UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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GREEN CROSS CORPORATION

Petitioner

v.

SHIRE HUMAN GENETIC THERAPIES, INC.

Patent Owner

_____

Case No. IPR2016-00258

Patent 9,051,556

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PATENT OWNER'S PRELIMINARY RESPONSE

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page(s)

CASES

STATUTES

I. INTRODUCTION

Pursuant to 35 U.S.C. § 313 and 37 C.F.R. § 42.107, Shire Human Genetic Therapies, Inc. ("Shire" or "Patent Owner") hereby submits this Preliminary Response to the Petition for *inter partes* review (the "Petition") of U.S. Patent No. 9,051,556 (the "'556 Patent") filed by Green Cross Corporation ("Green Cross" or "Petitioner").

The Petition should not be granted because the Petitioner failed to carry its burden of showing that there is a "reasonable likelihood" that any of the challenged claims of the '556 Patent are unpatentable under 35 U.S.C. § 314(a). As explained more fully below, Green Cross has not presented sufficient information in the Petition to meet this threshold burden. Instead, Green Cross relies solely on the declaration of its expert Dr. Mark Sands and presents arguments that are conclusory, speculative and too general to be persuasive. Worse yet, Green Cross uses Dr. Sands to merely track and repeat in declaration form the very same self-serving conclusions that appear in the Green Cross Petition. Neither Green Cross nor its expert provides any supporting scientific facts, actual data or other objective evidence that show either that: (1) Claims 1-3 and 16-17 of the '556 Patent are obvious over proffered prior art reference U.S. Patent Application Publication No. 2014/0242059 ("Jin"), in view of the published guidelines, the general knowledge of those in the art, and the

expectation of success (referred to as "Ground 2" in the Petition); or (2) Claims 9-13 of the '556 Patent are anticipated and/or obvious over Jin (referred to as "Ground 1" in the Petition).

With respect to claims 1-3 and 16-17, Green Cross has not provided sufficient evidence to support its assertion that the Host Cell Protein (HCP) content limitations required respectively by each of these claims of the '556 Patent (*i.e.*, less than 150 ng/mg HCP, less than 100/ng/mg HCP, and less than 80 ng/mg HCP) are disclosed in Jin, or even that the I2S composition disclosed in Jin was of high purity. For example, Green Cross 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. Petitioner however presented no evidence whatsoever of the actual HCP content of the Jin I2S composition, let alone whether Green Cross's clinical trial was even conducted under the FDA guidelines it now cites in its Petition. Indeed, Green Cross issued a press release in 2011 stating that a Hunterase clinical trial matching the trial described in Jin was conducted in Seoul, South Korea. Thus, there is no evidence that the FDA guidelines now cited by Green Cross were followed in, or would even apply to, clinical trials conducted using Jin's I2S composition. Similarly, the Petition fails

to provide any evidence that a person of ordinary skill in the art (a "POSITA") would have a reasonable expectation of success in isolating I2S with HCP content less than 80 ng/mg. For these reasons, Green Cross has not met its burden of showing a reasonable likelihood that its arguments will prevail with respect to Claims 1-3 and 16 and 17.

With respect to claim 9-13, Green Cross has not provided sufficient evidence to support its assertion that the specific activity of I2S recited in each of the claims of the '556 Patent, as determined by an *in vitro* 4-MUF-SO_4 conversion assay, was anticipated by and/or rendered obvious by the specific activity of I2S disclosed in Jin using an entirely different assay. Green Cross presents no evidence whatsoever that, the specific activity assay of I2S disclosed in Jin may be converted, *by 1:1 ratio*, to the specific activity assay claimed in claims 9-13 of the '556 Patent measured using a completely different assay. On the contrary, Green Cross's own cited references demonstrate that determining specific activity is highly dependent on the specific method employed and assay conditions used. Ex. 1013 at 4 (in the section entitled "2.1.4 Purity, impurities and contaminants"). Yet, Green Cross assumes, without any support, that the specific activity disclosed in Jin (as measured by an entirely different assay than that required by claims 9-13 of the '556 Patent) can be compared to the specific activity recited in those claims, and may even be more accurate. Without data or other evidence to support these

assumptions, however, Green Cross has not met its burden to show a reasonable likelihood that the specific activity limitation of Claims 9-13 of the '556 Patent are anticipated or rendered obvious by Jin.

