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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GREEN CROSS CORPORATION,
Petitioner,

v.

SHIRE HUMAN GENETIC THERAPIES, INC.,
Patent Owner.

Case IPR2016-00258
Patent 9,051,556 B2

Before LORA M. GREEN, RAMA G. ELLURU, and
ROBERT A. POLLOCK, *Administrative Patent Judges.*

POLLOCK, *Administrative Patent Judge*.

DECISION
Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Green Cross Corporation ("Petitioner") filed a Petition (Paper 2; "Pet.") to institute an *inter partes* review of claims 1–3, 9–13, 16, and 17 of US 9,051,556 B2 (Ex. 1001; "the '556 patent"). Shire Human Genetic Therapies, Inc. ("Patent Owner") filed a Patent Owner Preliminary Response ("Prelim. Resp."). Paper 10.

We have jurisdiction under 35 U.S.C. § 314. The standard for instituting an *inter partes* review is set forth in 35 U.S.C. § 314(a), which states that an *inter partes* review may not be instituted unless "the information presented in the [Petition and any Preliminary Response] shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." Upon consideration of the current record, we conclude that Petitioner has established that there is a reasonable likelihood that it would prevail with respect to at least one of the challenged claims. Accordingly, the Petition to institute an *inter partes* review as to claims 1–3, 16, and 17 of the '556 Patent is granted; for the reasons set forth below, we do not authorize institution with respect to claims 9–13.

A. Related Proceedings

Petitioner states that "[t]here are no related judicial proceedings involving U.S. Patent No. 9,051,556." Paper 5; *see* Pet. 7.

B. The '556 Patent

Iduronate-2-sulfatase ("I2S" or "IDS") is a lysosomal enzyme responsible for removing the terminal 2-O-sulfate moieties from glycosaminoglycans such as heparin sulfate and dermatan sulfate. Ex. 1001,

1:23–32. Hunter syndrome or Mucopolysaccharidosis type II ("MPS II") is a progressively debilitating condition resulting from a deficiency of I2S activity and the resulting cellular accumulation of sulfated glycosaminoglycans. *Id.* at 1:23–24, 33–51. "Enzyme replacement therapy (ERT) is an approved therapy for treating Hunter syndrome (MPS II), which involves administering exogenous replacement I2S enzyme to patients with Hunter syndrome." *Id.* at 52–55.

The '556 patent Specification discloses methods for isolating recombinant I2S "using a process involving as few as four chromatography columns." *Id.*, Abstract. In one aspect, this involves "purifying recombinant I2S protein from an impure preparation using a process based on one or more of anion-exchange chromatography, cation-exchange chromatography, mixed-mode chromatography, and hydrophobic interaction chromatography." *Id.* at 2:16–21. In some embodiments, the resultant recombinant I2S protein "contains less than 100 ng/mg Host Cell Protein (HCP)." *Id.* at 2:26–34. HCP levels may be measured using, for example ELISA (enzyme-linked immunosorbent assay) or SDS-PAGE (sodium dodecyl sulfate polyacrylamide gel electrophoresis) with silver staining. *Id.* at 22:11–25; 31:28–29, 65–66; 35:23.

"In some embodiments, purified recombinant I2S protein has a specific activity, as measured by in vitro sulfate release activity assay using heparin disaccharide as substrate." *Id.* at 22:53–61. Alternatively, "the enzymatic activity of recombinant I2S protein may also be determined using various other methods known in the art such as, for example, 4-MUF assay which measures hydrolysis of 4-methylumbelliferyl-sulfate to sulfate and naturally fluorescent 4-methylumbelliferone (4-MUF)." *Id.* at 23:20–25.

Using this assay, "[o]ne milliunit of activity is defined as the quantity of enzyme required to convert one nanomole of 4-MUF-SO_4 to 4-MUF in one minute at 37ºC." *Id.* at 23:43–46.

