NOTE: This disposition is nonprecedential.

United States Court of Appeals for the Federal Circuit

JENNEWEIN BIOTECHNOLOGIE GMBH,
Appellant

v.

INTERNATIONAL TRADE COMMISSION,
Appellee

GLYCOSYN LLC,
Intervenor

2020-2220

Appeal from the United States International Trade Commission in Investigation No. 337-TA-1120.

Decided: September 17, 2021

NICOLE A. SAHARSKY, Mayer Brown LLP, Washington, DC, argued for appellant. Also represented by GARY HNATH, BRYAN NESE, MINH NGUYEN-DANG; SCOTT MCMURRY, New York, NY.

HOUDA MORAD, Office of the General Counsel, United States International Trade Commission, Washington, DC, argued for appellee. Also represented by WAYNE W.

HERRINGTON.

MICHAEL NEWMAN, Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, PC, Boston, MA, argued for intervenor. Also represented by COURTNEY PATRICE HERNDON, MATTHEW A. KARAMBELAS, MICHAEL RENAUD, THOMAS H. WINTNER, JAMES M. WODARSKI.

Before LOURIE, BRYSON, and CHEN, *Circuit Judges*.

CHEN, *Circuit Judge*.

Glycosyn LLC (Glycosyn) filed a complaint against Jennewein Biotechnologie GmbH (Jennewein) with the International Trade Commission (Commission) under 19 U.S.C. § 1337, alleging that human milk oligosaccharides imported by Jennewein infringed Glycosyn's U.S. Patent No. 9,970,018 ('018 patent). Jennewein used several *Escherichia coli* (*E. coli*) bacterial strains to produce the human milk oligosaccharides it imported into the United States. The Commission determined that of the three Jennewein strains at issue, two of the strains infringed the '018 patent and one did not. *In the Matter of Certain Hum. Milk Oligosaccharides & Methods of Producing the Same*, Inv. No. 337-TA-1120, 2020 WL 3073788 (U.S.I.T.C. June 8, 2020) (Comm'n Opinion) (*Commission Opinion*); *see also In the Matter of Certain Hum. Milk Oligosaccharides & Methods of Producing the Same*, Inv. No. 337-TA-1120, 2019 WL 5677974 (U.S.I.T.C. Sept. 9, 2019) (Initial Determination) (*Initial Determination*); *see also In the Matter of Certain Hum. Milk Oligosaccharides & Methods of Producing the Same*, Inv. No. 337-TA-1120, 2018 WL 6837945 (U.S.I.T.C. Dec. 18, 2018) (Order No. 22: Construing the Terms of the Asserted Claims of the Patents at Issue) (*Claim Construction Order*).

Jennewein appeals aspects of the Commission's claim construction and infringement determination. Because we

conclude that the Commission did not err in its claim construction or in its finding of infringement, we *affirm* its limited exclusion order.

BACKGROUND

A

The '018 patent relates to methods for producing fucosylated oligosaccharides found in human milk. '018 patent col. 1 ll. 27–30. These oligosaccharides "serve critical roles in the establishment of a healthy gut microbiome, in the prevention of disease, and in immune function." *Id.* at col. 1 ll. 37–39. Through "use of an engineered bacterium *E. coli* (or other bacteria)," the claimed method enables synthesis of fucosylated human milk oligosaccharides (e.g., 2'-fucosyllactose (2'-FL)), *id.* at col. 15 l. 66–col. 16 l. 4, for use as dietary supplements, *id.* at col. 15 ll. 62–65, or for incorporation into products (e.g., infant formula), *id.* at col. 11 ll. 30–40. The engineered *E. coli* bacterium is genetically manipulated to comprise: (1) an increased intracellular guanosine diphosphate (GDP)-fucose pool; (2) an increased intracellular lactose pool; and (3) a fucosyltransferase. *Id.* at col. 5 ll. 1–5. The fucosyltransferase couples the lactose and GDP-fucose to form the desired human milk oligosaccharide, specifically 2'-FL. *Id.* at Figure 3.

To increase the intracellular lactose pool, the engineered *E. coli* bacterium of the claimed method is modified to delete or functionally inactivate the endogenous ß-galactosidase gene, *lacZ*. *Id.* at col. 5 ll. 13–14. As ß-galactosidase is the enzyme responsible for the breakdown of lactose in *E. coli*, eliminating its activity in the engineered bacterium results in the accumulation of intracellular lactose when culturing the bacterium in the presence of exogenous lactose. *Id.* at col. 16 ll. 47–49. This increased lactose pool ensures the availability of lactose for the production of 2'-FL. *Id.* at col. 5 ll. 16–19.

