United States Court of Appeals for the Federal Circuit

GENZYME THERAPEUTIC PRODUCTS LIMITED PARTNERSHIP,
Appellant

v.

BIOMARIN PHARMACEUTICAL INC.,
Appellee

2015-1720, 2015-1721

Appeals from the United States Patent and Trademark Office, Patent Trial and Appeal Board, in Nos. IPR2013-00534, IPR2013-00537.

Decided: June 14, 2016

FILKO PRUGO, O'Melveny & Myers LLP, New York, NY, argued for appellant. Also represented by ANTON METLITSKY, MARGARET O'BOYLE, EBERLE SCHULTZ; DEANNA MARIE RICE, Washington, DC; CHRISTINA A. L. SCHWARZ, Fitzpatrick, Cella, Harper & Scinto, New York, NY.

GERALD MYERS MURPHY, JR., Birch Stewart Kolasch & Birch, LLP, Falls Church, VA, argued for appellee. Also represented by MARYANNE ARMSTRONG, LYNDE FAUN HERZBACH, EUGENE PEREZ.

BENJAMIN T. HICKMAN, Office of the Solicitor, United States Patent and Trademark Office, Alexandria, VA, argued for intervenor Michelle K. Lee. Also represented by THOMAS W. KRAUSE, SCOTT WEIDENFELLER, FARHEENA YASMEEN RASHEED.

Before MOORE, BRYSON, and REYNA, *Circuit Judges.*

BRYSON, *Circuit Judge*.

This is an appeal from decisions of the Patent Trial and Appeal Board in two *inter partes* review proceedings. At the behest of petitioner Biomarin Pharmaceutical Inc. ("Biomarin"), the Board held various claims of two patents owned by Genzyme Therapeutics Products Limited Partnership ("Genzyme") to be unpatentable as obvious. We affirm.

I

A

The patents at issue in this case, U.S. Patent Nos. 7,351,410 ("the '410 patent") and 7,655,226 ("the '226 patent"), are both entitled "Treatment of Pompe's Disease" and are directed to treating Pompe's disease with injections of human acid α-glucosidase.

Pompe's disease (also known as "Pompe disease") is a genetic condition associated with a deficiency or absence of the lysosomal enzyme acid α-glucosidase ("GAA"). In a healthy individual, GAA breaks down glycogen, a larger molecule, into glucose. A person with Pompe's disease has significantly reduced levels of GAA, or no GAA at all, and so is unable to break down glycogen into glucose. That inability results in glycogen accumulating in the muscles of affected patients in excessive amounts.

Pompe's disease is found in two forms—early-onset and late-onset. Early-onset or infantile Pompe's disease presents shortly after birth and is associated with the patient having no measurable GAA activity. Glycogen accumulates in the patient's heart and skeletal muscles, causing a progressive deterioration of the heart muscles. Without treatment, a patient with early-onset Pompe's disease will die from cardiac or respiratory failure before reaching one year of age.

Patients who have some degree of GAA activity, but less than normal, first develop symptoms after infancy. That condition is referred to as late-onset or juvenile Pompe's disease. Those patients develop progressive muscle weakness and respiratory symptoms due to glycogen buildup in the skeletal muscles, but only rarely do they develop the cardiac symptoms associated with early-onset Pompe's disease.

Following the discovery that Pompe's disease is associated with GAA deficiency, research efforts were focused on treating the disease through enzyme replacement therapy. Experts hoped that by injecting patients with GAA from other sources they could counteract the effects of harmful glycogen buildup. Early efforts failed, however, because the injected enzyme was predominantly taken up by the patient's liver, reducing glycogen levels there but not in the skeletal or heart muscles where the excess glycogen does the most harm.

Later researchers theorized that the failure of early experiments could be overcome by modifying the injected GAA to include mannose-6-phosphate ("M-6-P"), which promotes GAA uptake in heart and skeletal muscle cells containing M-6-P receptors, including the cells that failed to take up GAA in prior treatment attempts.