C. Challenged Claims

Petitioner challenges claims 1–3, 9–13, 16, and 17 of the '556 patent. Claim 1 is illustrative of claims 1–3, 16, and 17 (italics added):

> 1. A composition comprising purified recombinant iduronate-2-sulfatase (I2S) having the amino acid sequence of SEQ ID NO:1, wherein the purified recombinant I2S comprises at least 70% conversion of the cysteine residue corresponding to Cys59 of SEQ ID NO:1 to Cα-formylglycine (FGly), *wherein the purified recombinant I2S contains less than 150 ng/mg Host Cell Protein (HCP).*

Claim 9 is illustrative of claims 9–13 (italics added):

> 9. A composition comprising purified recombinant iduronate-2-sulfatase (I2S) having the amino acid sequence of SEQ ID NO:1,
>
> wherein the purified recombinant I2S comprises at least 70% conversion of the cysteine residue corresponding to Cys59 of SEQ ID NO:1 to Cα-formylglycine (FGly), and *wherein the purified recombinant I2S protein has specific activity of at least 20 U/mg as determined by an in vitro 4-MUF-SO_4 to 4-MUF conversion assay.*

D. Prior Art and Supporting Evidence

Pursuant to 37 C.F.R. § 42.104(b), Petitioner identifies the following prior art as the basis of challenging claims 1–3, 9–13, 16, and 17 of the '556 patent. *See* Pet. 13.

> Jin et al. US 2014/0242059 Al, published Aug. 28, 2014. Ex. 1002 ("Jin").
>
> Wolter and Richter, *Assays for Controlling Host-Cell Impurities in Biopharmaceuticals*, BIOPROCESS INT'L 40–46 (Feb. 2005). Ex. 1011 ("Wolter").

U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, *Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use*, Docket No. 94D-0259 (February 28, 1997). Ex. 1012 ("CEBER").

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, *Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products Q6B* (March 10, 1999). Ex. 1013 ("ICH")

Champion, et al., *Defining Your Product Profile and Maintaining Control Over It, Part 2*, BIOPROCESS INT'L 52–57 (Sept. 2005). Ex. 1014 ("Champion").

Wang, et al., *Host Cell Proteins in Biologics Development: Identification, Quantitation and Risk Assessment*, 103(3) BIOTECHNOLOGY AND BIOENGINEERING 446–458 (Apr. 2009). Ex. 1-15 ("Wang").

Mihara et al., WO 2012/101671 Al, published August 2, 2012. Ex. 1016 ("Mihara").

Petitioner further relies on Exhibit 1010, the Declaration of its expert, Mark Sands.

E. Asserted Grounds of Unpatentability

Petitioner challenges the patentability of claims 1–3, 9–13, 16, and 17 of the '556 patent on the following grounds. Pet. 13.

References	**Basis**	**Claims Challenged**
Jin "in view of [any one of] [Wolter, CEBER, ICH, Champion, and Wang], the general knowledge of those in the art regarding purification steps (as reflected in, e.g., Jin) and the expectation of success as reflected in, e.g., any one of	§ 103	1–3, 16, 17

References	Basis	Claims Challenged
[Wolter, Champion, Wang, and Mihara]).”		
Jin	§ 102/103	9–13

II. ANALYSIS

A. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are interpreted according to their broadest reasonable constructions in light of the Specification of the patent in which they appear. *See* 37 C.F.R. §42.100(b); *In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1278–79 (Fed. Cir. 2015) (“Congress implicitly approved the broadest reasonable interpretation standard in enacting the AIA,” and “the standard was properly adopted by PTO regulation.”), *cert. granted*, *sub nom. Cuozzo Speed Techs. LLC v. Lee*, 136 S. Ct. 890 (mem.) (2016). Under the broadest reasonable construction standard, claim terms are presumed to have their ordinary and customary meaning, as would be understood by one of ordinary skill in the art[1] in the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Only claim terms which are in controversy need to be construed, and then only to the extent necessary to resolve the controversy. *See, e.g. Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999).

[1] On the current record, we accept Petitioner’s presently unopposed definition of a person of ordinary skill in the art. *See* Pet. 23–24; Ex. 1010 ¶ 10, Prelim. Resp. 11.

For purposes of this Decision, we agree with the parties that none of the terms in the challenged claims require express construction at this time. *See* Pet. 24; Prelim. Resp. 11–12.

B. Jin as Prior Art under 35 U.S.C. § 102(e)[2]

We consider first whether Jin, the primary reference asserted in the Petition, is properly applied as prior art under 35 U.S.C. § 102(e) against the '556 patent as Petitioner contends. *See* Pet. 4.

Jin issued from the U.S. national stage entry of PCT application No. KR2012/004734, filed on June 15, 2012, which in turn claims priority to its U.S. Provisional Application No. 61/500,994, filed on June 24, 2011. Ex. 1002, cover page. Patent Owner points out that in asserting Jin under § 102(e), Petitioner has not indicated whether it intends to rely on the June 24, 2011, date of Jin's provisional application, has not submitted the provisional application as an exhibit, and has not referred to the provisional application in the Petition. *See* Prelim. Resp. 9, 47–48. Accordingly, Patent Owner requests that we deny the Petition "regardless of the actual 102(e) date of Jin." Prelim. Resp. 48.

