written description requirement is set forth in the first paragraph of 35 U.S.C. § 112. *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1343–45 (Fed. Cir. 2010) (en banc). In pertinent part, § 112 provides that:

> 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

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DuPont's parallel motion for judgment as a matter of law on the issue of enablement.

> use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

35 U.S.C. § 112, ¶ 1 (2006).

To satisfy the written description requirement, "the applicant must 'convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention,' and demonstrate that by disclosure in the specification of the patent." *Carnegie Mellon Univ. v. Hoffmann-La Roche Inc.*, 541 F.3d 1115, 1122 (Fed. Cir. 2008) (quoting *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563–64 (Fed. Cir. 1991)). Accordingly, claims added during prosecution must find support sufficient to satisfy § 112 in the written description of the original priority application. *See, e.g.*, *Anascape, Ltd. v. Nintendo of Am., Inc.*, 601 F.3d 1333, 1335 (Fed. Cir. 2010). Assessing "possession as shown in the disclosure" requires "an objective inquiry into the four corners of the specification." *Ariad*, 598 F.3d at 1351. Ultimately, "the specification must describe an invention understandable to [a] skilled artisan and show that the inventor actually invented the invention claimed." *Id.* A "mere wish or plan" for obtaining the claimed invention does not satisfy the written description requirement. *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1566 (Fed. Cir. 1997). The written description inquiry presents an issue of fact. *Ariad*, 598 F.3d at 1351.

B. The Parties' Contentions

To begin, Novozymes argues that the level of skill in the art of alpha-amylase biotechnology is very high and that, at the time that the 2000 application was filed, a person of ordinary skill in that art would have recognized the field as well developed and predictable. Specifically, Novozymes contends that alpha-amylases have been studied since 1833 and that, by the time it filed the 2000 application, the amino acid sequences and three-

dimensional structures of many alpha-amylases had been solved, methods for introducing mutations into alpha-amylase proteins and measuring the resulting variants' enzymatic activity were well known, and the use of alpha-amylase structure-function relationships in designing variants was commonplace and effective. Novozymes further argues that the key to deriving functional alpha-amylase variants lies in finding the right position to mutate rather than the specific mutation(s) made at that position.

In that context, Novozymes asserts that sufficient evidence supported the jury's validity determination, emphasizing that the 2000 application expressly discloses each limitation of the asserted claims, namely (1) a parent BSG alpha-amylase; (2) a substitution at the S239 position; and (3) increased thermostability at 90°C, pH 4.5, and 5 ppm calcium. In Novozymes's view, a person of ordinary skill in the art thus would have understood the 2000 application as clearly describing the claimed invention. Moreover, Novozymes argues that the district court revisited factual issues without applying the deferential standard demanded by Rule 50(b). In particular, Novozymes complains that the district court discounted its experts' testimony indicating that a person of ordinary skill in the art would have had no difficulty deriving the claimed invention from the disclosure of the 2000 application.

In addition, Novozymes distinguishes *Boston Scientific* and like cases on the grounds that those cases concerned complex, unpredictable technologies and involved written descriptions that lacked express disclosure of the claimed subject matter. Relying on *Snitzer v. Etzel*, 465 F.2d 899 (CCPA 1972), Novozymes argues that the 2000 application's written description is not deficient simply because it discloses unclaimed inventions and inoperative species. Novozymes also points to *Union Oil Co. of California v. Atlantic Richfield Co.*, 208 F.3d 989 (Fed. Cir.

2000), as illustrating that the level of ordinary skill and predictability in an art inform the written description inquiry. According to Novozymes, *Union Oil* demonstrates that a disclosure is not lacking merely because it relies on the understanding of an ordinarily skilled reader.

For its part, DuPont defends the district court's judgment, arguing that the written description requirement precludes premature claims to a research plan and requires the disclosure of an actual invention. According to DuPont, Novozymes disclosed in its 2000 application no more than a theory or a laundry list of potential solutions, while DuPont performed the hard, inventive work of actually deriving a useful variant of BSG alpha-amylase.

Citing *In re Ruschig*, 379 F.2d 990 (CCPA 1967), DuPont argues that where a patentee adds claims during prosecution that, as here, were not included in the original priority application, courts require a detailed description and identification of the later-claimed invention in the original disclosure, particularly where the specification discloses numerous possibilities with scant guidance on which to select. In this case, DuPont points out that the 2000 application fails to disclose a single alpha-amylase variant substituted at position 239 that actually exhibits increased thermostability, noting that the only disclosed substitution at that position (S239W) disclosed in the 2000 application does not work as required by the '723 patent's claims. DuPont also asserts that the 2000 application's undifferentiated disclosure was no more than an "invitation to experiment" that failed to provide guidance toward the later-claimed solution.