Research along that pathway led to *in vitro* studies on extracted cells. Those studies were very promising and showed that GAA modified with M-6-P would be taken up

by skeletal and heart muscle cells much more efficiently than in the case of prior enzyme replacement therapies.

Another problem that needed to be solved was how to manufacture human GAA for injection into patients with Pompe's disease. Work on that problem led to the development of a means to manufacture human GAA modified to include M-6-P. Animals such as mice and other mammals could have their genomes altered so that they would produce human GAA that could be extracted by researchers.

Finally, researchers faced the challenge of developing a dosing schedule for the enzyme replacement therapy. Gaucher disease, a lysosomal protein deficiency condition like Pompe's disease, had been successfully treated with enzyme replacement therapy. Typical dosing schedules for Gaucher disease enzyme treatments were once every two weeks, or once a week if needed. Another known factor bearing on the dosing schedule was the half-life for GAA, which was known to be 6-9 days, suggesting a relatively long dosage interval for recombinant GAA of once per week or once every other week.

By 1997, research had progressed far enough that the Food and Drug Administration approved Duke University's application for Orphan Drug Designation for a new therapy for Pompe's disease based on the injection of a recombinant form of GAA. The University announced in a press release that it would begin testing that treatment on human patients suffering with Pompe's disease.

B

In 2013, Biomarin filed petitions requesting *inter partes* review of the '410 and '226 patents. For the single claim of the '410 patent, Biomarin sought review on four grounds. The Board instituted review on two of those grounds: the combination of the Duke press release and two references known as Barton and van der Ploeg '88;

and the combination of a reference known as Reuser with Barton and van der Ploeg '88. The Board declined to institute review on two other grounds as redundant. For the '226 patent, the Board instituted review of claims 1 and 3 for obviousness based on the Duke press release, Reuser, and a reference known as van Hove. It declined to institute review for anticipation on the basis of the Duke press release alone and for obviousness based on the Duke press release and Reuser. The Board instituted review on claims 4-6 of the '226 patent for obviousness based on the Duke press release, Reuser, Barton, and van der Ploeg '88.

In patent owner responses filed in both *inter partes* reviews, Genzyme argued that because all of the combinations of references described *in vitro* experiments, a person of ordinary skill would not find those experiments predictive of results in a human patient. Because the Board did not institute review based on any references that included *in vivo* data from studies on live animals, Genzyme argued that Biomarin should not be permitted to use any of the prior art showing successful *in vivo* tests to demonstrate obviousness.

In its reply, Biomarin responded to Genzyme's arguments by citing two *in vivo* studies, referred to as van der Ploeg '91 and Kikuchi. Van der Ploeg '91 found that the addition of M-6-P to GAA led to significantly increased uptake of GAA in mouse heart and skeletal muscle tissue. A. T. van der Ploeg et al., *Intravenous Administration of Phosphorylated Acid α-Glucosidase Leads to Uptake of Enzyme in Heart and Skeletal Muscle of Mice*, 87 J. Clinical Investigation 513 (1991). Kikuchi found that GAA deficiencies in Japanese quail suffering from symptoms similar to the symptoms of Pompe's disease could be successfully treated with intravenous injections of GAA modified with M-6-P. Kikuchi et al., *Clinical and Metabolic Correction of Pompe Disease by Enzyme Therapy in*

Acid Maltase-Deficient Quail, 101 J. Clinical Investigation 827 (1998).

In its final written decisions, the Board found by a preponderance of the evidence that the challenged claims of the '410 and '226 patents would have been obvious. In its analysis of the two patents, the Board noted that Reuser disclosed every claim limitation other than a bi-weekly dosing schedule, and that the claimed dosing schedule would have been arrived at by routine optimization. For claim 6 of the '226 patent, which is directed to reducing heart muscle symptoms, the Board found that a person of ordinary skill would have understood that an effective treatment for Pompe's disease would treat that condition as well.