We decline to deny the Petition on this basis. The '556 patent claims the benefit of priority to U.S. Provisional Application No. 61/666,733, filed on June 29, 2012. Accepting, for the sake of argument, that '556 patent is entitled to the June 29, 2012, filing date, Jin, nevertheless, qualifies as prior art under § 102(e) based on the June 15, 2012, filing date of PCT application

[2] The relevant sections of the Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112–29 took effect on March 16, 2013. Because the application from which the '556 patent issued was filed before that date, our citations to Title 35 are to its pre-AIA version.

No. KR2012/004734. Accordingly, Petitioner's assertion that Jin "is prior art with respect to the '556 patent under pre-AIA 35 U.S.C. § 102(e)" is evident from the face of the reference.[3] *See* Pet. 4.

Relying on *Globus Medical, Inc. v. DePuy Synthes Prods., LLC*, IPR2015-00107, Paper 11 (PTAB May 1, 2015), Patent Owner further contends that Petitioner "has not met its burden to establish that the Jin reference is entitled to its provisional filing date as of its § 102(e) date and has waived its right to do so." Prelim. Resp. 47–50. This panel does not consider *Globus* binding as the Board has not designated it as precedential. Moreover, *Globus* is distinguishable insofar as the prior art at issue there would have qualified as prior art under 102(e) *only* if it were entitled to the benefit of the filing date of an earlier-filed provisional application. In contrast, Petitioner has established, based on the face of the reference, that Jin bears a § 102(e) date, based on PCT application No. KR2012/004734, which renders it prior art with respect to the '556 patent. For the purposes of institution, we have no need to determine priority with respect to Jin's provisional application.[4]

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[3] Patent Owner admits that "[t]he facts here are distinguishable over *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375 (Fed. Cir. 2015)." Prelim. Resp. 49 n.11. We, nevertheless, leave open the possibility that Patent Owner may challenge at trial Jin's entitlement to the June 15, 2012, filing date on grounds other than the filing date of the PCT application.

[4] Patent Owner also asserts that Petitioner has not established Mihara (Ex. 1016) as prior art under § 102(e). Prelim. Resp. 32 n.7. As with Jin, Mihara, on its face, qualifies as § 102(e) prior art to the '556 patent based on the January 25, 2011, filing of PCT application JP201l/000392. As with Jin, Patent Owner may challenge other aspects of Mihara's entitlement to priority on the record developed at trial.

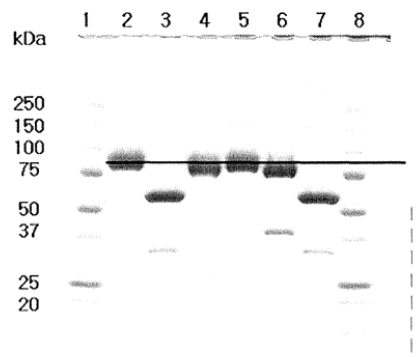
C. Challenged Claims 1–3, 16, and 17.

Petitioner asserts that claims 1–3, 16, and 17 are anticipated by Jin, and/or obvious over Jin in light of some combination of Wolter, CEBER, ICH, Champion, and Wang, and/or Mihara and the understanding of one of ordinary skill in the art. Pet. 36–50. Patent Owner disagrees. Prelim. Resp. 16–34. In particular, Patent Owner argues that Petitioner has not provided sufficient evidence to support its assertion that Jin discloses the purity limitations of claims 1–3, 16 and 17, "or even that the I2S composition disclosed in Jin was of high purity." Prelim. Resp. 2. Patent Owner has not challenged Petitioner's arguments with respect to the other limitations of claims 1–3, 16, and 17.

i. Overview of Jin with Respect to Purity

Jin discloses a method for preparing recombinant I2S for the treatment of Hunter syndrome using anion exchange chromatography, hydrophobic chromatography, cation exchange chromatography, and affinity chromatography. Ex. 1002, ¶¶ 1, 2, 30–38; Prelim. Resp. 9. Jin teaches that the purified I2S protein "is safe and efficacious thanks to its purity of 99.9% or higher." Ex. 1002, ¶ 53. Jin Figure 11 is reproduced below.

