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Paper 79
Entered: February 23, 2015

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BIOMARIN PHARMACEUTICAL INC.,
Petitioner,

v.

GENZYME THERAPEUTIC PRODUCTS LIMITED PARTNERSHIP,
Patent Owner.

Case IPR2013-00537
Patent 7,655,226

Before LORA M. GREEN, JACQUELINE WRIGHT BONILLA, and SHERIDAN K. SNEDDEN, *Administrative Patent Judges.*

SNEDDEN, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

I. INTRODUCTION

BioMarin Pharmaceutical Inc. ("Petitioner") filed a Petition to institute an *inter partes* review of claims 1 and 3–6 (Paper 1, "Pet.") of Patent No. 7,655,226 B2 (Ex. 1065, "the '226 patent"). We instituted trial for the challenged claims on the following grounds of unpatentability asserted by Petitioner:

Reference(s)	**Basis**	**Claims challenged**
Duke Press Release,[1] Reuser,[2] and Van Hove[3]	§ 103(a)	1 and 3
Duke Press Release, Reuser, Barton, [4] and Van der Ploeg[5]	§ 103(a)	4–6

Decision to Institute (Paper 9, "Dec.") 9.

After institution, the Board of Trustees of Genzyme Therapeutic Products Limited Partnership ("Patent Owner"), filed its Patent Owner's Response ("Resp."). Paper 40. Petitioner filed a Reply (Paper 49, "Reply."). Patent Owner did not file a motion to amend claims.

Petitioner relies upon the declarations of Dr. Gregory M. Pastores

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[1] Duke University, "Duke Obtains FDA Designation for Pompe Disease Therapy", press release dated September 2, 1997, 2 pages (Ex. 1002).

[2] Reuser et al., WO 97/05771, published Feb. 20, 1997 (Ex. 1005).

[3] Van Hove et al., "Purification of recombinant human precursor acid α-glucosidase," 43(3) BIOCHEM. MOL. BIOL. INT. 613-23 (1997) (Ex. 1012).

[4] Barton et al., "Replacement Therapy for Inherited Enzyme Deficiency – Macrophage-Targeted Glucocerebrosidase for Gaucher's Disease," 324 N. ENG. J. MED. 1464-1470 (1991) (Ex. 1004).

[5] Van der Ploeg et al., "Receptor-Mediated Uptake of Acid α-Glucosidase Corrects Lysosomal Glycogen Storage in Cultured Skeletal Muscle," 24(1) PEDIATRIC RESEARCH 90-94 (1988) (Ex. 1032).

("Pastores Declaration") (Ex. 1030) and Dr. Matthew Croughan ("Croughan Declaration") (Ex. 1033) in support of its Petition. Patent Owner relies upon the declaration of William Canfield, M.D., Ph.D. ("Canfield Declaration") (Ex. 2041) in support of its Response.

Petitioner filed a Motion to Exclude certain of Patent Owner's evidence. Paper 53. Patent Owner filed an Opposition (Paper 62), and Petitioner filed a Reply (Paper 64).

Patent Owner filed a Motion to Exclude certain of Petitioner's evidence. Paper 55. Petitioner filed an Opposition (Paper 58), and Patent Owner filed a Reply (Paper 65).

Oral argument was conducted on October 3, 2014. A transcript is entered as Paper 77 ("Tr.").

This Final Written Decision addresses challenges to the patentability of claims 1 and 3–6. Petitioner has shown by a preponderance of the evidence that claims 1 and 3–6 of the '226 patent are unpatentable.

Petitioner's Motion to Exclude is dismissed as moot. Patent Owner's Motion to Exclude is denied-in-part and dismissed-in-part.

A. Related Matters

The parties represent that there are no related matters. Pet. 1; Paper 7; Paper 35.

On the same day Petitioner filed its Petition in this proceeding, however, it also filed two other Petitions seeking *inter partes* review of U.S. Patent No. 7,056,712 (IPR2013-00535) and U.S. Patent No. 7,351,410 (IPR2013-00534), both of which are related to methods of treating Pompe disease

B. The ’226 patent (Ex. 1065)

The technology of the patent is enzyme-replacement therapy for patients with Pompe disease, which is caused by deficiency of the lysosomal enzyme acid α-glucosidase (“GAA”). Ex. 1065, 1:18–2:6. The patent discloses a method for treating Pompe disease comprising administering to the patient a therapeutically effective amount of human GAA. *Id.* at 2:30–43. The amount is preferably at least 10 mg of enzyme per kilogram of body weight, which may be administered weekly or two weeks apart. *Id.* at 14:1–18. The claimed treatment results in the arrest or reduction of clinical and biochemical characteristics of Pompe disease, which include, generally, an accumulation of glycogen in various tissues such as heart and skeletal muscle, and more specifically, hypertrophic cardiomyopathy. *Id*. at 13:50–15:43.