Although clinical trials had not been conducted as of December 7, 1998, the priority date of the patents, the Board found that a person of ordinary skill would have been motivated to pursue the clinical development of the therapy disclosed in Reuser. In response to Genzyme's arguments that there would have been no reasonable expectation that the treatment would succeed, the Board said that by December 7, 1998, "all that remained to be achieved over the prior art was the determination that a specific dose within a previously suggested dose range, and its corresponding dosing schedule, would have been safe and effective for the treatment of human patients."

By the 1998 priority date, the Board found, the field related to the development of an enzyme replacement therapy for Pompe's disease had matured to the point that it was recognized that GAA had to be translationally modified with M-6-P; *in vivo* studies had been performed in which GAA containing M-6-P had been intravenously administered to mice and Japanese Quail; it was known that human GAA containing M-6-P could be produced in the milk of transgenic animals; and the FDA was granting applications for orphan drug designation for enzyme

replacement therapy for Pompe's disease. The Board referred to the Kikuchi and van der Ploeg '91 references as support for its findings as to the state of the art regarding the *in vivo* studies. Based on the evidence before it, the Board concluded that "a person of ordinary skill in the art would have had a reasonable expectation of success at the time the invention was made," and "no more than routine processes were needed" to achieve the results recited in the disputed claims.

II

A

On appeal, Genzyme first argues that the Board violated the requirements of notice and an opportunity to respond found in the Administrative Procedure Act ("APA"). Genzyme argues that in finding that the claims at issue were unpatentable, the Board relied on "facts and legal arguments" that were not set forth in the institution decisions. Therefore, according to Genzyme, it was denied notice "of the issues to be considered by the Board and an opportunity to address the facts and legal arguments on which the Board's patentability determination [would] rest."

In a formal adjudication, such as *inter partes* review, the APA imposes certain procedural requirements on the agency. The Patent and Trademark Office must provide the patent owner with timely notice of "the matters of fact and law asserted," and an opportunity to submit facts and argument. 5 U.S.C. §§ 554(b)-(c), 557(c); *Dell Inc. v. Acceleron, LLC*, 818 F.3d 1293, 1301 (Fed. Cir. 2016). The notice and opportunity to be heard provisions of the APA have been applied "to mean that 'an agency may not change theories in midstream without giving respondents reasonable notice of the change' and 'the opportunity to present argument under the new theory.'" *Belden v. Berk-Tek LLC*, 805 F.3d 1064, 1080 (Fed. Cir. 2015) (quoting

Rodale Press, Inc. v. FTC, 407 F.2d 1252, 1256-57 (D.C. Cir. 1968)).

In this case, the Board did not "change theories in midstream," much less deny Genzyme notice of any such change. The Board's final written decisions were based on the same combinations of references that were set forth in its institution decisions. The Board instituted trial on two grounds of unpatentability with respect to the '410 patent and two grounds of unpatentability with respect to the '226 patent. In its final written decisions, the Board found the claims at issue unpatentable based on those same grounds and no others. Genzyme therefore cannot argue that it lacked notice of the specific combinations of references that the Board relied on in finding the claims invalid.[1]

The principal thrust of Genzyme's APA challenge is that the Board cited references in its final written decisions that were not specifically included in the combina-

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[1] Genzyme relies on a series of cases involving the "new ground of rejection" doctrine, as applied to examination and reexamination decisions appealed to the Board. *See In re Biedermann*, 733 F.3d 329 (Fed. Cir. 2013); *Rambus Inc. v. Rea*, 731 F.3d 1248 (Fed. Cir. 2013); *In re Leithem*, 661 F.3d 1316 (Fed. Cir. 2011); *In re Stepan Co.*, 660 F.3d 1341 (Fed. Cir. 2011). The *inter partes* review proceeding at issue in this case is not an appeal from an examiner's decision, but is a unitary trial proceeding before the Board, so those cases are not directly applicable here. Even if the "new ground of rejection" doctrine is applicable by analogy to trial proceedings before the Board, the Board did not adopt a new ground of rejection or its equivalent in this case because, as noted, the grounds on which the Board invalidated the disputed claims in its final written decisions were the same as those set forth in its institution decisions.