FIG. 11

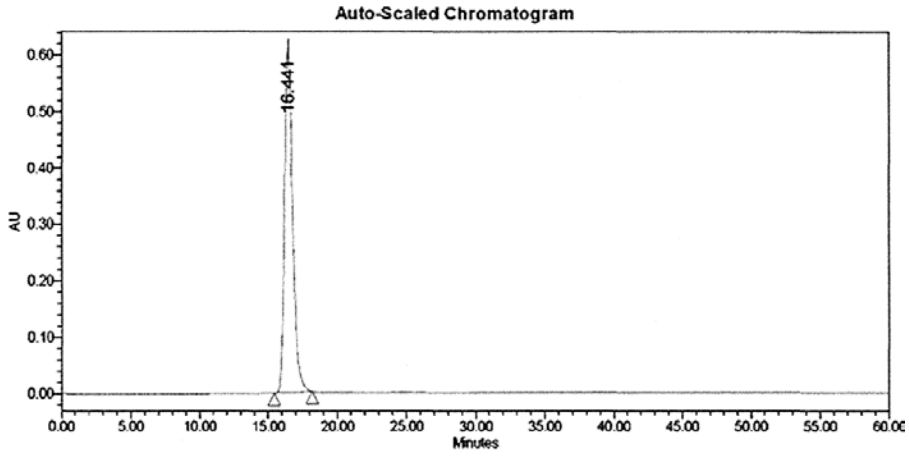


Lane 1, 8: Molecular size marker
Lane 2: IDS
Lane 3: IDS treated with PNGase F
Lane 4: IDS treated with Endo H
Lane 5: IDS treated with O-glycosidase
Lane 6: IDS treated with Sialidase
Lane 7: IDS treated with PNGase F and O-glycosidase

Figure 11 is a photograph showing I2S run by SDS-PAGE with (Lanes 3–7) and without (Lane 2) treatment with glycoside hydrolase enzymes. *Id.* ¶¶ 65, 165. According to Petitioner's expert, Dr. Sands, the SDS-PAGE "assay is highly sensitive to contaminating protein and the presence of only one band [in Lane 2] indicates that essentially no host cell protein was detected." Ex. 1010, ¶ 43. Petitioner similarly argues that "[t]he absence of additional bands on the SDS-PAGE gel indicates that the sample does not contain impurities – including host cell proteins – at detectable levels." Pet. 44 (footnote omitted).

Figure 13 of Jin, reproduced below, "show[s] the purity of the [I2S]" prepared by Jin. Ex. 1002 ¶ 67.

FIG. 13



Peak Results

	Name	RT	Area	Height	Amount	Units	% Area
1		16.441	24773954	609564			100.00

According to Jin, Figure 13 is a size exclusion chromatogram showing that monomers of I2S "were eluted with 100% purity." *Id.* ¶¶ 67, 157. Petitioner's expert, Dr. Sands, notes that Jin Figure 13 shows "a single discrete peak of protein from the final I2S preparation . . . . Contaminating host cell proteins would appear as additional protein peaks on the chromatogram, and yet no such peaks exist." Ex. 1010 ¶ 43.

Jin teaches that Elaprase is used for enzyme replacement therapy in treating Hunter's syndrome, but that the drug "suffers from the drawbacks of being poor in effect and safety." Ex. 1002 ¶ 9. Jin discloses that in a clinical trial comparing Elaprase to its purified recombinant I2S preparation, Hunter syndrome patients treated with the I2S preparation showed increased reductions in urinary GAG levels and greater improvement in the 6-minute walk test as compared to those treated with Elaprase. *Id.* ¶¶ 167–0173. With respect to these results, Dr. Sands opines that, "[i]f the enzyme purified by the method of Jin contained unacceptable levels of host cell proteins, these patients would not have responded as well to the treatment." Ex. 1010

¶ 45. Dr. Sands concludes that one of ordinary skill in the art would have expected Jin's I2S preparation "to be substantially free of host cell protein." *Id.* ¶ 46.

ii. Analysis

A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 18 (1966). A rejection on the ground of obviousness must include "articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006). The obviousness analysis "should be made explicit" and it "can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR*, 550 U.S. at 418.

For the limited purpose of deciding whether to institute proceedings with respect to claims 1–3, 16, and 17, we focus on claim 1, which recites a purity limitation of "less than 150 ng/mg Host Cell Protein (HCP)."