Yet complete elimination of ß-galactosidase activity creates purification issues at the end of the manufacturing process, as it is difficult to separate any remaining lactose from the desired 2'-FL product. *See id.* at col. 7 ll. 37–45; *see also* Appellant's Br. 10 ("After production ends, there can be a significant amount of lactose remaining in the fermentation broth, and it can be difficult (and costly) to separate lactose from 2'-FL."). To overcome this challenge, the engineered *E. coli* bacterium of the claimed method includes an exogenous functional ß-galactosidase gene "to direct the expression of a low, but detectable level of ß-galactosidase activity." '018 patent col. 6 ll. 7–11. The result is an engineered bacterium comprising a low level of cytoplasmic ß-galactosidase activity, between 0.05 and 200 Miller units.[1] *Id.* at col. 7 ll. 22–37. This low level of ß-galactosidase activity does not "significantly diminish the intracellular lactose pool" but can degrade any residual lactose remaining after the fermentation process, simplifying 2'-FL purification. *Id.* at col. 7 ll. 37–45. In addition to being helpful for the removal of undesired residual lactose,

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[1] To define a Miller unit, the '018 patent points to the assay of ß-galactosidase activity provided in Jeffrey H. Miller, EXPERIMENTS IN MOLECULAR GENETICS 352–55 (1972) (Miller). *See* '018 patent col. 7 ll. 34–37. In short, the Miller protocol includes the following steps: (1) taking a sample from a culture of growing bacterial cells; (2) permeabilizing the bacterial cells with chloroform or toluene; (3) incubating the permeabilized bacterial cells with *o*-nitrophenyl-ß-D-galactoside (ONPG), a colorless compound specifically recognized and cleaved by ß-galactosidase to produce a yellow product; and (4) measuring with a spectrophotometer the amount of yellow color that develops over a set period of time. *See* J.A. 60224–28. The values recorded by the spectrophotometer are then entered into a mathematical equation to provide the level of ß-galactosidase activity in Miller units. *See* J.A. 60227.

the low level of ß-galactosidase activity can also be useful for phenotypic marking or for detection of cell lysis due to bacteriophage contamination during fermentation. *Id.* at col. 7 ll. 40–43.

The only independent claim of the '018 patent, claim 1, covers Glycosyn's method and engineered *E. coli* bacterium. The claim recites:

> 1. A method for producing a fucosylated oligosaccharide in a bacterium, comprising providing an isolated *E. coli* bacterium comprising,
>
> (i) a deletion or functional inactivation of an endogenous ß-galactosidase gene;
>
> (ii) an *exogenous functional β-galactosidase gene* comprising a detectable level of ß-galactosidase activity that is reduced compared to that of a wild-type *E. coli* bacterium, wherein *the level of β-galactosidase activity comprises between 0.05 and 200 units*;
>
> (iii) an inactivating mutation in a colanic acid synthesis gene; and
>
> (iv) an exogenous lactose-accepting fucosyltransferase gene;
>
> culturing said bacterium in the presence of lactose; and
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> retrieving a fucosylated oligosaccharide from said bacterium or from a culture supernatant of said bacterium.

Id. at claim 1 (emphases added). Claims 2, 3, 5, 8, 10, 12, 18, and 24–28, also at issue in this appeal, all depend from claim 1.

B

In April 2018, Glycosyn filed a complaint against Jennewein with the Commission under § 1337. Glycosyn alleged that Jennewein violated § 1337(a)(1)(B) by importing 2'-FL produced by a process covered by the '018 patent.[2] The Commission instituted an investigation based on Glycosyn's complaint.

At issue in the proceeding was whether three Jennewein *E. coli* strains engineered for making 2'-FL infringed certain claims of the '018 patent. All three strains lack the *lacZ* gene. But two of the strains, #1540 and #2410, comprise the gene fragments *lacZa* and *lacZΩ*, which when expressed together produce ß-galactosidase, resulting in ß-galactosidase activity. *See* J.A. 45901–45902; J.A. 45912; Appellant's Br. 17–19. Expression of the *lacZΩ* gene fragment in both strains is controlled by a temperature regulator. *See id.* Accordingly, the ß-galactosidase activity of the strains may be modulated by changing the culture temperature from 30 °C to 42 °C, turning the activity on as desired. *See* J.A. 45901–45902. The third strain, TTFL12, lacks a functional ß-galactosidase gene as it comprises the *lacZa* gene fragment but not the *lacZΩ* gene fragment. *See Commission Opinion*, 2020 WL 3073788, at *14; J.A. 63549–63550. Further, unlike the other two strains at issue, TTFL12 does not use lactose to produce 2'-FL. *See Commission Opinion*, 2020 WL 3073788, at *10. Jennewein has Food and Drug Administration (FDA) approval to use the #1540 and #2410[3] strains to produce 2'-FL for