tions of prior art on which the Board instituted review. In particular, Genzyme objects to the Board's citation of two references dealing with *in vivo* testing, the Kikuchi and van der Ploeg '91 references.[2] However, the introduction of new evidence in the course of the trial is to be expected in *inter partes* review trial proceedings and, as long as the opposing party is given notice of the evidence and an opportunity to respond to it, the introduction of such evidence is perfectly permissible under the APA.

Genzyme's argument that the institution decision must refer to every bit of evidence that is relied on by the Board in its final written decision reflects a misunderstanding of the role of the institution decision in *inter partes* review proceedings before the Board. There is no requirement, either in the Board's regulations, in the APA, or as a matter of due process, for the institution decision to anticipate and set forth every legal or factual issue that might arise in the course of the trial. *See Boston Carrier, Inc. v. ICC*, 746 F.2d 1555, 1560 (D.C. Cir. 1984) (even when adjudicating charges of misconduct, an agency "is not burdened with the obligation to give every applicant a complete bill of particulars as to every allegation that carrier will confront"). Because the institution decision comes at the outset of the proceedings and the patentee is not obligated to respond before the Board makes its institution decision, it is hardly surprising that the Board cannot predict all the legal or factual questions that the parties may raise during the litigation.

The development of evidence in the course of the trial is in keeping with the oppositional nature of an *inter partes* review proceeding. "The parties present their evidence up front, the patent owner offers any amend-

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[2] Kukuchi was referred to in the institution decision on the '410 patent, but only in the portion of the decision citing the prior art relied upon by the petitioner.

ments, and the PTO simply decides whether the challenger has met his burden of proving invalidity." S. Rep. No. 111-18, at 57 (2009) (views of Sens. Kyl, Feingold, and Coburn). The purpose of the trial in an *inter partes* review proceeding is to give the parties an opportunity to build a record by introducing evidence—not simply to weigh evidence of which the Board is already aware.

The critical question for compliance with the APA and due process is whether Genzyme received "adequate notice of the issues that would be considered, and ultimately resolved, at that hearing." *Pub. Serv. Comm'n of Ky. v. FERC*, 397 F.3d 1004, 1012 (D.C. Cir. 2005) (Roberts, J.). As to that question, Genzyme has not shown that the Board's decisions rested on any factual or legal issues as to which Genzyme was denied notice or an opportunity to be heard at a meaningful point in the proceedings.

Genzyme cannot plausibly argue that it lacked notice that the Board might cite Kikuchi and van der Ploeg '91 in its final written decisions. Genzyme itself raised the issue of the *in vivo* studies in its patent owner responses, where it argued that Kikuchi and other *in vivo* studies that the petitioner had cited in its petitions should not be considered as rebuttal evidence. Genzyme argued:

> In fact, permitting Petitioner to rely on *in vivo* data with GAA here would require Genzyme to analyze prior art and prior art combinations involving references both (1) not included in this Board's grounds (and for Kikuchi, in particular, already denied as redundant); and (2) upon which Petitioner itself did not include in its own suggested grounds.

Biomarin then addressed both of the *in vivo* references in its replies, arguing that the *in vivo* references were relevant to show the state of the art at the time of the inventions. With both parties addressing the rele-

vance of the *in vivo* references, Genzyme had ample notice that the references were in play as potentially relevant evidence and that the Board might well address the parties' arguments regarding those references in its final written decisions.