Patent Owner argues that Petitioner "has failed to establish that either size exclusion chromatography or SDS-PAGE described in Jin can be used

to assess purity." Prelim. Resp. 30. On its face, however, Jin appears to disclose an I2S preparation showing a single band on SDS-PAGE and a size exclusion chromatogram showing monomers of I2S of "100% purity." Ex. 1002, Figs. 11, 13, ¶ 157.

With respect to the SDS-PAGE data, we do not discern where Jin identifies the staining protocol used. Wang, however, notes that "the most common methods [for staining proteins in a polyacrylamide gel] include Coomassie Blue, silver staining, and Sypro Ruby staining" and notes that "[t]he sensitivity of Coomassie Blue is in the range of 0.05–0.1 mg/band or 2D spot, whereas both silver and Sypro Ruby staining could have 1–5 ng/spot sensitivity." Ex. 1015, 449. Wang further indicates that "Sypro Ruby staining has about a 1,000-fold dynamic range whereas silver or Coomassie Blue staining only have 10- to 100-fold dynamic range."[5] *Id.* at 449–500. At this stage in the proceedings, however, we accept Dr. Sand's testimony that SDS-PAGE "is highly sensitive to contaminating protein and the presence of only one band indicates that essentially no host cell protein was detected." Ex. 1010 ¶ 43.

With respect to the size exclusion chromatogram, Jin also does not expressly discuss the sensitivity or dynamic range of the detection system employed. We, nevertheless, accept, for purposes of this decision, Dr. Sands' presently unrebutted testimony that "[c]ontaminating host cell proteins would appear as additional protein peaks on the chromatogram, and yet no such peaks exist." *Id.*

[5] By way of context, we note that there are one million nanograms per milligram, such that HCP contamination of 150 ng/mg corresponds to about one part in 6667.

Taken in context, and on the present record, the above evidence supports the inference that Jin's I2S preparation contains "less than 150 ng/mg Host Cell Protein (HCP)," as set forth in claim 1.

Petitioner further appears to argue that, although Jin "does not quantify the exact amount of host cell protein remaining" in Jin's I2S preparation (Pet. 40), Jin's administration of this material to Hunter syndrome patients in a clinical trial indicates that it would have met regulatory guidelines for medical use. *See* Pet. 39, 16–18. According to Dr. Sands, these "[w]ell-accepted guidelines suggest that host cell protein impurities should be in the range of 1-100 ppm (e.g., 1-100 ng/mg) in approved drug products." Ex. 1010 ¶22 (citing Ex. 1001, 31:66–32:2 (indicating that HCP levels of <100 ppm are required for pharmaceutical products "in many markets including the US"); Ex. 1014, 54 ("Most biotechnology products reviewed by the FDA contain ELISA-based host cell protein levels of 1–100 ppm.")); *see* Pet. 44–45.

Patent Owner responds that Petitioner, "apparently contends that FDA-issued guidance recommends host cell protein levels in the range of 1-100 ppm for therapeutic biologics and, therefore that the I2S composition disclosed in Jin inherently must contain less than 100 ng/mg HCP because Jin's I2S composition was used for human treatment in a clinical trial." Prelim. Resp. 2. Responding to this interpretation of Petitioner's argument, Patent Owner contends that there is no evidence that FDA-issued guidance regarding the permissible amount of HCP applies to the I2S composition used in Jin's clinical trial because a Green Cross press release suggests that

Jin's trial may have been conducted in South Korea. *See* Prelim. Resp. 2, 22–23 (citing Ex. 2003[6]).

We do not find Patent Owner's argument persuasive on the present record in light of Dr. Sands' testimony regarding guidelines for HCPs in approved drug products (Ex. 1010 ¶22); the statement in the '556 patent that HCP levels of <100 ppm are required for pharmaceutical products "in many markets including the US" (Ex. 1001, 31:66–32:2); and the disclosure in the cited press release that "Green Cross plans to introduce the drug to the domestic market in the first half of 2012, after obtaining drug application approval from the KFDA" (Ex. 2003, 1; *see also* Ex. 1015, 447 ("Many biotechnology companies are using [the range 1–100 ppm] as a guideline for process development and for setting HCP specifications.")).