Moreover, Green Cross has failed to set forth a meaningful obviousness analysis or offer any evidence whatsoever regarding potential objective indicia of non-obviousness.

Because Green Cross has not presented sufficient information to meet its threshold burden to show a reasonable likelihood that the challenged claims are anticipated or obvious, institution should be denied.

II. BACKGROUND

Hunter Syndrome (also called mucopolysaccharidosis Type II or MPS II) is a very rare, inherited, progressive and life-threatening lysosomal storage disease that affects approximately 1 out of every 162,000 births (primarily males). An inherited condition involving a deficiency or dysfunction in the Iduronate-2-sulfatase ("I2S") enzyme within cells of the body, Hunter Syndrome is typically diagnosed in children between the ages of 1 and 3. In patients with Hunter Syndrome, certain types of sugar molecules within the body are not correctly broken down and, over time, can build up and cause symptoms such as difficulties with growing normally and with hearing, skin changes, frequent ear, nose and throat infections, joint stiffness, breathing difficulties and, in some patients,

respiratory and cardiac problems, enlargement of the liver and spleen, neurological deficits, and death.

Treatment of Hunter Syndrome requires replacement of the deficient I2S enzyme with a replacement I2S enzyme. Shire's ELAPRASE® product, approved in July 2006, was the first product in the United States indicated for patients with Hunter Syndrome. The active substance in ELAPRASE® is I2S, produced by recombinant DNA technology in a human cell line. ELAPRASE® replaces the enzyme (I2S) that is missing or defective in patients with Hunter Syndrome to prevent the build-up of mucopolysaccharides in patients' cells, which might otherwise lead to tissue destruction and organ dysfunction.

A. The '556 Patent

In the course of researching potential improvements of their ELAPRASE® product, Shire scientists made the surprising discovery that recombinant I2S protein can be purified from unprocessed biological materials, such as I2S-containing cell culture medium, using a process involving as few as four chromatography columns. Ex. 1001 ('556 Patent) at 1:60-66. In particular, the purification process of the '556 Patent includes anion exchange chromatography, cation exchange chromatography, mixed mode chromatography and hydrophobic interaction chromatography. *Id.* at 2:16-21. Shire's improved methods resulted in an I2S composition with improved characteristics, such as higher purity and

specific activity. *Id.* at 2:11-15. Specifically, as claimed in the '556 Patent, using Shire's improved methods for purifying I2S proteins for enzyme replacement therapy, the resulting purified recombinant I2S contained less than 150 ng/mg Host Cell Protein (HCP) or had specific activity of at least 20 U/mg, as measured using a 4-MUF-SO_4 to 4-MUF conversion assay. Obtaining I2S compositions with these improved characteristics required significant effort and real innovation on the part of Shire.

The application that ultimately issued as the '556 Patent (i.e., U.S. Patent Application No. 13/829,706) was filed on March 14, 2013, and claims priority from U.S. Provisional Patent Application Ser. No. 61/666,733, filed June 29, 2012. Notably, the prosecution history of the '556 Patent was relatively short – just over two years passed between the application's first filing and the examiner's issuance of the notice of allowance. During that time, the examiner issued a Restriction Requirement, restricting the claims to one of three Groups: (1) composition claims directed to recombinant iduronate-2-sulfatase; (2) method claims direct to purifying recombinant iduronate-2-sulfatase, and (3) method claims directed to treatment of Hunter syndrome. Ex. 1004. Shire elected the composition claims. Ex. 1005. The examiner issued a non-final Office Action on August 21, 2014. Ex. 1006. On January 27, 2015, Shire had a telephonic interview with the Examiner to discuss the invention, the distinction over the

alleged prior art, and to explain that the claimed purified I2S composition has improved characteristics, such as low HCP level and high specific activity, and that such improvement directly and materially impacts the safety and efficacy of the I2S protein, which can lead to a significantly improved therapeutic protein drug for Hunter patients. On February 23, 2015, Shire filed a response to the Office Action to amend the claims, summarize the interview with the examiner, and address the rejections raised in the Office Action, together with the declaration of David Nichols in support of its arguments. Exs. 1007 and 1008. Notably, in an Information Disclosure Statement also filed on February 23, 2015 (Ex. 2006), Shire cited PCT publication WO2012177020, which is the parent of US20140242059 (Jin) and shares the identical specification[1]. The examiner considered the Jin reference cited on the Information Disclosure Statement of February 23, 2015 on March 8, 2015 (Ex. 2007) and issued a notice of allowance on April 6, 2015. Ex. 1009.