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[2] Glycosyn initially alleged that Jennewein also infringed U.S. Patent No. 9,453,230 ('230 patent), related to the '018 patent, but subsequently terminated the '230 patent from the investigation.

[3] Although the #2410 strain was not included in Jennewein's Generally Recognized as Safe (GRAS) notice, *see, e.g.*, J.A. 45902, Jennewein asserts that the #2410

human consumption. *See* Appellant's Br. 20–21. The TTFL12 strain is not yet approved. *See* Appellant's Letter, No. 20-2220 (July 7, 2021), ECF No. 54.

The administrative law judge (ALJ) issued a claim construction order in December 2018. Relevant to this appeal, the ALJ construed the limitation "ß-galactosidase activity comprises between 0.05 and 200 units" to mean "ß-galactosidase activity is measurable at between exactly 0.05 and exactly [200] Miller Units, as defined in Miller." *Claim Construction Order*, 2018 WL 6837945, at *18. The ALJ declined to include a temporal requirement in the construction, asserting that the claimed activity need only be met "at some point in time." *Id.* at *17–18. As for "functional ß-galactosidase gene," the ALJ construed this limitation to mean "a functional sequence of DNA that encodes ß-galactosidase." *Id.* at *22–23. The ALJ gave the term "exogenous" its plain and ordinary meaning of "originating outside an organism, tissue, or cell." *Id.* at *9.

Using these constructions, the ALJ's September 2019 *Initial Determination* found that Jennewein's #1540 and #2410 strains infringe claims 1–3, 5, 8, 10, 12, 18, and 24–28 of the '018 patent under the doctrine of equivalents. *See Initial Determination*, 2019 WL 5677974, at *26–32. According to the ALJ, the combination of the *lacZa* and *lacZΩ* gene fragments in Jennewein's #1540 and #2410 strains is equivalent to the "exogenous functional ß-galactosidase gene" claim limitation because the combination is exogenous and the expression of the fragments results in production of ß-galactosidase. *See id.* At the time of the *Initial Determination*, the ALJ left open the question of whether the TTFL12 strain infringed any of the '018 patent claims

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strain is FDA approved to produce 2'-FL for human consumption, *see* Appellant's Br. 20–21.

because the ALJ felt "the discovery on TTFL12 was not adequate" to adjudicate infringement. *See id.* at *25.

The ALJ was unconvinced by Jennewein's arguments that to assess infringement of the claim limitation "wherein the level of ß-galactosidase activity comprises between 0.05 and 200 units," the ß-galactosidase activity of a negative control strain measured in Miller units should be subtracted from the measured activity of Jennewein's #1540 and #2410 strains. In other words, Jennewein wanted the activity of its accused strains measured against a bacterial strain lacking a functional ß-galactosidase gene (i.e., a negative control strain) rather than in absolute terms. Instead, the ALJ concluded that subtraction of the Miller unit value of a negative control strain was inappropriate for evaluating infringement because the Miller assay—"*the* test to be used to determine if a bacterium falls within the scope of the claims," *id.* at *32—does not include such a step and, moreover, Jennewein's proposed negative controls were unreliable. *See id.* at *34–35 (noting that in many cases, Jennewein's subtraction of a negative control strain resulted in negative Miller units for an accused strain).

In January 2020, the Commission decided to review in part the ALJ's *Initial Determination*, and in May 2020, issued its decision, adopting the ALJ's findings "not inconsistent" therewith. *See Commission Opinion*, 2020 WL 3073788, at *1. The Commission affirmed the ALJ's finding of infringement under the doctrine of equivalents, agreeing that the combination of the *lacZa* and *lacZΩ* gene fragments in Jennewein's #1540 and #2410 strains is equivalent to an "exogenous functional ß-galactosidase gene." *See id.* at *7. In arriving at this conclusion, the Commission agreed with the ALJ that (1) the combination of *lacZa* and *lacZΩ* gene fragments does not exist in BL21(DE3), the engineered *E. coli* bacterium used by Jennewein to make the #1540 and #2410 strains; (2) the exogenous nature of *lacZΩ*—incorporated into the #1540