Further, to the extent Jin's I2S preparation did exceed "[w]ell-accepted guidelines . . . in the range of . . . 1-100 ng/mg," Dr. Sands testifies that starting with Jin's method, one of ordinary skill in the art would have found it obvious to further decrease HCP levels using well-known and routine purification methods with a reasonable expectation of success. Ex. 1010 ¶¶ 22, 77–81; *see* Pet. 40, 45–50 (citing, e.g., Ex. 1010 ¶¶ 23–29, 42, 47).

We find ample evidence supporting motivation to decrease HCP levels in pharmaceutical products to "less than 150 ng/mg," as required in claim 1. In addition to the above discussion regarding regulatory guidelines for HCP levels in pharmaceutical products, Champion teaches that "it is

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[6] Samsung, Green Cross (Korea) Press Release, *Green Cross Has Filed an Application for Approval of the World's Second Drug for the Treatment of Hunter Syndrome*, http://www.evaluategroup.com/Universal/View.aspx?type=Story&id=273949 (October 11, 2011).

considered good practice to minimize HCP levels and thus limit the potential for unexpected adverse events such as molecular mimicry, anaphylaxoid reactions, and adjuvant effects." Ex. 1014, 54. Similarly, Wang teaches that "HCPs are undesirable in the final drug substance," and, although HCPs are "commonly present in small quantities (parts per million expressed as nanograms per milligrams of the intended recombinant protein) much effort and cost is expended by industry to remove them." Ex. 1015, Abstract.

With respect to the availability of routine methods of protein purification and reasonable expectation of success, Petitioner argues that Jin teaches methods for producing I2S with a high degree of purity (Pet. 49), whereas Mihara teaches similar methods for the purification of I2S having only 12 ppm HCPs (*id.* (citing Ex. 1016 ¶ 70)).[7] Petitioner also relies on Dr. Sands' testimony regarding, e.g., the routine nature of purifying a heavily-glycosylated protein like I2S using anion exchange chromatography. *Id.* at 46–47 (citing Ex. 1010 ¶ 46).

Patent Owner argues that Petitioner has not presented sufficient data or objective evidence to support a finding that Jin's I2S preparation can be further purified using well-known and routine purification methods with a reasonable expectation of success of achieving the purity levels specified in claims 1–3, 16, and 17. Prelim. Resp. 27–34. We have considered these and other arguments raised by Patent Owner in the Preliminary Response,

[7] Patent Owner does not presently contest Petitioner's characterization of Mihara (*see* Prelim. Resp. 32 n.6), but argues that the reference discloses "a lengthy purification process that includes a total of five column purification steps," which Petitioner has not established as "sufficiently similar to that disclosed in Jin." *Id.* at 31–32. We do not find this argument persuasive on the current record, and note that the challenged claims do not include method steps.

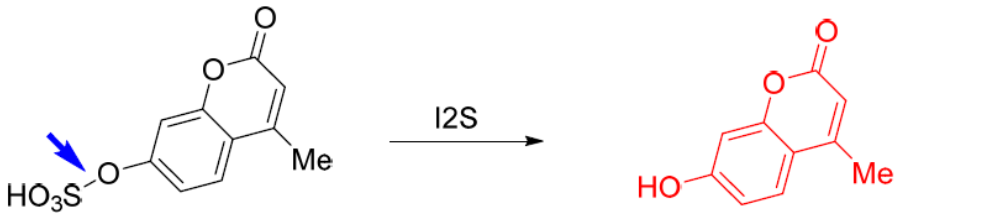
but do not consider them sufficient to persuade us that Petitioner has failed to established a reasonable likelihood of prevailing in challenging claims 1–3, 16, and 17. Although Patent Owner's arguments may raise genuine issues of material fact, the parties will have the opportunity to further develop these facts during trial, and the Board will evaluate the fully-developed record at the close of the evidence.

D. Challenged Claims 9–13.

Petitioner asserts that claims 9–13 are anticipated by, or obvious in light of, Jin. Pet. 29–36. Patent Owner disagrees. Prelim. Resp. 34–47.

Independent claim 9 requires that the "the purified recombinant I2S protein has specific activity of at least 20 U/mg as determined by an in vitro 4-MUF-SO_4 to 4-MUF conversion assay." Depending from claim 9, claims 10–13, respectively, recite a specific activity of at least 30, 40, 50, or 60 U/mg using the same assay.