C. The Claim

Claims 1 and 6 are the independent claims of the ’226 patent, and are reproduced below:

> 1. A method of treating a human patient with Pompe’s disease, comprising administering intravenously 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.
>
> 6. 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 hypertrophic cardiomyopathy in the patient is reduced and/or arrested.

Claims 3–5 depend from claim 1.

II. DISCUSSION

A. Claim Interpretation

In an *inter partes* review, claim terms in an unexpired patent are interpreted according to their broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,766 (Aug. 14, 2012). Claim terms are given their ordinary and customary meaning, as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc*., 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definition for a claim term must be set forth in the specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

We expressly interpret below only those claim terms that require analysis to resolve arguments related to the patentability of the challenged claims.

1. Construction of the phrase "whereby the concentration of accumulated glycogen in the patient is reduced and/or further accumulation of glycogen is arrested"

We construe claim 1 to be directed to a method of treating a human patient with Pompe disease. 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 accumulated 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.

As to what is required in order to achieve the result defined by the whereby clause, Patent Owner proposes a construction that would necessarily include "lysosomal glycogen in the skeletal muscle" within the meaning of the phrase "glycogen in a patient." Resp. 12–16. Patent Owner argues that such a construction is necessary because skeletal muscle must be targeted in order to effectively treat Pompe disease. *Id.* (citing Ex 1162, 62:5–22). Patent Owner further directs our attention to a section of the '226 patent that describes complications and treatment for both the infantile and adult forms of Pompe disease. *Id.* (citing Ex 1065, 15:22–39). For the infantile form, "lysosomal glycogen storage is observed in various tissues, and is most pronounced in heart and skeletal muscle." Ex. 1065, 15:26–28. For the adult form, "skeletal muscle weakness is the major problem; cardiomegaly, hepatomegaly, and macroglossia can be seen, but are rare." *Id.* at 15:48–50.

Petitioner notes that the whereby clause of claim 1 was added during the prosecution of the claim in the parent application, which issued as U.S. Patent No. 7,351,410 (Ex. 1001).[6] Reply, 1–2 (citing Ex. 1022, 3). The paper that introduces the claim language directs the reader to where written description support for the addition of the whereby clause may be found in

[6] The '226 patent is a continuation of US 7,351,410. The claim of US 7,351,410 is challenged by the Petitioner in IPR2013-000534.

the Specification. Ex. 1022, 3. The passage of the Specification cited by the inventor during prosecution for support of the amendment provides as follows:

> 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. No effects were observed in skeletal muscle tissues with regard to total glycogen. . . .
>
> 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. One animal showed increased activity in muscles, although there was no significant decrease of glycogen in muscle.

Ex. 1001, 35:1–3, 31–34. That passage of the Specification summarizes an *in vivo* experiment that resulted in "a marked decrease of total cellular glycogen was observed in both heart and liver," but not in skeletal muscle tissue.

After consideration of the arguments presented by the parties, we do not find that the record supports Patent Owner's construction that would necessarily include "lysosomal glycogen in the skeletal muscle" within the meaning of the phrase "glycogen in a patient." We note that 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. In that regard, the evidence highlighted by Petitioner supports a conclusion that the whereby clause is reasonably interpreted to encompass the scenario where the reduction or arrest of glycogen is observed solely in the heart or liver. Accordingly, we conclude

that the broadest reasonable interpretation of the phrase "glycogen in a patient" does not necessarily include "lysosomal glycogen in the skeletal muscle." Rather, the broadest reasonable interpretation of the phrase "glycogen in a patient," as would be understood by the ordinary artisan in light of the Specification, encompasses lysosomal glycogen in the skeletal muscle, heart, or liver.

B. The Prior Art

1. Summary of Duke Press Release (Ex. 1002)

The Duke Press Release reports the U.S. Food and Drug Administration (FDA) approval of Duke University's application for Orphan Drug Designation for a new therapy for Pompe disease. Ex. 1002; Ex. 1182. The Duke Press Release describes Pompe disease as an inherited deficiency of the enzyme acid alpha glucosidase and provides a discussion of how the therapy, developed at Duke, "will be tested in infants with the most severe symptoms and for whom the disease is fatal." *Id*. With regard to how the therapy would be tested, the Duke Press Release provides as follows:

> The Duke clinical trial will test a genetically engineered form of the enzyme, expressed in a cell line developed in the laboratory of Dr. Y. T. Chen, chief of the Division of Medical Genetics in the department of pediatrics. Initially, the drug will be tested in a small number of Pompe disease infants to evaluate the safety and efficacy of the recombinant enzyme treatment. . . .
>
> Chen, who will lead the clinical trial, anticipates that recombinant enzyme injected into infants will be taken up by their muscle cells and restore normal glycogen levels. This treatment, known as an enzyme replacement therapy, would be required for the rest of these patients' lives.
>
> He said he hopes to expand the treatment to additional Pompe disease patients as safety and efficacy are demonstrated and

> supplies of the enzyme are available. Chen's team at Duke has spent more than five years developing the cell line that produces the recombinant drug.