and #2410 strains by Jennewein through genetic manipulation—is enough to make the resulting combination exogenous; and (3) "any difference between the claim term 'an exogenous functional ß-galactosidase gene' and the accused products is insubstantial." *See id.* Additionally, the Commission found that the *lacZa* gene fragment, which exists in the BL21(DE3) strain because of genetic engineering, is exogenous to a wild-type *E. coli* bacterium, making both the *lacZa* and *lacZΩ* gene fragments exogenous to the #1540 and #2410 strains. *See id.* at *8–9. In so finding, the Commission determined that the bacterium of the claimed method should be compared to a wild-type bacterium, not a modified, engineered one, like the BL21(DE3) strain. *See id.* Regarding the TTFL12 strain, the Commission found, contrary to the ALJ's finding, that it could adjudicate infringement because "Jennewein presented sufficient documentary evidence as well as fact and expert testimony to put Glycosyn on notice of the relevant features of the TTFL12 strain."[4] *See id.* at *12. The Commission also found "that Glycosyn failed to satisfy its burden of establishing infringement with respect to Jennewein's TTFL12 strain," as there was no evidence that the strain includes a *lacZΩ* gene fragment. *See id.* at *13–14. Therefore, the strain lacks an "exogenous functional ß-galactosidase gene comprising a detectable level of ß-galactosidase activity."[5] *See id.* at *14.

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[4] One Commissioner dissented as to this finding. *In the Matter of Certain Hum. Milk Oligosaccharides & Methods of Producing the Same*, Inv. No. 337-TA-1120, 2020 WL 3073787 (U.S.I.T.C. June 8, 2020) (Separate Views of Comm'r Schmidtlein Concurring in Part & Dissenting in Part).

[5] Jennewein's strain #1242, not at issue in the present appeal, was found by the Intellectual Property Rights Branch of the U.S. Customs and Border Patrol not to

Accordingly, the Commission entered a limited exclusion order against the 2'-FL produced by Jennewein's #1540 and #2410 strains. J.A. 5. The order did not apply to 2'-FL produced using the TTFL12 strain. J.A. 6. Jennewein timely appealed. We have jurisdiction under 28 U.S.C. § 1295(a)(6).

DISCUSSION

A

The Commission's final determinations are reviewed under the Administrative Procedure Act. 5 U.S.C. § 706; *Honeywell Int'l, Inc. v. Int'l Trade Comm'n*, 341 F.3d 1332, 1338 (Fed. Cir. 2003). We review the Commission's legal determinations de novo and its factual findings for substantial evidence. *See Finnigan Corp. v. Int'l Trade Comm'n*, 180 F.3d 1354, 1361–62 (Fed. Cir. 1999); *Linear Tech. Corp. v. Int'l Trade Comm'n*, 566 F.3d 1049, 1060 (Fed. Cir. 2009).

B

Jennewein presents three main arguments on appeal, namely that the Commission incorrectly determined that: (1) Jennewein's #1540 and #2410 strains satisfy the claim limitation requiring that "the level of ß-galactosidase activity comprises between 0.05 and 200 units"; (2) Jennewein's #1540 and #2410 strains satisfy the "exogenous functional ß-galactosidase gene" claim limitation; and (3) "the level of ß-galactosidase activity comprises between 0.05 and 200 units" claim limitation does not require the ß-galactosidase activity to occur "within the claimed range at substantially all times during 2'-FL production and retrieval,"

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infringe the asserted claims of the '018 patent for reasons similar to those detailed for the TTFL12 strain. *See* J.A. 63561–63569. Strain #1242 is FDA approved. *See* J.A. 63553; Appellee's Br. 9.

Appellant's Br. 25. We disagree with Jennewein and address each issue in turn.

1

We first consider Jennewein's argument that its #1540 and #2410 strains do not produce any ß-galactosidase activity, let alone at the level recited in the claims. Patent infringement, whether literal or under the doctrine of equivalents, is a question of fact, which we review for substantial evidence. *See Linear Tech.*, 566 F.3d at 1060. The patent owner bears the burden to prove infringement by a preponderance of the evidence. *See Spansion, Inc. v. Int'l Trade Comm'n*, 629 F.3d 1331, 1349 (Fed. Cir. 2010). Here, substantial evidence supports the Commission's finding that Jennewein's #1540 and #2410 strains literally meet the limitation requiring that "the level of ß-galactosidase activity comprises between 0.05 and 200 units."