The 4-MUF-SO_4 to 4-MUF conversion assay is graphically illustrated on page 38 of the Patent Owner Preliminary Response and reproduced below:



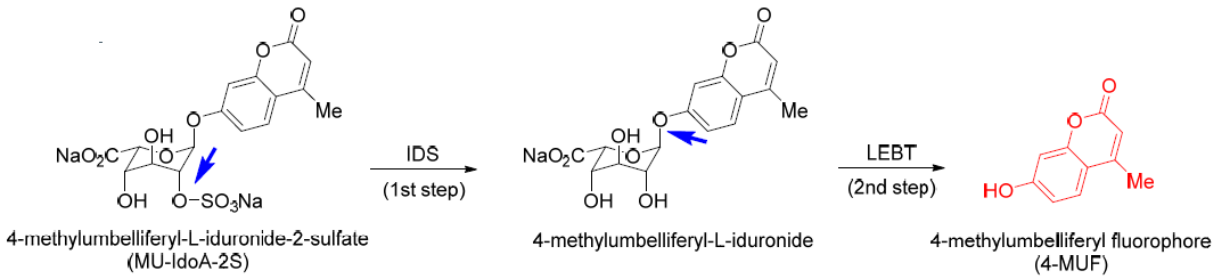
4-methylumbelliferyl-sulfate

4-methylumbelliferyl fluorophore (4-MUF)

As shown above, the 4-MUF-SO_4 to 4-MUF conversion assay is a one-step assay involving the cleavage (shown by arrow) of the sulfate moiety from 4-MUF-SO_4 (4-methylumbelliferyl-sulfate) to yield 4-MUF (4-methylumbelliferone), a fluorescent molecule which can be quantitatively

measured using a fluorimeter. *See* Ex. 1001 23:20–58; Ex. 1010 ¶¶ 32–33. "Because the assay is not specific to any particular sulfatase, it may be used to measure the activity not just of I2S, but also of other sulfatases such as arylsulfatase A and arylsulfatase B (*see,* Dean, C. *Clin Chem* 52:4; 643-649)." Ex. 1010 ¶ 33.

Jin reports the specific activity of purified recombinant I2S in the range of 19 to 55 nmol/min/ug using a different assay in which the primary substrate is MU-IdoA-2S (methylumbelliferyl-L-iduronide-2-sulfate Na_2), rather than 4-MUF-SO_4 Ex. 1002 ¶ 159. The MU-IdoA-2S assay is graphically illustrated on page 38 of the Patent Owner Preliminary response and is reproduced below:



In this two-stage assay, the sulfate moiety of MU-IdoA-2S is specifically cleaved by I2S, thereby generating 4-methylumbelliferyl-L-iduronide (4-MUF). Ex. 1002 ¶ 159; *see* Prelim. Resp. 38; Pet. 21–22 (citing Sands ¶ 34). Upon completion of the primary reaction, LEBT (a mixture of lysosomal enzymes from bovine testes) is added to separate the L-iduronide from the fluorogenic 4-MUF moiety. Ex. 1002 ¶ 159. I2S activity is then evaluated by measuring the fluorescence of the 4-MUF produced. *Id.*

Petitioner takes the position that there is a one-to-one correspondence between units of sulfatase activity as measured by the above two assays. Relying on the testimony of Dr. Sands, Petitioner argues that the 19 to 55 nmol/min/ug disclosed in Jin corresponds to 19–55 U/mg of I2S activity

such that "the range of specific activity disclosed for I2S [in Jin] is substantially identical to that disclosed for the embodiment of the '556 patent." Pet. 30–32 (citing Ex. 1010 ¶ 41). Moreover, Petitioner contends, because the MU-IdoA-2S assay used by Jin is specific for I2S activity, whereas the 4-MUF-SO_4 to 4-MUF conversion assay of claims 9–13 may reflect the activity of other, contaminating sulfatases, "the I2S of Jin must necessarily have a specific activity level of 19-55 U/mg or higher when measured using an enzyme-generic 4-MUF SO_4 to 4-MUF assay." Pet. 30 (citing Ex. 1010 ¶¶ 32–36, 40).

For the reasons set forth on pages 34–47 of the Patent Owner Preliminary Response, we agree with Patent Owner that the Petition fails to demonstrate a reasonable likelihood that claims 9–13 are anticipated by and/or obvious in view of Jin. In particular, Petitioner has not provided any data or evidence correlating the two-stage MU-IdoA-2S assay used in Jin with the single-stage 4-MUF-SO_4 to 4-MUF conversion assay of claims 9–13. To the contrary, Petitioner's own evidence indicates that the determination of enzymatic specific activity is "highly method dependent." Ex. 1013, 4. Likewise, both Petitioner and Petitioner's expert, Dr. Sands, admit that "[s]pecific activity is a measure of the amount of enzyme required to catalyze the transformation of substrate per time per total mass of protein *under a specific set of assay conditions*." Pet. 21 (italics added); Ex. 1010 ¶ 30 (same).