Id.

2. Summary of Reuser (Ex. 1005)

Reuser discloses the production of phosphorylated lysosomal proteins using transgenic nonhuman mammals for use in enzyme replacement therapy as treatment for lysosomal enzyme deficiencies. Ex. 1005, Abstract, 18:12–14. Reuser expressly discloses Pompe disease[7] as such a lysosomal enzyme deficiency. *Id.* at 2:13–29. With regard to the treatment of Pompe disease, Reuser discloses as follows:

> For lysosomal diseases other than Gaucher disease the evidence suggests that enzyme therapy is most effective when the enzyme being administered is phosphorylated at the 6' position of a mannose side chain group. *For [Pompe disease] this has been tested by intravenously administering purified acid α-glucosidase in phosphorylated and unphosphorylated forms to mice and analyzing uptake in muscle tissue.* The highest uptake was obtained when mannose 6-phosphate-containing enzyme was used (Van der Ploeg et al., Pediat. Res. 28, 344-347 (1990); J. Clin. Invest. 87, 513-518 (1991)). [8]

Id. at 2:35–3:10 (emphasis added).

Reuser expressly identifies GAA as an enzyme useful for production in the disclosed transgenic animal systems. *Id.* at 4:36–37.[9] Specific to

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[7] Also referred to as Glycogen Storage Disease Type II (GSD II).

[8] Citations provided by Petitioner as Ex. 1051 and Ex. 1009, respectively.

[9] Reuser also discloses the use of a stable eukaryotic cell line transfected with the acid α-glucosidase gene for the purposes of producing the human acid α-glucosidase protein. *Id.* at 3:15–18.

human GAA, Reuser discloses a map of several transgenes containing GAA cDNA[10] or genomic DNA,[11] and details experiments in which a mannose 6-phosphate containing human GAA was produced in the milk of transgenic mice. *Id.* at 21:14–28:24. Reuser discloses that the main forms of GAA are the 110/100 kDa precursor, a 95 kDa intermediate, and 76 kDa and 70 kDa mature forms. *Id.* at 9:15–17, 28:19–24.

Reuser contemplates pharmaceutical compositions for use in enzyme replacement therapeutic procedures, and specifically pharmaceutical compositions for intravenous administration. *Id.* at 18:36–20:28. Furthermore, Reuser provides general guidance with regard to dosage and dosage regimen. Specifically, Reuser provides as follows:

> For individuals at risk of lysosomal enzyme deficiency disease, the pharmaceutical composition [sic] are administered prophylactically in an amount sufficient to either prevent or inhibit accumulation of metabolite. An amount adequate to accomplish this is defined as a "therapeutically-" or "prophylactically-effective dose." Such effective dosages will depend on the severity of the condition and on the general state of the patient's health, but will generally range from about 0.1 to 10 mg of purified enzyme per kilogram of body weight.

Id. In the case of Pompe disease, glycogen is the metabolite. *Id.* at 2:13–29.

With regard to dose, Reuser discloses as follows:

> For therapeutic applications, the pharmaceutical compositions are administered to a patient suffering from established disease in an amount sufficient to reduce the concentration of accumulated metabolite and/or prevent or arrest further accumulation of metabolite. For individuals at risk of lysosomal enzyme deficiency disease, the pharmaceutical

[10] Ex. 1005, Fig. 1.

[11] Ex. 1005, Fig. 2.

> composition are administered prophylactically in an amount sufficient to either prevent or inhibit accumulation of metabolite. An amount adequate to accomplish this is defined as a "therapeutically-" or "prophylactically-effective dose." Such effective dosages will depend on the severity of the condition and on the general state of the patient's health, but will generally range from about 0.1 to 10 mg of purified enzyme per kilogram of body weight.

Id. at 20:15–28.

3. Summary of Van Hove (Ex. 1012)

Van Hove discloses a purification of large quantities of recombinant precursor GAA for the purposes of enzyme replacement therapy in Pompe disease. Ex. 1012, 613. In particular, Van Hove provides as follows:

> Large quantities of recombinant enzyme are required for in vivo experimentation in the animal model, and eventually for use in medicine. A method amenable to scale up is now needed to efficiently purify recombinant precursor enzyme from tissue culture medium. The preferred method should result in a high level of purification with a considerable yield, while preserving the mannose-6-phosphorylation of the protein required for efficient lysosomal targeting. It should be highly reproducible, avoid toxic buffers, preferably use commercially available gels on standard equipment. We aimed to develop such a purification method as described below.