At the oral hearing before the Board, the parties disputed what use the Board could make of the *in vivo* references, but even Genzyme conceded that the *in vivo* references could be used for some purposes. In the course of the hearing, the judges questioned Genzyme's counsel about Kikuchi, van der Ploeg '91, and one other *in vivo* reference. Counsel contended that because those references were not among the combinations of references on which the Board granted review, they could not be used to show "a reasonable expectation of success." Counsel acknowledged, however, that the "prior art as a whole" could be used "in order to figure out what's common knowledge."[3] The pertinent portion of the argument is reproduced below:

> [Genzyme's Counsel:] [Van der Ploeg is] advocating for testing in in vivo models, and, Judge Green, I think that goes in part to what you were asking me earlier, well, what is it you would need? Well, if we look at the prior art, people are talking about testing in animal models.

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[3] Genzyme argues that the Board must have used the *in vivo* references to establish a reasonable expectation of success, and that it was improper for the Board to use the references for that purpose. But the Board itself cited those references as indicators of how far "the field related to the development of an enzyme replacement therapy for the treatment of Pompe disease had developed" at the time of the inventions, which is exactly what Genzyme's counsel conceded the Board could properly do.

> JUDGE GREEN: But then I'm still unsure why Grabowski or the Japanese quail doesn't meet that.
>
> [Genzyme's Counsel]: The—so the Bijvoet reference or Kikuchi, which is the Japanese quail, we submit, Your Honors, cannot, absolutely cannot be part of the reasonable expectation of success analysis.
>
> JUDGE GREEN: So they're not—so we have to ignore that this is what would have been known to the ordinary artisan.
>
> [Genzyme's Counsel]: I think when you—when we talk about using the prior art as a whole, you can use the prior art as a whole in order to figure out what's common knowledge, but you can't, after instituting trial on certain references, bring in additional evidence that's required, that's required to show a reasonable expectation of success.

From the record as a whole, it is clear that Genzyme had actual notice of the *in vivo* references and an opportunity to respond to them—an opportunity that Genzyme took advantage of in arguing that those references could be used only for limited purposes.

Beyond that, the regulations governing *inter partes* review proceedings provide patent owners with procedural mechanisms either to respond to evidence raised in the petitioner's reply or to move to exclude it. Biomarin raised the *in vivo* data issue in its reply, stating that the fact that Biomarin's expert, Dr. Gregory M. Pastores, "testified that *in vitro* data was sufficient and was confirmed by *in vivo* data . . . should not allow Genzyme to hide behind an improper redundancy argument to prevent the Board from considering relevant references."

If Genzyme had wanted the Board to disregard those references, it could have filed a motion to exclude them.

See 37 C.F.R. § 42.64(c); *Belden*, 805 F.3d at 1081. If it had wished to submit a further substantive response to those references, it could have asked for leave to file a surreply, as longstanding Board practice allows. *See Belden*, 805 F.3d at 1081. But despite having actual notice that Biomarin was relying on the *in vivo* references to rebut Genzyme's arguments, Genzyme failed to take advantage of its procedural options to seek to exclude that evidence or to respond to Biomarin's arguments.

Although Genzyme characterizes this case as being about the sufficiency of notice and an opportunity to be heard, the substance of Genzyme's argument is to challenge the propriety of the Board's use, for any purpose, of a reference that was not part of the combinations set forth in the institution decisions.[4] It is in that context that Genzyme focuses on the Board's references in its final

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[4] Genzyme's argument is actually even broader than that. Genzyme contends that it was denied proper notice when the Board referred in its final written decisions to a portion of the Reuser reference that it did not specifically cite in the institution decisions, even though the Board cited the Reuser reference generally. Genzyme also complains that the Board referred to the Duke press release as relating to an FDA orphan drug designation, even though the orphan drug designation was not mentioned in the institution decisions when those decisions cited the Duke press release. There is no force to those arguments. Under the regime imagined by Genzyme, the Board would not only be prohibited from discussing any references not cited in its institution decisions, but it would be confined strictly to the quoted or cited portions of even those references that were included in the institution decisions, requiring something approaching word-for-word parity between the institution and final written decisions.

written decisions to Kikuchi and van der Ploeg '91. But those brief references by the Board merely served to describe the state of the art as of December 7, 1998; they were not among the prior art references that the Board relied upon to establish any claim limitations.