Additionally, DuPont discounts *Union Oil* as conflating the written description requirement with "enablement reasoning," an approach that it claims is no longer viable in view of *Ariad*. DuPont also distinguishes *Union Oil* on the ground that the disclosure in that case taught exactly

how to make compositions with the claimed properties, while the disclosure of the 2000 application offers no insight as to how any given mutation at any of the disclosed amino acid positions would affect the functional properties of a resulting variant.

Finally, DuPont accuses Novozymes and its experts of relying on hindsight to work backward from the claims of the '723 patent, filed in 2009, to show that, given knowledge of the claimed invention, each limitation could be retroactively derived from the disclosure of the 2000 application.

III. Analysis

A. Holding

In view of the record before us, including the disclosure of the 2000 application, we hold that no reasonable jury could find that the claims of the '723 patent meet the written description requirement of § 112, ¶ 1, and that the district court therefore correctly entered judgment as a matter of law invalidating those claims. In contrast to the claims—which narrowly recite specific alpha-amylase variants that result from mutating a particular parent enzyme at a single amino acid position to yield distinctive functional properties—the supporting disclosure of the 2000 application provides only generalized guidance listing several variables that might, in some combination, lead to a useful result. Taking the claims as a whole rather than as the sum of their individual limitations, nothing in the 2000 application indicates that Novozymes then possessed what it now claims. Finally, the testimony of Novozymes's experts does not overcome the fundamental deficiencies of the 2000 application's written description.

B. Legal Framework

Numerous prior decisions addressing the written description requirement guide our analysis in this case. We

have consistently held that, to satisfy § 112, a patent's written description "must 'clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.'" *Ariad*, 598 F.3d at 1351 (alteration in original) (quoting *Vas-Cath*, 935 F.2d at 1563). A "mere wish or plan" to obtain the claimed invention is not sufficient. *Regents of the Univ. of Cal.*, 119 F.3d at 1566.

We have often applied those fundamental concepts to hold claims invalid in cases where a patent's written description disclosed certain subject matter in terms of a broad genus but its claims specified a particular subgenus or species contained therein. For example, in *Ruschig*, our predecessor court affirmed the holding of the Patent Office Board of Appeals that a claim to a specific drug molecule, added after filing, lacked sufficient description in the underlying application, which disclosed only a generic structure that could yield the claimed molecule given the proper selections at several variable positions. 379 F.2d at 993–94. In that case, the application's undifferentiated description was deficient because it failed to provide sufficient "blaze marks" to guide a reader through the forest of disclosed possibilities toward the claimed compound, which resided among the myriad others that also could have been made. *Id.* at 994–95.

We have reached similar conclusions in subsequent cases. For example, the claims at issue in *Boston Scientific* required drug-eluting stents incorporating a particular drug or a "macrocyclic triene analog" of that drug. 647 F.3d at 1367. The supporting written description disclosed a broad genus of "analogs" and made passing reference to the term "macrocyclic triene" but failed to describe or identify any member of the claimed sub-genus of macrocyclic triene analogs. *Id.* Because "nothing in the [disclosure] indicate[d] that the claimed triene analogs might be of special interest," and because the disclosure did not identify any such analogs or any reliable means

for divining one, we held that the written description failed to demonstrate that the inventors were in possession of the claimed invention. *Id.* at 1367–69. In *Purdue Pharma*, the disputed claims recited an extended-release drug formulation requiring a certain ratio between the drug's maximum blood concentration and its concentration at twenty-four hours after administration. 230 F.3d at 1323. The supporting disclosure included seven examples, two of which could be shown to meet the claimed ratio limitation by piecing together the disclosed data, but "neither the text accompanying the examples, nor the data, nor anything else in the specification in any way emphasize[d] the [claimed] ratio." *Id.* at 1326. Accordingly, we upheld the district court's conclusion that "one of ordinary skill in the art would not be directed to the [claimed] ratio as an aspect of the invention." *Id.* Finally, in *University of Rochester*, we affirmed a summary judgment of invalidity for lack of written description because the claimed methods required administering a drug having a certain, selective activity, but the specification did not disclose any suitable drugs, and none were known in the art at the time of filing. 358 F.3d at 927. At most, the specification provided screening assays for identifying suitable drug candidates. *Id.* We therefore held that the claims failed the written description requirement. We stated that the disclosure represented no more than a "wish or plan for obtaining the claimed chemical invention" and did "not provide any guidance that would steer the skilled practitioner toward compounds that can be used to carry out the claimed methods." *Id.* at 927, 929.