Id. at 614. Precursor GAA is the 110 kDa form of the enzyme. *Id.* at 617.

4. Summary of Barton (Ex. 1004)

Barton describes a clinical trial in which patients with Gaucher Disease[12] were administered glucocerebrosidase for enzyme replacement

[12] Gaucher disease is a lysosomal storage disorder caused by an insufficiency of glucocerebrosidase. Ex. 1004, 1464.

therapy on a biweekly intravenous administration schedule. Ex. 1004, Abstract.

5. Summary of Van der Ploeg (Ex. 1032)

Van der Ploeg describes an *in vitro* study using cultured skeletal muscle cells from a patient with Pompe disease. Ex 1032, Abstract. Cultured skeletal muscle cells were incubated with GAA containing mannose-6-phosphate purified from human urine. *Id.* Van der Ploeg reports that the "[e]fficient uptake of acid α-glucosidase was achieved by using the mannose-phosphate receptor on the cell surface as a target for an enzyme precursor with phosphorylated high-mannose types carbohydrate chains purified from human urine." *Id.* The enzyme was reported to have a half-life of 6–9 days. *Id.* at 91.

C. Obviousness of Original Claims

1. Obviousness of Claims 1 and 3 over the Combination of Duke Press Release, Reuser, and Van Hove

Petitioner contends that claims 1 and 3 are obvious over the combination of Duke Press Release 1997, Reuser, and Van Hove. Pet. 41–44. In our Decision to Institute, we found that the combination of Duke Press Release, Reuser, and Van Hove disclosed each element of claims 1 and 3. Dec. 7–8. Patent Owner does not contend that the combination of references fail to address each element of the claims. Rather, Patent Owner contends that a person of ordinary skill in the art would not have had a reasonable expectation of successfully reducing or arresting further accumulation of glycogen in a patient's muscle cells. Resp. 35–40.

We are not persuaded. First, Patent Owner's argument is premised on a claim construction that would require the phrase "glycogen in the patient" in claim 1 necessarily to include lysosomal glycogen in skeletal muscle. *Id.* at 14–16. As discussed above in Section II.A.1, however, we do not adopt Patent Owner's proposed claim construction in this regard. As such, we do not understand Patent Owner's arguments with regard to a reasonable expectation of success to be applicable to the question of whether or not a person of ordinary skill in the art would have had a reasonable expectation of successfully reducing or arresting further accumulation of glycogen in a patient's other tissues such as heart and liver.

To the extent that Patent Owner's arguments are applicable under our claim construction, we note that a reasonable expectation of success does not require absolute predictability. *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). The fact that a suggested dose (as taught in Reuser) and dosing schedule had not been established yet as safe and effective in human clinical trials at the time of invention does not demand a conclusion of nonobviousness. While we recognize that there would have been some degree of unpredictability for the successful treatment of Pompe disease from the administration of GAA, the preponderance of evidence of record indicates that 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 December 7, 1998, the field related to the development of an enzyme replacement therapy for the treatment of Pompe disease had developed to the point at which 1) it was recognized that GAA must be post-

translationally modified with mannose-6-phosphate to promote cellular uptake through a mannose-6-phosphate receptor *in vitro*;[13] 2) *in vivo* studies had been performed in which GAA containing mannose-6-phosphate was intravenously administered to mice[14] and Japanese Quail;[15] 3) it was known that mannose 6-phosphate containing human GAA could be produced in the milk of transgenic animals;[16] and 4) the FDA was granting applications for orphan drug designation for enzyme replacement therapy for Pompe disease using recombinant GAA.[17] Thus, this is not a case where the prior art teaches merely to pursue a "general approach that seemed to be a promising field of experimentation" or "gave only general guidance as to the particular form of the claimed invention or how to achieve it." *O'Farrell*, 853 F.2d at 903; *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1167 (Fed. Cir. 2006).

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[13] Ex. 1005 at 2:35–3:10.

[14] Ex. 1009 presents data suggesting that GAA containing mannose 6-phosphate is taken up in the skeletal muscle and heart of mice after intravenous administration.

[15] Ex. 1007 presents data suggesting that the intravenous administration of human GAA to GAA-deficient Japanese reduced glycogen levels in the heart, liver and muscle and produced muscle improvement. Ex. 1007, Abstract. The authors conclude that "[t]hese data also suggest enzyme replacement with recombinant human GAA is a promising therapy for human Pompe disease." *Id.*

[16] Ex. 1005 at 21:14–28:24.

[17] Ex. 1002; Ex. 1182. We further note that the FDA application process requires an applicant to provide "enough information to establish a medically plausible basis for expecting the drug to be effective in the rare disease." Ex. 1029. Furthermore, as stated by Dr. Canfield, "a [skilled artisan] would know, and would understand from Ex 1002, that the purpose of the proposed clinical trial would be to evaluate whether the administered enzyme was safe and effective in humans and to determine the appropriate dose." Ex 2041 ¶ 81 (citing Ex 1002, 2).