This court has made clear that the Board may consider a prior art reference to show the state of the art at the time of the invention, regardless of whether that reference was cited in the Board's institution decision. In *Ariosa Diagnostics v. Verinata Health, Inc.*, 805 F.3d 1359 (Fed. Cir. 2015), this court vacated the Board's decision because it appeared that the Board had declined to consider a reference simply because the reference "had not been identified at the petition stage as one of the pieces of prior art defining a combination for obviousness." *Id.* at 1365. The court in *Ariosa* held that such references "can legitimately serve to document the knowledge that skilled artisans would bring to bear in reading the prior art identified as producing obviousness." *Id.* That is exactly how the Board used the Kikuchi and van der Ploeg '91 references—as part of the Board's survey of "the field related to the development of an enzyme replacement therapy for the treatment of Pompe disease" as of the priority date of the patents.

In sum, Genzyme was not denied notice of the *in vivo* references or an opportunity to respond to them. And to the extent it contends that the Board used those references for an improper purpose, it is wrong.

B

Genzyme next argues that the Board erred in its claim construction in two respects. Genzyme's first claim construction argument is that the Board changed its construction of the "whereby" clause in the '226 and '410 patents between the institution decisions and the final written decisions. We see no merit in that argument.

Claim 1 of the '410 patent reads as follows, with the whereby clause in italics:

> A method of treating a human patient with Pompe's disease, comprising intravenously administering biweekly to the patient a therapeutically effective amount of human acid alpha glucosidase, *whereby the concentration of accumulated glycogen in the patient is reduced and/or further accumulation of glycogen is arrested*.

Claim 1 of the '226 patent contains the same whereby clause.

In the institution decisions, the Board construed the whereby clause as describing the result achieved when a patient is given a therapeutically effective dose of GAA:

> The claim feature of "whereby the concentration of accumulated glycogen in the patient is reduced and/or further accumulation of glycogen is arrested" is not a separate step, but rather a result of administering a therapeutically effective amount of human acid alpha glucosidase according to the claimed method. Such results are not generally considered a patentable feature separate from the expressly recited steps of the claimed method.

In the final written decisions, the Board construed the whereby clause in the same way, as describing the result of administering an effective dose of GAA:

> The claimed method comprises a single step: "intravenously administering biweekly to the patient a therapeutically effective amount of human acid alpha glucosidase." Claim 1 further recites the result achieved from the practice of the method recited in claim 1. Specifically, the step of intravenously administering biweekly to the patient a therapeutically effective amount of human GAA results in the reduction in the concentration of ac-

> cumulated glycogen in the patient and/or the arrest of further accumulation of glycogen. Thus, the recited whereby clause defines what is achieved from the administration of "a therapeutically effective amount of human acid alpha glucosidase" to a human patient with Pompe disease.

The Board's construction of the claim language did not change between the institution decisions and the final written decisions. In both instances the Board explained that the whereby clause defines the result of administering an effective amount of GAA rather than constituting a separate step of a method.

Genzyme's second claim construction argument is that the whereby clause should be construed to require that the reduction of glycogen occur in the patient's skeletal muscles, rather than occurring anywhere in the patient's body, including the heart, skeletal muscles, or liver.

In an *inter partes* review, the Board accords unexpired claims their broadest reasonable interpretation consistent with the specification. *In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1278 (Fed. Cir. 2015), *cert. granted*, 136 S. Ct. 890 (2016). The broadest reasonable construction of the whereby clause encompasses a reduction of accumulated glycogen anywhere in the patient, rather than necessarily in the skeletal muscles, as Genzyme argues.

As the Board noted in its final written decisions, "the claim does not recite specific organs or tissue, does not recite any specific form of Pompe disease, and does not require, for example, the patient to experience an increased life-span. The whereby clause merely requires the reduction or arrest of glycogen in the patient." Because the claim language does not expressly or implicitly require that the administration of GAA reduce glycogen in any particular organ of the body, the Board was correct to reject Genzyme's narrower construction.