On the other hand, in some cases, broad or generic disclosures can adequately describe particular constituent species. Thus, in *Snitzer*, our predecessor court held that claims requiring a specific laser-active ytterbium ion had been adequately described in an accompanying disclosure naming that ion among a group of fourteen individually enumerated ions that were described as useful separately

or in various combinations. The written description challenge in that case cast the disclosure as speculative and misleading because several of the fourteen disclosed ions had proven to be inoperative. 465 F.2d at 902. The court nonetheless held that the literal description of the ytterbium ion provided adequate support for claiming that species, whether or not a larger group containing several inoperative species was also disclosed. *Id.* The court similarly held that certain species claims had been adequately described in *In re Driscoll*, 562 F.2d 1245 (CCPA 1977). In that case, the disputed claim recited a chemical compound having a specific substituent at one of several variable positions. *Id.* at 1246. The disclosure listed a number of possible structures that could be incorporated at the position in question, including one option that ultimately appeared in the claims. *Id.* at 1249. Again, the court held that the written description was sufficient because the particular claimed compound had been individually described as one of several possibilities. *Id.* at 1250.

In addition, in *Union Oil*, we affirmed a district court's finding that claims to gasoline compositions capable of reducing tailpipe emissions had adequate written description support. 208 F.3d at 996–1001. Rather than reciting a recipe of specific ingredients, the claims in that case defined the claimed gasoline compositions in terms of various chemical and physical properties. *Id.* at 992. The supporting specification disclosed that the properties recited in the claims correlated with emission levels, but the specification did not set forth specific compositions that would achieve those properties. *Id.* at 998–99. The record in the case, however, demonstrated that ordinarily skilled petroleum refiners would immediately appreciate that the qualitative chemical properties recited in the claims translated to specific, manifest compositions that would yield those properties. In other words, given the target properties, anyone having ordinary skill in the art

of petroleum refining would have been able to envision and readily produce a composition having those characteristics. The written description thus showed that "the inventors possessed the claimed invention at the time of filing in the assessment of those of ordinary skill in the petroleum refining art." *Id.* at 999.

C. The Present Case

Turning to the case at hand, the question before us is whether the 2000 application demonstrates to one of ordinary skill in the art that, by the application's filing date, Novozymes had invented the particular alpha-amylase variants that Novozymes claimed almost a decade later in the '723 patent. We conclude that it does not.[5]

As described, claim 1 of the '723 patent recites an alpha-amylase variant that (1) has at least 90% sequence identity to BSG alpha-amylase, (2) includes an amino acid substitution at serine 239, and (3) has increased thermostability at pH 4.5, 90°C, and 5 ppm calcium. '723 patent col. 87 ll. 40–50. Novozymes is correct that each of those

[5] Novozymes expends considerable effort emphasizing that the district court submitted the written description issue—an issue of fact—to the jury, which then found the claims not invalid. Novozymes thus appears to suggest that it was inherently inappropriate for the district court to overturn a jury verdict concerning the written description requirement. But a verdict on written description is no more immune from review than any other factual issue, and we have in past cases held that the entry of judgment as a matter of law on written description grounds was appropriate. *See, e.g.*, *Centocor*, 636 F.3d at 1353 (holding claims invalid for inadequate written description and reversing the denial of a post-verdict motion for judgment as a matter of law); *Ariad*, 598 F.3d at 1340 (same).

individual limitations is expressly stated in the disclosure of the 2000 application. Specifically, the 2000 application (1) lists BSG as one of seven disclosed parent alpha-amylase enzymes, *see* '723 patent col. 3 ll. 1–50; (2) includes amino acid position 239 among a group of thirty-three positions that could be mutated to produce a variant alpha-amylase, *see id.* col. 7 ll. 36–58; and (3) states that the disclosed alpha-amylase variants should function at high temperatures ("especially 85-95° C"), low pH ("especially 4.5-5"), and at low calcium concentrations ("especially 5 ppm calcium"), *see id.* col. 7 l. 6–32; col. 16 ll. 42–47.