Finally, we note that the absence in the record of evidence identifying a difference between the prior art and the subject matter of the claims further persuades us that no more than routine processes were needed to achieve the results recited in claim 1. For example, the absence of any discussion with regard to unexpected or superior results associated with any feature of claims 1 or 3 further persuades us that the claimed subject matter was a product of routine clinical trial processes. That is, the prior art brought the subject matter of the claims within the technical grasp of a person of ordinary skill in the art rendering it obvious, absent objective evidence of nonobviousness. *Pfizer*, 480 F.3d at 1344 ("[O]bviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success.").

In view of the above, we conclude that a person of ordinary skill in the art would have had a reasonable expectation of success at the time the invention was made. What remained was the execution of human clinical trials, arguably "routine" to a person of ordinary skill in the art, to verify the expectation that a specific dosage (within a previously suggested dosage range) and corresponding dosage regimen would have been safe and effective. *Cf. Pfizer*, 480 F.3d at 1367 ("[E]xperiments used by Pfizer's scientists to verify the physicochemical characteristics of each salt are not equivalent to the trial and error procedures often employed to discover a new compound where the prior art gave no motivation or suggestion to make the new compound nor a reasonable expectation of success."); *Velander v. Garner*, 348 F.3d 1359, 1368 (Fed. Cir. 2003) (stating that one skilled in the art would view variability in producing fibrinogen in transgenic mammals as

evidence that "expense, time and effort" would be involved did not equate to a conclusion that success was unlikely).

2. Obviousness of Claims 4–6 over the Combination of Duke Press Release, Reuser, Barton, and Van der Ploeg

a. Obviousness of the recited dose and dosing schedule

Claim 4 depends directly from claim 1 and requires weekly administration of GAA. Independent claim 6 differs from claim 1, *inter alia*, in that the method of claim 6 requires biweekly administration of the enzyme. Petitioner relies on Barton (Ex. 1004) and Van der Ploeg (Ex. 1032) to reach the "weekly" and "biweekly" elements of claims 4 and 6.

Claim 5 depends from claim 4 and requires that the therapeutically effective amount of human GAA is at least 10 mg/kg body weight of the patient. Petitioner relies on Reuser to meet that limitation, as Reuser discloses a dosage range from 0.1 to 10 mg/kg of purified enzyme per kilogram of body weight. Pet. 47 (citing Ex. 1005, 20:27–28).

Petitioner argues that "[d]etermination of how much and how often to administer the enzyme . . . is a matter of routine optimization" and that "[t]he '226 patent is claiming the result of a typical drug development pathway based on previous testing, such as *in vitro* and *in vivo* animal model studies." Pet. 4–5; *see also, id.* at 9 ("All the inventors of the van Bree '226 patent did was to follow a typical drug development pathway laid out in the prior art, where the use of GAA to successfully treat Pompe disease in a human patient was a predictable outcome based on previous *in vitro* and *in vivo* studies.").

Patent Owner makes several arguments related to the dose and dosing schedule elements of the claims. First, Patent Owner contends that a person

of ordinary skill in the art would not have had motivation to combine Barton with Duke Press Release, Reuser, and Van der Ploeg due to the significant differences between Gaucher disease and Pompe disease. Resp. 41.

Second, Patent Owner argues that reliance on Van der Ploeg is flawed because "mere knowledge of the target receptor plus *in vitro* data indicating uptake via that receptor" is insufficient to predict success and further notes particular complications that arise when transitioning from an *in vitro* model to an *in vivo* model. *Id.* at 23–24.

Patent Owners remaining arguments are directed to the predictability of clinical trials in general. *Id.* at 44–46. Additionally, Patent Owner argues that the grant of orphan drug designation disclosed in Duke Press Release would not be understood by a person of ordinary skill in the art to mean that the therapy had a reasonable expectation to be effective for its intended use. *Id.* at 32–35. Patent Owner adds that that the standards used by the FDA to grant of orphan drug designation is low and ultimately "unrelated to the standard regulatory requirements for marketing approval or authorization to begin clinical trials." *Id.* at 33–34 (citing Ex 2043 ¶¶ 24, 27–28, 42–43; Ex 2023; Ex 2027, 368; Ex 2006; Ex. 2036, 520 (Fig. 1a)).