To assess infringement of the claimed activity range, all parties acknowledge that the Miller protocol is the appropriate test. *See, e.g.*, Reply Br. 5. Yet the parties disagree on how to conduct the assay. Jennewein argues that the plain meaning of the claim language requires that the Miller unit readings reflect the activity of the inserted ß-galactosidase gene and not activity from a different source. Therefore, to assess infringement, Jennewein asserts that a negative control strain lacking a functional ß-galactosidase gene must be used to ensure that the measured ß-galactosidase activity of an accused strain is from the inserted ß-galactosidase gene, not from another source or from background noise. Per Jennewein, the Commission erred by not requiring a negative control strain in the Miller assay.

The Commission acknowledged Jennewein's contention that, to assess infringement of the activity claim limitation, one must "properly identify exactly [the] amount of Miller Unit activity . . . attributable to what would be the 'functional ß-galactosidase gene' (*i.e.*, the combination of

the *lacZα* and *lacZΩ* gene fragments) in the strain." *Initial Determination*, 2019 WL 5677974, at *32.[6] Yet the Commission, agreeing with Glycosyn, concluded that the inclusion of a negative control strain was unnecessary to measure this activity. *See id.* at *34–35. Ample evidence supports the Commission's conclusion.

As an initial matter, the record evidence links the Miller unit activity detected in both parties' assays to the inserted functional ß-galactosidase gene, not to background noise or other enzyme activity. As discussed by the Commission, the "record [did] not identify any . . . 'other enzyme besides ß-galactosidase'" in Jennewein's strains that would result in Miller assay activity. *See id.* at *34; J.A. 29596; Appellee's Br. 36 (discussing Jennewein's expert's testimony "that he does not know of 'any enzymes other than beta-galactosidase that will cleave ONPG'" (quoting J.A. 29822)). Because of "Jennewein's expert's immense metabolic engineering experience . . . and the well-studied properties of *E. coli*," the Commission did not understand how another agent with ß-galactosidase activity was not identified if it existed. *Initial Determination*, 2019 WL 5677974, at *34. And the "parties' experts testified they were unaware of such substances." *See id.*; J.A. 29596; Appellee's Br. 36.

Jennewein further argues that the #1540 and #2410 strains cannot produce ß-galactosidase activity at the low temperature (i.e., 30 °C) it uses for 2'-FL production, so any observed activity must be background noise. *See* Reply Br. 20. But possible "leakage" rebuts Jennewein's argument. The temperature regulator controlling expression of the *lacZΩ* gene fragment in Jennewein's #1540 and #2410 strains can "leak," resulting in a low-level of temperature-

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[6] Because the Commission adopted the ALJ's findings, we refer to these findings herein as the Commission's findings.

independent ß-galactosidase production and activity. *See Initial Determination*, 2019 WL 5677974, at *30; J.A. 29682 (Glycosyn's expert stating, "I don't think I've ever met a repressor that didn't leak, and it's very common to measure leakiness of promoters when you're dealing with repressible systems."); Appellee's Br. 33–34 (Glycosyn's expert stating, "'I have no reason to suspect it was anything other than beta-galactosidase activity, because I have a strain that I know possesses beta-galactosidase activity.'" (quoting J.A. 29685)). Regardless, the Miller assay specifies several controls to account for any background noise and does not use a negative control strain to do so. *See Initial Determination*, 2019 WL 5677974, at *34 n.3; J.A. 47486–47487. Glycosyn included these controls in its testing for ß-galactosidase activity. *See Initial Determination*, 2019 WL 5677974, at *37; J.A. 62173–62174.

Turning to Jennewein's proposed negative control strains, Jennewein asserts that it tested two such strains using the same procedure Glycosyn used to assess Jennewein's #1540 and #2410 strains. As the Miller unit values for the two control strains were greater than Glycosyn's Miller unit values for the #1540 and #2410 strains, Jennewein contends that Glycosyn's results for the #1540 and #2410 strains must represent only background noise. Appellant's Br. 41–42. Jennewein argues that if Glycosyn had used the negative control strains, Glycosyn's results for the #1540 and #2410 strains would have fallen below the claimed range. *Id.*