The 2000 application, however, contains no disclosure of any variant that actually satisfies the claims, nor is there anything to suggest that Novozymes actually possessed such a variant at the time of filing. First, the bulk of the specification focuses on using BLA (Termamyl™) alpha-amylase, rather than BSG alpha-amylase, as the parent enzyme. BLA alpha-amylase is described as the "preferred" parent in the 2000 application, *see* '723 patent col. 5 ll. 21–26, and appears in the two disclosed working examples.[6] BLA alpha-amylase, though, shares only 65.4% sequence identity with BSG alpha-amylase—i.e., less than the 90% identity required by the claims. *Id.* col. 3 ll. 6–20 (Table 1). In addition, amino acid position 239 is disclosed in the 2000 application as only one among a list of thirty-three positions that could be altered by

[6] One of the few differences between the written description of the 2000 application and that of the later-filed '723 patent is that the 2000 application names only BLA alpha-amylase as a "preferred" parent enzyme, while language was added to the '723 patent denoting BSG alpha-amylase as another "preferred" option. '723 patent col. 21 ll. 47–50; *see also* Appellants' Br. 37 n.7 (acknowledging that "[t]he November 2000 Application does not refer to BSG variants as preferred").

deletion, insertion, or substitution, either alone or in combination. *See id.* col. 7 ll. 35–52. And while the bulk of the disclosure concerns substitutions, the only specifically described substitution at position 239 is S239W, *see id.* col. 8 l. 12, which the parties agree *does not* confer increased thermostability in alpha-amylase enzymes and thus would fall outside of the claims.

Nevertheless, the 2000 application's written description might superficially appear to differ from those exemplified in cases like *Ruschig* and *Boston Scientific*, where undifferentiated generic disclosures provided no description regarding the particulars of a claimed species, and to more closely resemble the written description in *Snitzer* or *Driscoll*, where claims to a specific member of a more broadly disclosed group were upheld because the claimed species had been literally described. In particular, BSG alpha-amylase, amino acid position 239, and improved thermostability—all recited as limitations in the claims of the '723 patent—are literally described in the disclosure of the 2000 application.

On closer examination, however, such analogies fall flat. While the 2000 application provides formal textual support for each individual limitation recited in the claims of the '723 patent, it nowhere describes the actual functioning, thermostable alpha-amylase variants that those limitations together define. Taking each claim—as we must—as an integrated whole rather than as a collection of independent limitations, one searches the 2000 application in vain for the disclosure of even a single species that falls within the claims or for any "blaze marks" that would lead an ordinarily skilled investigator toward such a species among a slew of competing possibilities. "Working backward from a knowledge of [the claims], that is by hindsight," Novozymes seeks to derive written description support from an amalgam of disclosures plucked selectively from the 2000 application. *Ruschig*, 379 F.2d at 995. Indeed, Novozymes' expert, Dr.

Arnold, in effect admitted that her testimony suffered from this flaw when she "point[ed] to [a] part of the claim" and told the judge she was "going back and finding if there's a written description for that" in the specification. With such an approach "it is all very clear what route one would travel through the forest of the specification to arrive at [the claimed invention]." *Ruschig*, 379 F.2d at 995. However, viewing the matter from the proper vantage point "of one with no foreknowledge of the specific compound," we agree with the district court that the particular variants claimed in the '723 patent lack meaningful support in the written description of the 2000 application. *Id.*

Furthermore, while the disclosure of an inoperative embodiment like the S239W substitution is not necessarily invalidating, *see Snitzer*, 465 F.2d at 902, the 2000 application lacks any indication that Novozymes had invented any thermostable alpha-amylase variants substituted at amino acid position 239 by the time of filing, much less one specifically produced from a BSG parent. The specification does provide examples showing that Novozymes had tested and verified at least some thermostable variants for the sixteen amino acid positions identified by random mutagenesis, but nothing in the 2000 application demonstrates that it had verified whether any of the remaining seventeen positions predicted by rational protein design (including position 239) actually yielded a thermostable variant. In fact, the 2000 application's limited disclosure compels the opposite conclusion—if Novozymes had possessed a working variant substituted at position 239, it surely would have disclosed that substitution instead of, or at least along with, the nonfunctional S239W substitution in the several pages of the 2000 application devoted to listing exemplary substitutions. *See* '723 patent col. 7 l. 40 – col. 16 l. 37.