After consideration of the evidence and arguments summarized above, we find that Petitioner has the better position. We recognize that the record shows that human clinical trials were not initiated prior to December 7, 1998, the priority date of the '226 patent. The record shows also that an ordinary artisan would have understood that to treat Pompe disease effectively using GAA, sufficient quantities of enzyme would have to reach the patient's muscle cells, which could potentially require high doses that could introduce safety and efficacy hurdles resolvable only with human

clinical trials.[18] Resp. 55–57 (citing Ex 2041 ¶ 105; Ex 2042 ¶¶ 67-68, 86, 99, 121-122; Ex 1162, 63:14-64:13, 67:2-11; Ex. 1030 ¶ 75; Ex 1011). Accordingly, a person of ordinary skill in the art could not have predicted with absolute certainty that a safe and effective dosing regimen for using GAA in a method of treating Pompe disease could be achieved.[19]

Despite this recognized difficultly, however, we are persuaded that, under the facts of this case, a person of ordinary skill would have been motivated to pursue the clinical development of the therapy disclosed in Reuser. *See* Section II.B.2 for summary of Rueser. Given that Reuser discloses a pharmaceutical composition containing GAA, a dose range that includes the recited dose range of 1–10 mg of enzyme per kilogram of body weight of the individual, a method of making the composition using transgenic animals, and a method of using the composition in an enzyme replacement therapy for the treatment of Pompe disease, what remained to

[18] As discussed in Section II.A.1, we do not interpret the claim to necessarily require the reduction or arrest of stored glycogen in skeletal muscle, but understand that achieving such a result is important for the complete treatment of both forms of Pompe disease. Nonetheless, we include the concept of reduction or arrest of stored glycogen in skeletal muscle in our analysis as we do not find its inclusion to hinder our analysis. That is, whether we include or exclude the result of reduction or arrest of stored glycogen in skeletal muscle within the scope of the claims, our conclusions remain the same, albeit achievement of the reduction of glycogen in the heart and liver appear to be less controversial, and thus the evidence suggests there was a greater expectation of success with regard to these tissues.

[19] We recognize that "absolute predictability of success" is not the criterion "[f]or obviousness under § 103, all that is required is a reasonable expectation of success." *O'Farrell*, 853 F.2d at 903.

be achieved to arrive at the claimed subject matter was the selection of a specific dose and dosing schedule for a treatment regimen. Pet. 4–5.

For example, in 1973, an infant with Pompe disease was intravenously administered GAA derived from human placenta. Resp. 1–2; Ex. 1010; Ex. 2041 ¶ 31. That patient died. *Id.* Since that time, however, it was discovered that "mannose-6-phosphate receptors are present at the cell surface of myotubes and mediate efficient uptake of lysosomal enzymes containing carbohydrate chains with mannose-6-phosphate residues." Ex. 1032, 90 (citations omitted). The record suggests that it was this discovery, combined with the ability to produce large quantity of enzyme using recombinant technology, which led the field toward human clinical trials. Ex. 1030 ¶ 29 (citing Ex. 1006). Patent Owner does not direct us sufficiently to hurdles that needed to be overcome by the inventors of the '226 patent to achieve the claimed subject matter.

Thus, our decision rests on the answer to the question of whether the dose and dosing schedule recited in the claims were nothing more than the result of routine optimization that would have been obvious to one of ordinary skill in the art. We conclude that a preponderance of the evidence establishes that the selection of the dose and dosing schedule would have been a routine optimization of the therapy outlined in Reuser (Ex. 1005, 18:36–20:28), which would have been achievable through the use of standard clinical trial procedures (Ex. 1030 ¶¶ 74–90). Stated differently, the subject matter of the claims was disclosed in the prior art and the experimentation needed to confirm the successful application of the method disclosed in the prior art was "'nothing more than the routine' application of a well-known problem-solving strategy, . . . 'the work of a skilled [artisan],

not of an inventor.'" *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1368 (Fed. Cir. 2007) (quoting *Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804, 809 (Fed. Cir. 1989); *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1371 (Fed. Cir. 2006); *see also In re Aller*, 220 F.2d 454, 456 (CCPA 1955) ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."); *In re Boesch*, 617 F.2d 272, 276 (CCPA 1980) ("[D]iscovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art."). The motivation to optimize the therapy disclosed in Reuser "flows from the 'normal desire of scientists or artisans to improve upon what is already generally known.'" *Pfizer*, 480 F.3d at 1348 (quoting *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003)).

We further note that this is not a case where there were "numerous parameters" to try. *Pfizer*, 480 F.3d at 1364 (citing *Medichem*, 437 F.3d at 1165 ("to have a reasonable expectation of success, one must be motivated to do more than merely to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.") (internal quotations omitted)). Rather, we are persuaded by Dr. Pastores' 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 (Ex. 1030 ¶ 38), would have been informed by the clinical experience with Gaucher disease (*id.* at ¶ 74 (citing Ex. 1004, 1056, 1057)), 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 administration of GAA to patients would be immediately understood upon reading [Reuser]" (*id.* at ¶ 58).