Genzyme's references to portions of the common specification of the two patents that describe the reduction of glycogen buildup in the skeletal muscles do not support its proposed construction. Rather than limiting "glycogen in the patient" to the skeletal muscles, the specification describes how GAA is taken up by the heart, liver, and skeletal muscles, supporting the broader interpretation. *See* '410 patent, col. 13, ll. 41-46 ("These methods [of treating Pompe's disease] are premised in part on the availability of large amounts of human acid alpha glucosidase in a form that is catalytically active and in a form that can be taken up by tissues, particularly, liver, heart and muscle (e.g., smooth muscle, striated muscle, and cardiac muscle), of a patient being treated."); '226 patent, col. 13, ll. 27-32 (same).

The prosecution history confirms the Board's construction. In support of the amendment that added the whereby clause to the application that matured into the '410 patent, Genzyme relied, for written description support, on the following passages, which are now found in the '410 patent at col. 22, ll. 46-48, and col. 23, ll. 18-21, and in the '226 patent at col. 21, ll. 48-50, and col. 22, ll. 60-63:

> When two KO mice were injected 4 times every 6 days (experiment B), a marked decrease of total cellular glycogen was observed in both heart and liver. . . .
>
> The results showed that mice treated 13 weeks with 0.5 mg/mouse (Group A, 3 animals/Group) had an increase of activity in the liver and spleen and decreased levels of glycogen in liver and perhaps in heart.

Neither passage includes any suggestion that a decrease in skeletal muscle glycogen is required to satisfy the whereby clause. In addition, immediately following the first cited passage, the specification stated that "[n]o

effects were observed in skeletal muscle tissues with regard to total glycogen." '410 patent, col. 22, ll. 48-50; '226 patent, col. 21, ll. 50-52.

Although it was understood at the time of the invention that the claimed therapeutic effect of the patented methods would typically result in a reduction in the glycogen level in either the heart or the skeletal muscles, the evidence before the Board suggests that the patentees chose not to restrict the whereby clause in that fashion, but instead elected to describe the effects of the therapy in a more general manner, claiming any effective GAA therapy.

Based on the indications in the specification and the prosecution history that some of the experimental results did not show a reduction in the glycogen levels in skeletal muscle tissue in *in vivo* testing, it was reasonable for the Board to conclude that the patentees elected to describe the result of their method as reducing (or arresting the accumulation of) the concentration of glycogen anywhere in the patient's body. Accordingly, we conclude that the Board was correct that the broadest reasonable interpretation of the clause "whereby the concentration of accumulated glycogen in the patient is reduced" does not require a showing of a reduction in the glycogen level in the skeletal muscles, or any other particular organ, of patients treated according to the patented method.

Genzyme argues that the Board's construction cannot be correct because "reduction of glycogen in liver alone does not treat Pompe Disease, as everyone at the time of the invention fully understood." But the claims already required that the method include the administration of "a therapeutically effective amount" of GAA, so it was not necessary for the whereby clause to specify the particular organ or organs where the glycogen level was affected. Regardless of the specificity of the whereby clause, the method was required to be therapeutically effective. The

Board's construction is therefore consistent with the patentees' apparent choice to draft their claims broadly to reach any method of GAA administration that had therapeutic effects and reduced glycogen concentrations somewhere in the body.

C

Genzyme's third argument is that the Board erred by not making an explicit finding as to the level of skill of a person of ordinary skill as part of its obviousness analysis. This court has explained that the failure to make explicit findings regarding the level of skill in the art does not constitute reversible error when "the prior art itself reflects an appropriate level and a need for testimony is not shown." *Okajima v. Bourdeau*, 261 F.3d 1350, 1354-55 (Fed. Cir. 2001) (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163-64 (Fed. Cir. 1985)).