In this way, the present case is also distinguishable from *Union Oil*, upon which Novozymes relies. *Union Oil*

involved claims to gasoline compositions capable of reducing tailpipe emissions, and the claims defined the compositions in terms of various chemical and physical properties. There, the patentee described relationships linking certain chemical and physical properties of gasoline compositions to the compositions' emissions profiles. In doing so, the patentee relied on the knowledge of those skilled in the relevant art to extrapolate the undisclosed, but claimed, compositions from their recited properties. In that case, the record indicated that a recitation of particular physical and chemical properties of a gasoline composition necessarily conveyed simultaneous possession of the actual recipe for making that composition because of the recognized level of standardization and predictability in mixing various petroleum stocks to achieve particular properties in the resulting gasoline products. *See Union Oil*, 208 F.3d at 999.

In contrast, one of ordinary skill in the art reading the 2000 application would have understood that Novozymes had only predicted that at least some mutations at position 239 would yield variants with increased thermostability, not that it possessed or had definitively identified any mutations that would do so. The parties' experts agreed that one could not know which, if any, individual substitutions at any of the seventeen sites selected by rational protein design would yield increased thermostability without actually making and testing the variants. In fact, DuPont's later empirical work showed that only six of the nineteen possible substitutions at position 239 actually conferred increased thermostability. Novozymes nonetheless maintains that one of ordinary skill in the art directed to position 239 would have known how to test every possible variant at that position and thus would have found the claimed variants as a matter of course. That argument misses the point, however. The question before us is not whether one of ordinary skill in the art presented with the 2000 application would have been

enabled to take those final steps, but whether the 2000 application "discloses the [variants] to him, specifically, as something appellants actually invented." *Ruschig*, 379 F.2d at 995.

In this case, to actually possess the variant enzymes claimed in the '723 patent would have required Novozymes to confirm its predictions by actually making and testing individual variants or at least identifying subclasses of variants that could be expected to possess the claimed properties, which it did not do before filing the 2000 application. At best, the 2000 application describes a roadmap for producing candidate alpha-amylase variants and then determining which might exhibit enhanced thermostability. A patent, however, "is not a reward for the search, but compensation for its successful conclusion." *Ariad*, 598 F.3d at 1353 (quoting *University of Rochester*, 358 F.3d at 930 n.10). For that reason, the written description requirement prohibits a patentee from "leaving it to the . . . industry to complete an unfinished invention." *Id.*

In our view, this case is very analogous to *University of Rochester*, where the patent specification failed to disclose any compounds that could be used in the claimed methods, which required administering a drug having a certain selective activity (inhibiting PGHS-2 activity in a human host).[7] We stated: "[T]he '850 patent does not disclose just *which* peptides, polynucleotides, and small organic molecules have the desired characteristic of selectively inhibiting PGHS-2. Without such disclosure, the claimed methods cannot be said to have been de-

[7] PGHS-2, also known as COX-2, is an enzyme produced by human cells in response to certain inflammatory stimuli. PGHS-2 is believed to play an important role in the inflammation associated with diseases such as arthritis. *University of Rochester*, 358 F.3d at 917.

scribed." 358 F.3d at 927 (citation and internal quotation marks omitted).

In sum, we agree with the district court that no reasonable jury could conclude that the 2000 application provides adequate written description to support the later-filed claims of the '723 patent.

CONCLUSION

We have considered Novozymes's remaining arguments and find them unpersuasive. Accordingly, we conclude that the claims of the '723 patent are invalid for failure to satisfy the written description requirement of § 112, ¶ 1. We therefore affirm the district court's entry of judgment as a matter of law on that basis.

AFFIRMED

COSTS

No costs.

United States Court of Appeals for the Federal Circuit

NOVOZYMES A/S, AND NOVOZYMES NORTH AMERICA, INC.,
Plaintiffs-Appellants,

v.

DUPONT NUTRITION BIOSCIENCES APS (formerly Danisco A/S), GENENCOR INTERNATIONAL WISCONSIN, INC., DANISCO US INC., AND DANISCO USA INC.,
Defendants-Appellees.

2012-1433

Appeal from the United States District Court for the Western District of Wisconsin in No. 10-CV-0251, Senior Judge Barbara B. Crabb.

RADER, *Chief Judge*, dissenting.