b. Reducing or Arresting Hypertrophic Cardiomyopathy

Independent claim 6 further differs from claim 1, *inter alia*, in that the method of claim 6 requires hypertrophic cardiomyopathy in the patient to be reduced and/or arrested, as oppose to the concentration of accumulated glycogen in the patient to be reduced and/or arrested. The preponderance of evidence shows that the concentration of accumulated glycogen in the patient is related to the condition of hypertrophic cardiomyopathy. *See also*, Ex 2041, ¶ 24 ("[Pompe disease] patients develop accumulation of glycogen in the heart and skeletal muscle, which results in progressive deterioration of the heart muscle (cardiomyopathy) and generalized muscle weakness"). As such, we conclude that if the concentration of accumulated glycogen in the patient is arrested, for example, then the condition caused by this accumulation is also necessarily arrested, at least in some fashion. Accordingly, we conclude that independent claim 6 is unpatentable for the reasons set forth above with regard to claim 1.

3. Secondary Considerations

As to secondary considerations, we note that factual inquiries for an obviousness determination include secondary considerations based on evaluation and crediting of objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). Notwithstanding what the teachings of the prior art would have suggested to one with ordinary skill in the art at the time of the invention, the totality of the evidence submitted,

including objective evidence of nonobviousness, may lead to a conclusion that the claimed invention would not have been obvious to one with ordinary skill in the art. *In re Piasecki*, 745 F.2d 1468, 1471–1472 (Fed. Cir. 1984).

However, such a conclusion requires the finding of a nexus to establish that the evidence relied upon traces its basis to a novel element in the claim and not to something in the prior art. *Institut Pasteur & Universite Pierre et Marie Curie v. Focarino*, 738 F.3d 1337, 1347 (Fed. Cir. 2013). All types of objective evidence of nonobviousness must be shown to have nexus. *In re GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995) (nexus generally); *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996) (commercial success); *Rambus Inc. v. Rea*, 731 F.3d 1248, 1256 (Fed. Cir. 2013) (long-felt need); *Muniauction, Inc. v. Thomson Corp.*, 532 F.3d 1318, 1328 (Fed. Cir. 2008) (praise); *Stamps.com Inc. v. Endicia, Inc.*, 437 F. App'x 897, 905 (Fed. Cir. 2011) (skepticism).

Patent Owner argues that several lines of objective evidence (or "secondary considerations") demonstrate the non-obviousness of the challenged claims. Resp. 56–60. In particular, Patent Owner argues long-felt but unmet need, skepticism, praise, and commercial success. *Id.* Patent Owner's arguments with regard to each of the secondary considerations, however, fail to establish a nexus between any feature of the claims and any asserted objective evidence of non-obviousness. Rather, the discussion of secondary considerations relates to the merits of the therapeutic compositions of GAA brought to market by Patent Owner. Such compositions, however, were known in the art. *See* discussion in Sections II.C.1 and II.C.2. Accordingly, the objective evidence does not persuade us that claim 1 and 3–6 are non-obvious.

4. Conclusion

In view of the above, we conclude that Petitioner has demonstrated the unpatentability of claims 1 and 3–6 by a preponderance of the evidence.

III. MOTIONS TO EXCLUDE

A. PETITIONER'S MOTION TO EXCLUDE

Petitioner seeks to exclude paragraphs 61, 62, 63, and 66 of the Canfield Declaration, Ex. 2041, because the testimony allegedly is based on insufficient facts or data. Paper 55. Because we do not rely on any of paragraphs 61, 62, 63, and 66 of Ex. 2041 to reach the final decision, we dismiss Petitioner's motion as moot.

B. PATENT OWNER'S MOTION TO EXCLUDE

1. Ex. 1002

Patent Owner seeks to exclude Ex. 1002 as not properly authenticated under Federal Rules of Evidence ("FRE") 901–902. Paper 55, 2–5. Patent Owner further seeks to exclude Ex. 1002 as inadmissible hearsay under FRE 802. *Id.* at 6–7. Patent Owner seeks also to exclude Ex. 1002 under FRE 402 and 403 because it cannot qualify as a printed publication and thus "Exhibit 1002 is irrelevant (FRE 402), can serve only to prejudice Genzyme, [and] is confusing in this context (FRE 403) as it cannot have any bearing on the issue of validity." *Id.* at 7–8.

Federal Rule of Evidence 901(a) states that the authentication requirement is satisfied if the proponent presents "evidence sufficient to support a finding that the item is what the proponent claims it is." Here, Petitioner has presented evidence to authenticate Ex. 1002. That evidence

includes an article from the Herald-Sun (Durham, NC) (Ex. 1144)[20] published September 3, 1997,[21] discussing the content of the Duke Press Release, and the affidavit of Ms. Beth Nichol, an Investigative Associate at Nichol Investigative Services, LLC, who obtained a copy of the original Duke Press Release from a Duke University library having a Duke University trade inscription (Ex 1182, Ex C). Under FRE 902(6)–(7),[22] Ex. 1144 and Ex. 1182, Ex. C are self-authenticating. Based on the evidence before us, we determine that Ex. 1002 has been authenticated under FRE 901(b)(1), 901(b)(4), 902(6), and 902(7) to warrant its admissibility. The fact that the Duke Press Release was reported in the Herald-Sun newspaper establishes the Duke Press Release as a printed publication.