Yet in almost every sample tested, the two negative control strains selected by Jennewein had higher Miller unit values than the #1540 and #2410 strains. *See Initial Determination*, 2019 WL 5677974, at *34–35; *see also* Appellant's Br. 41 (citing J.A. 44238–44246 (data from Miller assays of the #1540 and #2410 strains), J.A. 60031–60033 (data from Miller assays of the two control strains)). Jennewein argues this is due to background noise. But because the negative control strains should be almost

identical to the accused strains, differing only in the amount of ß-galactosidase activity observed as a result of the inserted ß-galactosidase gene, the expected Miller unit values for the negative control strains should be equal to or less than the values measured for the accused strains. Therefore, one rational inference to be drawn from Jennewein's data is that its two proposed negative controls are not valid. Additionally, Jennewein's proposed negative controls inexplicably have Miller unit values quite different from each other, with the values for one strain about twice as high as the values for the other. In view of these data, we believe substantial evidence supports the Commission's finding that the resulting negative Miller unit values produced by Jennewein's assays for its accused strains "should have put Jennewein on notice that its negative control technique was unreliable on its face, or implemented unreliably, or some other assumption was incorrect." *Initial Determination*, 2019 WL 5677974, at *35.

Moreover, communications between Jennewein and a third-party company it hired to conduct infringement testing suggest that the two negative control strains preferred by Jennewein are not suitable. *See* Appellee's Br. 38–39 ("'unfortunately, the Miller activity at your 1540 (30 °C) batch is still above 0.05 after subtracting [a third possible negative control strain],' and 'if we subtract [one of the two previously discussed negative control strains] instead of the [third possible negative control strain] as reference, the value would fall below 0.05'" (quoting J.A. 51523–51524) (cleaned up)). Because of these communications, the Commission found that "Jennewein sought a control strain that would minimize the measured Miller Units." *Initial Determination*, 2019 WL 5677974, at *35. Substantial evidence supports this finding.

The Commission reasonably found that use of a negative control strain was unnecessary for assessing infringement in light of the unreliability in Jennewein's testing

with negative control strains and after accounting for possible sources of background noise or enzyme activity in the Miller protocol, detailed *supra*.[7] *See Spansion, Inc.*, 629 F.3d at 1344 (noting that under the substantial evidence test, we "must affirm a Commission determination if it is reasonable and supported by the record as a whole, even if some evidence detracts from the Commission's conclusion" (internal quotation marks omitted)); *see also Nutrinova Nutrition Specialties & Food Ingredients GmbH v. Int'l Trade Comm'n*, 224 F.3d 1356, 1359 (Fed. Cir. 2000) (discussing that as an appellate court, we are not "to reweigh the evidence and reexamine the credibility of the witnesses"). Once the Commission concluded a negative control was not needed, it credited Glycosyn's testing of Jennewein's #1540 and #2410 strains, finding "Glycosyn's testing simply hewed more closely to the Miller protocol, *i.e.*, the terms in which the invention is defined."[8] *Initial Determination*, 2019 WL 5677974, at *37. The Commission then determined that "a large majority of [the] samples exhibit[ed] Miller Unit activities within the claimed range." *Id.*

In view of the above, substantial evidence supports the Commission's finding that Jennewein's #1540 and #2410

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[7] Jennewein argues that peer-reviewed studies in the scientific literature report that *E. coli* strains without a functional ß-galactosidase gene can register Miller units. *See, e.g.*, Appellant's Br. 35. But we do not know the exact testing conditions in these studies, making comparison to the testing in the present litigation difficult.

[8] Because Jennewein does not challenge the Commission's determinations that Jennewein's incubation time for the Miller assay and ONPG control were improper, *Initial Determination*, 2019 WL 5677974, at *32–37, we do not review those findings here. *See SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1319 (Fed. Cir. 2006).

strains satisfy the limitation "the level of ß-galactosidase activity comprises between 0.05 and 200 units."

2

The Commission's finding that Jennewein's #1540 and #2410 strains satisfy the "exogenous functional ß-galactosidase gene" claim limitation, at least under the doctrine of equivalents, is supported by substantial evidence. As for the "exogenous" claim term, Jennewein argues that the Commission's construction reads the term "exogenous" out of the patent and that the combination of the *lacZα* and *lacZΩ* gene fragments in its #1540 and #2410 strains is not equivalent to an *exogenous* functional ß-galactosidase gene. Jennewein appears to contest only the Commission's findings as to the term "exogenous," not the Commission's conclusion that the combination of the *lacZα* and *lacZΩ* gene fragments in Jennewein's #1540 and #2410 strains is equivalent to a "functional ß-galactosidase gene."