Consistent with this teaching, the '556 patent itself provides multiple conditions for measuring and reporting the specific activity of I2S. Ex. 1001 22:26–23–58. For example, "[i]n some embodiments, purified recombinant I2S protein has a specific activity, as measured by in vitro sulfate release

activity assay using heparin disaccharide as substrate." *Id.* at 22:44–53; *see id.* at claims 6–8. In other embodiments, "the enzymatic activity of recombinant I2S protein may also be determined using various other methods known in the art such as, for example, [the] 4-MUF assay" recited in claims 9–13. *See id.* at 23:20–25.

In contrast to the evidence of record, we find no evidentiary support for Dr. Sands' conclusions that: (1) "There is essentially no difference between the two reported specific activities of Jin and that of the '556 patent"; (2) "For 100% pure I2S preparations, there should be no difference between specific activity as measured by the enzyme-specific [e.g., the MU-IdoA-2S assay used by Jin] and enzyme-generic 4-MUF tests"; and, thus, (3) "the I2S of Jin must necessarily have a specific activity level of 19-55 U/mg or higher when measured using an enzyme-generic 4-MUF SO_4 to 4-MUF assay." Ex. 1010 ¶¶ 41, 36, 40, respectively; *see* Pet. 30. At best, Dr. Sands generally refers to Uribe[8] for the proposition that "use of a more general substrate decreases the confidence that the enzyme is pure and could artificially increase the apparent specific activity." Ex. 1010 ¶ 35 (citing Ex. 1019). Dr. Sands does not, however, point to, nor do we discern, where Uribe teaches any correlation between the specific activity assays used by Jin, and that recited in claims 9–13.

"Expert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight." 37 C.F.R. § 42.65(a); *see also* Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756,

[8] Uribe and Giugliani, *Selective Screening for Lysosomal Storage Diseases with Dried Blood Spots Collected on Filter Paper in 4,700 High-Risk Colombian Subjects*, JIMD REPORTS 107–116 (Apr. 2013). Ex. 1019 ("Uribe").

48,763 (Aug. 14, 2012) ("Affidavits expressing an opinion of an expert must disclose the underlying facts or data upon which the opinion is based."). Mere lawyer's arguments and conclusory statements, unsupported by factual evidence, are similarly entitled to little probative value. *See In re Geisler*, 116 F.3d 1465, 1470 (Fed. Cir. 1997). Accordingly, we do not find persuasive either Petitioner's assertions or Dr. Sands' testimony with respect to any quantitative relationship, let alone a one-to-one correlation, between the specific activity measurements in Jin as compared to those in claims 9–13 of the '556 patent.

For the reasons set forth above, we conclude that Petitioner has not established a reasonable likelihood that claims 9–13 are anticipated or rendered obvious by Jin.

III. CONCLUSION

For the foregoing reasons, we find that based on the current record, Petitioner has established a reasonable likelihood that it will prevail in showing that claims 1–3, 16, and 17 of the '556 patent are obvious over the combination of Jin and any one of Wolter, CEBER, ICH, Champion, and Wang, and further in view of the general knowledge in the art as reflected in Jin and any one of Wolter, Champion, Wang, and Mihara. In addition, we determine that the Petitioner has not established a reasonable likelihood that claims 9–13 of the '156 patent are unpatentable.

This is not a final decision as to the construction of any claim term or the patentability of claims 1–3, 16, and 17. Our final decision will be based on the full record developed during trial.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that an *inter partes* review is granted with regard to claims 1–3, 16, and 17 of the ’556 patent under 35 U.S.C. § 103 over the combination of Jin and any one of Wolter, CEBER, ICH, Champion, and Wang, and further in view of the general knowledge in the art as reflected in Jin and any one of Wolter, Champion, Wang, and Mihara;

ORDERED that pursuant to 35 U.S.C. § 314(a), *inter partes* review of the ’556 patent is hereby instituted commencing on the entry date of this Order, and pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial;

FURTHER ORDERED that the trial is limited to the grounds listed in the Order. No other grounds are authorized.

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