We further note that Patent Owner fails to identify specifically the portions of Ex. 1002 that it believes to be prejudicial and confusing, or why we would be unable to weigh this evidence without prejudice or confusion. Rather, Patent Owner's objections go more to the weight that Ex. 1002 should be afforded, rather than to its admissibility. A motion to exclude is

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[20] Exhibit 1144 has the LexisNexis® trade inscription.

[21] The Duke Press Release is dated September 2, 1997.

[22] Fed. R. Evid. 902. Evidence that Is Self-Authenticating

The following items of evidence are self-authenticating; they require no extrinsic evidence of authenticity in order to be admitted:

. . . .

(6) Newspapers and Periodicals. Printed material purporting to be a newspaper or periodical.

(7) Trade Inscriptions and the Like. An inscription, sign, tag, or label purporting to have been affixed in the course of business and indicating origin, ownership, or control.

not the proper vehicle to challenge the sufficiency of evidence. It is within our discretion to assign the appropriate weight to be accorded evidence.

Moreover, we note that there is a strong public policy for making all information filed in an administrative proceeding available to the public, especially in a *inter partes* review, which determines the patentability of claims in an issued patent. It is better to have a complete record of the evidence submitted by the parties than to exclude particular pieces of evidence.

With regard to Patent Owner's hearsay argument, we agree with Petitioner that Ex. 1002 is offered as evidence of what it describes to an ordinary artisan, not for proving the truth of the matters addressed in the document. Paper 65, 8. Accordingly, Ex. 1002 is not hearsay requiring the remedy of exclusion.

Patent Owner further argues that the existence of minor typographical errors in Ex. 1002 prove that Ex. 1002 was not created by Duke University. Paper 65. We are not persuaded. Ex. 1002 appears to be an Internet copy of the original press release, obtainable from a Duke University library. Ex. 1182. Ex. 1002 and the original press release (Ex. 1182, Ex. C) are substantively the same. The presence of minor typographical errors in Ex. 1002 does not persuade us that the content of Ex. 1002 was not created and released by Duke University on September 2, 1997.

2. Exs. 1030 and 1033

Patent Owner seeks to exclude portions of the declarations of Petitioner's experts Dr. Pastores (Ex. 1030) and Dr. Croughan (Ex. 1033), based on their alleged admissions that they lack expertise on in the areas of pre-clinical studies or scaling, and because their testimony allegedly is based

on insufficient facts or data. Paper 55, 10–14 (citing FRE 702). Specifically, Patent Owner seeks to exclude paragraphs 25, 26, 31, 38, 39, 44–47, 51–57, 59, 63, 66–71, 74–79, 84–89, 91, 93, and 94 of Ex. 1030 and paragraphs 77–85, 87, 92, 93, 96–100, 102, 108–111, and 114–116 of Ex. 1033.

We have reviewed the cited portions of the testimony provided by Dr. Pastores and Dr. Croughan, and see no basis which would warrant the extreme remedy of exclusion. Patent Owner's objections go to the weight and sufficiency of the testimony, rather than its admissibility. We are capable of discerning from the testimony, and the evidence presented, whether the witness' testimony should be entitled to any weight, either as a whole or with regard to specific issues. We weigh such testimony on an issue-by-issue basis, as appropriate. Furthermore, Patent Owner had the opportunity to address any alleged deficiencies in the testimony of Dr. Pastores and Dr. Croughan in its Patent Owner's Response and we are capable of taking note of those inadequacies and weighing that testimony accordingly.

Thus, we deny Patent Owner's motion seeking to exclude the testimony of Dr. Pastores and Dr. Croughan in this proceeding.

3. Exs. 1021, 1063, 1064, 1071, 1072, 1116, 1174, and 1175

Patent Owner seeks to exclude Exhibits 1021, 1063, 1064, 1071, 1072, 1116, 1174, and 1175 as inadmissible hearsay. Paper 55, 9 and 14–15. Because we do not rely on any of these exhibits to reach the final decision, we dismiss Patent Owner's motion to exclude Exhibit 1021, 1063, 1064, 1071, 1072, 1116, 1174, and 1175 as moot.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1 and 3–6 of the ’226 patent is determined to be unpatentable;

FURTHER ORDERED that Petitioner’s Motion to Exclude is dismissed as moot;

FURTHER ORDERED that Patent Owner’s Motion to Exclude is denied-in-part and dismissed-in-part; and

FURTHER ORDERED that because this is a Final Written Decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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