Jennewein does not dispute that the *lacZΩ* gene fragment is exogenous to the #1540 and #2410 strains. *See* Appellant's Br. 47. Jennewein instead contends that the *lacZα* gene fragment is not exogenous but endogenous, making the combination of *lacZα* and *lacZΩ* gene fragments endogenous because the combination does not "originate outside" of the host strain. We disagree.

As found by the Commission, "the combination [of *lacZα* and *lacZΩ* gene fragments] does not exist in the original strain [used to make the #1540 and #2410 strains], and therefore the combination itself does not originate from within the organism," making it exogenous. *Commission Opinion*, 2020 WL 3073788, at *7. That finding is supported by substantial evidence. Thus, the exogenous nature of the *lacZΩ* gene fragment is enough to make the accused strains meet the exogenous claim limitation, regardless of whether the *lacZα* gene fragment is endogenous or exogenous. As to Jennewein's contentions that the *lacZα* gene fragment is endogenous, substantial evidence

supports the Commission's finding that the fragment is exogenous. The *lacZa* gene fragment originates outside of a wild-type *E. coli* bacterium—it was derived from a prophage—and exists in the BL21(DE3) genome only because of human intervention. *See id.* at *8–9. Substantial evidence therefore supports the Commission's finding that Jennewein's #1540 and #2410 strains satisfy the "exogenous" claim term of the "exogenous functional ß-galactosidase gene" limitation.

3

Finally, Jennewein challenges the Commission's construction of the limitation "the level of ß-galactosidase activity comprises between 0.05 and 200 units," arguing that its proper interpretation requires that the modified bacterium's level of ß-galactosidase activity be "within the claimed range substantially throughout 2'-FL production and retrieval." Appellant's Br. 56. But the claim language and intrinsic evidence support the Commission's construction, which does not adopt Jennewein's proposed temporal requirement: The level of "ß-galactosidase activity is measurable at between exactly 0.05 and exactly [200] Miller units, as defined in Miller."

Claim construction is a question of law. *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 135 S. Ct. 831, 841–42 (2015). When the Commission relies only on intrinsic evidence, such as the patent claims, specification, and prosecution history, we review that construction de novo. *Id.* at 841. Subsidiary factual findings are reviewed under the substantial evidence standard. *See Finnigan*, 180 F.3d at 1361–62. Although we begin any claim construction analysis with the language of the claim itself, *see Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (en banc), the claims "do not stand alone. Rather, they are part of 'a fully integrated written instrument,' . . . consisting principally of a specification that concludes with the claims," *id.* at 1315 (quoting *Markman v. Westview Instruments, Inc.*,

52 F.3d 967, 978 (Fed. Cir. 1995) (en banc)). Thus, "claims 'must be read in view of the specification, of which they are a part.'" *Id.* (quoting *Markman*, 52 F.3d at 979). Additionally, "the prosecution history can often inform the meaning of the claim language by demonstrating how the inventor understood the invention." *Id.* at 1317.

Looking initially to the claim language, we see nothing suggesting that the recited ß-galactosidase activity must be present substantially throughout 2'-FL production and retrieval. Three aspects of the claim language guide us to this conclusion. First, the claimed method comprises three steps: (1) *providing* an isolated *E. coli* bacterium comprising four characteristics, one of which is "an exogenous functional ß-galactosidase gene comprising a detectable level of ß-galactosidase activity that is reduced compared to that of a wild-type *E. coli* bacterium, wherein the level of ß-galactosidase activity comprises between 0.05 and 200 units"; (2) culturing said bacterium in the presence of lactose; and (3) retrieving a fucosylated oligosaccharide from said bacterium or from a culture supernatant of said bacterium. The Miller unit limitation is one of the four characteristics the engineered bacterium must possess to meet the claim's first step. In other words, the recited level of ß-galactosidase activity, measured and detected in the context of the Miller assay, is an inherent property of the provided bacterium, not the level of activity required throughout performance of the claimed method.[9] Second, the claim language