Although a separate written description requirement, and the vague notion of "possession" that it embodies, still troubles me, *see Ariad Pharm., Inc. v. Eli Lilly and Co.*, 598 F.3d 1336, 1361 (Fed. Cir. 2010) (Rader, J., dissenting-in-part and concurring-in-part), I write today to ask the court instead to give full attention to the rules that it has created. The written description inquiry is a question of fact. *Ariad*, 598 F.3d at 1351. In this case, a jury found—in its role as a finder of fact—that the specifica-

tion of U.S. Patent No. 7,713,723 (the '723 patent) satisfies the written description requirement. In my judgment, substantial evidence supports the jury's verdict, which deserves significant deference. Therefore, I would respectfully suggest that our written description rules urge reversing the district court's post-verdict grant of judgment.

I.

The written description analysis requires an "objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art." *Ariad* at 1351. In this field of technology, the level of skill is high. A skilled artisan would possess an advanced degree and have experience in sophisticated protein design and engineering techniques. *See* J.A. 11242–43. The jury found as a matter of fact that a skilled artisan would know to substitute an amino acid as the invention suggests. Indeed, the patent identifies thirty-three positions for beneficial mutation on a Termamyl-like alpha-amylase. In this field, the highly skilled artisan would find that disclosure more than adequate to direct the substitution of an amino acid at one of those positions. The jury made that finding. Substantial evidence supports that finding.

The specification of the '723 patent discusses variants of Termamyl-like alpha-amylases with altered stability at "high temperature and/or low pH conditions, in particular at low calcium concentrations." '723 patent col. 1 ll. 30–33. The specification includes listings for seven different parent alpha-amylases (including both BSG and BLA), and explains that variants can be made "comprising an alteration at one or more positions . . . selected from the group of [thirty-three positions]." *Id.* col. 7 ll. 36–43. The specification teaches that any amino acid can be substituted at those positions. *Id.* col. 2 ll. 21–30; *see also* J.A. 10256–57.

The specification also discloses two working examples, which used random mutagenesis to identify sixteen positions at which substitutions led to increased thermostability at pH 4.5, 90 ° C and 5 ppm calcium (the claimed conditions). '723 patent col. 25–26. The examples all use BLA as the parent alpha-amylase. Dr. Arnold testified that the specification fully discloses the tests for determining activity and thermostability at the claimed conditions. *See* J.A. 11248 (discussing disclosure in the '723 patent relating to assays). She also noted that these procedures were well-known in this field. *Id.*

The jury heard expert testimony that "finding the position where you can make a beneficial mutation is, in fact, the inventive step," and that once those positions are known, the procedure for making the substitutions was routine and well known, as was the process for determining which substitutions would result in the desired properties. *See* J.A. 11228–48. Novozymes also presented expert testimony to support its assertion that, while the specification explains that each alteration may be a deletion, insertion, or substitution of an amino acid, or a combination of these, a skilled artisan reading the specification would have focused on substitutions. *See* J.A. 11263–70. Making and testing all nineteen amino acid substitutions at one position was routine and would only take one week. J.A. 11251. In other words, a team of ten scientists could test all thirty-three positions with relative ease.

The court states: "the 2000 application disclosed a potentially enormous number of alpha-amylase variants, encompassing all possible combinations among the seven disclosed parent enzymes, the thirty-three disclosed positions for mutations possible at each position, and the various possible combinations of individual mutations. . . ." Majority Op. at 12. This conclusion overstates the problem in a way that appeals to a lay audience but is routine to this field. Novozymes offered expert testimony

that this calculation, while mathematically correct, is unrealistic because skilled artisans would not blindly try random combinations. J.A. 10935–36; *see also Snitzer v. Etzel*, 465 F.2d 899, 903 (CCPA 1972) (concluding appellee's reliance on a theoretical calculation of billions of possible combinations was "hopelessly exaggerated" when the specification directed persons of skill in the art to fourteen ions that could be used "in various combinations"). This court might also have credited the patentee with reducing the original 500 total amino acid positions down to a mere thirty-three. J.A. 10936.

II.

In conclusion, the jury received expert testimony, heard from skilled protein engineers, reviewed visual aids and publication excerpts, and examined the patent document as guided by those skilled in the art, over an eight day trial. The jury was given a special verdict form asking whether DuPont had proven by clear and convincing evidence that the claims at issue were invalid for lack of written description. J.A. 216. The jury answered in favor of Novozymes, and substantial evidence supports this determination. Therefore, I would reverse the grant of judgment as a matter of law and reinstate the jury's verdict.