Here the Board's failure to make an explicit finding as to the level of skill is not reversible error because both parties proposed nearly identical language to describe a person of ordinary skill. Both proposed that such a person is a medical doctor or a Ph.D. in a biology-related field, has experience in lysosomal diseases, and has experience developing drugs and treatments for patients. Genzyme has not shown that there are any meaningful differences between its proposed definition of a person of ordinary skill and Biomarin's, or that the outcome of this case would have been different based on which definition the Board used. The Board's failure to make a specific finding as to the level of skill is therefore not reversible error.

D

Finally, Genzyme argues that substantial evidence does not support the Board's finding of a likelihood of success from the combination of the prior art references.

Genzyme claims in particular that the testimony of Biomarin's expert, Dr. Pastores, did not provide evidence as to the knowledge of a person of ordinary skill in the art at the time of the invention. Genzyme bases that argument on Dr. Pastores's use of the word "I" in several instances in his declaration rather than referring to "a person of ordinary skill in the art." Because he used the word "I," Genzyme argues, it is clear that Dr. Pastores was testifying to his own subjective view of the prior art rather than providing evidence of how a person of ordinary skill at the relevant date would have viewed the art.

There is no merit to Genzyme's argument. Dr. Pastores described "how someone knowledgeable and skilled in the field of enzyme replacement therapy of lysosomal storage diseases would approach the task of developing a treatment for Pompe disease using enzyme replacement therapy as of December 6, 1997." He then referred to various facts that were "well-known," were "known at the time," were "clear," were "well-appreciated," "would have been recognized," "would have been readily known," and "would have been further appreciated."

It is clear that the Board understood Dr. Pastores's testimony as being directed to the knowledge of persons of skill in the art, even though some of his statements about the prior art were prefaced with the word "I" rather than with repeated incantations of the "person of ordinary skill in the art" formulation. ("[W]e are persuaded by Dr. Pastores's testimony that the knowledge in the art regarding the treatment of Pompe disease with human GAA would have provided the motivation to select a suitable dose and dosing schedule . . . would have been informed by the clinical experience with Gaucher disease . . . and that, because 'it was well known that any enzyme replacement therapy for Pompe disease would be required for the rest of a patient's life, . . . repeated spaced admin-

istration of GAA to patients would be immediately understood upon reading [Reuser].").[5]

Finally, contrary to Genzyme's contention, Dr. Pastores's testimony was sufficient to support the Board's conclusion that a person of ordinary skill would have had a reasonable expectation of success in arresting or reducing the accumulation of glycogen through the injection of GAA. As he explained, the prior art disclosed that GAA modified to include M-6-P was effectively taken up by muscle cells and that it reduced the concentration of glycogen in those cases. And the dosage experience with Gaucher disease, in conjunction with the known half-life of GAA in the body, provided a sound basis for belief that

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[5] Genzyme argues in passing that Dr. Pastores's testimony was "hindsight-infected," based on an answer he gave in the course of his deposition. We do not discern any hindsight bias in his testimony. He testified that he was asked to review the state of the art in the early to mid-1990s, and in particular "what I understood was available in the general medical literature. And I looked at it also within the context of what I would have understood then the body of literature was telling me based on my knowledge and experience at that time." He was then asked, "Did you apply all of the knowledge you have obtained up to the present day in conducting that analysis?" to which he answered, "I would think so. I don't know how one would separate your current body of knowledge from what your knowledge was way back in time." In context, it appears that in answering that question, Dr. Pastores was simply saying that in seeking to determine what was known in the mid-1990s, he brought to that inquiry his current knowledge and experience. That is not hindsight; it is simply the use of one's current knowledge to determine, as well as possible, what the state of the art was at some point in the past.

a dosage interval of one to two weeks would be effective. In sum, there was little left to do but to confirm that the strategy suggested by the various prior art references would work. Substantial evidence therefore supports the Board's finding that a person of ordinary skill would have had a reasonable expectation of success based on the combinations of references set forth in the institution decisions.

AFFIRMED