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[9] The ALJ discusses this issue at several points in the *Initial Determination*. *See, e.g.*, *Initial Determination*, 2019 WL 5677974, at *33 ("Jennewein's manufacturing process could involve . . . [a] number of variations, but that would not bear on whether the *E. coli* which Jennewein 'provides' to its process exhibits Miller Unit activity within the claimed range when put through Miller's protocol."); *Id.* at *36 (discussing the "flexibility in the temporal scope of

specifies that the fucosylated oligosaccharide product is retrieved *from the bacterium* or from the culture supernatant. As retrieval from the bacterium involves killing the bacterium (e.g., lysis of the bacterium), adopting Jennewein's proposed construction requiring the bacterium to have the recited ß-galactosidase activity during retrieval would improperly exclude a key embodiment identified in the claim. *See Primos, Inc. v. Hunter's Specialties, Inc.*, 451 F.3d 841, 848 (Fed. Cir. 2006) ("[W]e . . . should not normally interpret a claim term to exclude a preferred embodiment."); *see also MobileMedia Ideas LLC v. Apple Inc.*, 780 F.3d 1159, 1181 (Fed. Cir. 2015). Last, the claims do not mandate monitoring of the ß-galactosidase activity via the Miller assay throughout 2'-FL production and retrieval nor is there a limit on which stage or stages of the process the claimed ß-galactosidase activity must be observed. Accordingly, the claim language supports the Commission's construction.

The written description also confirms the Commission's decision not to include a temporal limitation in its construction. As with the claim language, the written description indicates that the recited Miller unit activity is an inherent characteristic of the provided bacterium, *see* '018 patent col. 6 ll. 7–11, col. 7 ll. 22–37, and discusses retrieval of the fucosylated oligosaccharide product from the bacterium as one of two favored embodiments, *see id.* at col. 2 ll. 58–62, col. 19 ll. 42–46. Further, to successfully carry out the invention, the written description does not require that ß-galactosidase activity (1) remain low during both 2'-FL production and retrieval or (2) be monitored while performing the claimed method. In fact, the written description makes clear that a low level of ß-galactosidase activity is

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the claim" in the context of when to stop the Miller assay and noting that the claimed ß-galactosidase activity range "need only be met at some point in time").

not necessary during the entirety of the method but may be useful at particular, distinct stages. *See id.* at col. 5 l. 65–col. 6 l. 11; *see also id.* at col. 7 ll. 37–45 ("This low level of cytoplasmic ß-galactosidase activity, while not high enough to significantly diminish the intracellular lactose pool, is nevertheless very useful for tasks such as phenotypic marking of desirable genetic loci during construction of host cell backgrounds, for detection of cell lysis due to undesired bacteriophage contamination in fermentation processes, or for the facile removal of undesired residual lactose at the end of fermentations."); *see also id.* at col. 9 ll. 34–50. Thus, despite Jennewein's assertions to the contrary, a low level of ß-galactosidase activity substantially throughout the claimed process is not the only way for there to be a beneficial effect. The written description therefore supports the Commission's construction. *See Hill-Rom Servs., Inc. v. Stryker Corp.*, 755 F.3d 1367, 1373 (Fed. Cir. 2014) (declining to narrowly construe a claim term "absent some language in the specification or prosecution history suggesting that the [feature] is important, essential, necessary, or the 'present invention'").

Finally, we note that the prosecution history does not support Jennewein's preferred construction of "the level of ß-galactosidase activity comprises between 0.05 and 200 units." Per Jennewein, "[d]uring the prosecution of the [related] '230 patent, Glycosyn explained that the claimed activity range 'maximizes 2'-FL end product production while preserving the advantage of depleting . . . residual lactose at the end of production runs.'" Appellant's Br. 59 (quoting J.A. 32294) (cleaned up). Jennewein contends that this statement demonstrates "that the inventors understood that the ß-galactosidase gene would register Miller unit readings throughout production and retrieval." *Id.* We disagree. At most the statement implies that ß-galactosidase activity may be useful at the end of production to eliminate remaining lactose. It is not an unequivocal disavowal of claim scope supporting Jennewein's proposed construction.

See Schindler Elevator Corp. v. Otis Elevator Co., 593 F.3d 1275, 1285 (Fed. Cir. 2010) ("The doctrine of prosecution disclaimer attaches where an applicant, whether by amendment or by argument, unequivocally disavowed a certain meaning to obtain his patent." (internal quotation marks omitted)); *see also id.* ("An argument made to an examiner constitutes a disclaimer only if it is clear and unmistakable." (internal quotation marks omitted)).

* * *

For the foregoing reasons, we affirm the Commission's claim construction and its finding of infringement under the doctrine of equivalents.

CONCLUSION

We have considered Jennewein's remaining arguments and find them unpersuasive. For the reasons stated above, we *affirm* the Commission's claim construction and judgment as to infringement, and hence its issuance of the limited exclusion order.

AFFIRMED