The now-challenged claims of the '556 Patent (with the relevant limitations bolded) are set forth below:

> 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%

[1] US20140242059 (Jin) is the publication of the U.S. National Phase entry of the PCT publication WO2012177020.

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)***.

2. The composition of claim 1, wherein the purified recombinant I2S comprises at least 75% conversion of the cysteine residue corresponding to Cys59 of SEQ ID NO:1 to Cα-formlyglycine (FGly).

3. The composition of claim 1, wherein the purified recombinant I2S comprises at least 85% conversion of the cysteine residue corresponding to Cys59 of SEQ ID NO:1 to Cα-formlyglycine (FGly).

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 ***a specific activity of at least 20 U/mg as determined by an in vitro 4-MUF-SO4 to 4-MUF conversion assay***.

10. The composition of claim 9, wherein the purified recombinant I2S protein has ***a specific activity of at least 30 U/mg as determined by an in vitro 4-MUF-SO_4 to 4-MUF conversion assay***.

11. The composition of claim 9, wherein the purified recombinant I2S protein has ***a specific activity of at least 40 U/mg as determined by an in vitro 4-MUF-SO_4 to 4-MUF conversion assay***.

12. The composition of claim 9, wherein the purified recombinant I2S protein has ***a specific activity of at least 50 U/mg as determined by an in vitro 4-MUF-SO_4 to 4-MUF conversion assay***.

13. The composition of claim 9, wherein the purified recombinant I2S protein has ***a specific activity of at least 60 U/mg as determined by an in vitro 4-MUF-SO_4 to 4-MUF conversion assay***.

16. The composition of claim 1, wherein the purified recombinant I2S protein contains ***less than 100 ng/mg HCP***.

17. The composition of claim 1, wherein the purified recombinant I2S protein contains ***less than 80 ng/mg HCP***.

Ex. 1001 ('556 Patent) at 49:20-35, 50:20-45, 51:1-5.

B. The Jin Reference

In its Petition, Green Cross proffered a single reference, its own filing US20140242059 ("Jin"), published August 28, 2014, as alleged prior art to the '556 Patent under pre-AIA 35 U.S.C. §102(e). Petition at 4, 25 and Ex. 1002. Notably, Green Cross does not specifically identify in its Petition the actual § 102(e) date on which it is relying. Jin is a US National Stage Application of PCT/KR2012/004734, which was filed on June 15, 2012 and published in English as WO2012177020 on April 4, 2013. Ex. 1002. On its front page, under "Related U.S. Application Data", Jin identifies "Provisional application No. 61/500,994, filed on June 24, 2011". However, nothing in Green Cross's Petition demonstrates that Jin is entitled to the priority date of that provisional application and Green Cross did not submit the provisional application as an exhibit with its Petition.

Jin discloses a composition for the treatment of Hunter syndrome, comprising recombinant human iduronate-2-sulfatase having an amino acid sequence represented by SEQ ID NO: 1. Ex. 1002 at [0001]-[0002]. Specifically, Jin states that the object of its invention is "to overcome the problems encountered

in the prior art and to provide a composition for the therapy of Hunter syndrome, comprising recombinant IDS[2] as an active ingredient, which guarantees high therapeutic efficacy and safety, as produced by improved culturing and purifying processes, and a formulation comprising the same" *Id.* at [0011]. Jin generally discloses a purification process that includes four chromatographic steps: anion exchange chromatography, hydrophobic chromatography, cation exchange chromatography and affinity chromatography. *Id.* at [0005]. However, Jin's purification process differs in several critical respects from the purification process disclosed in the '556 Patent because (1) Jin uses affinity chromatography instead of mixed mode chromatography; and (2) Jin carries out the chromatographic steps in a different order.

Jin discloses that the I2S composition purified using its purification process has a specific activity level of 19-55 U/mg when measured using a MU-IdoA-2S to 4MUF conversion assay, which is, as explained more fully below, a completely different enzymatic assay than the 4-MUF-SO_4 to 4-MUF conversion assay required by the '556 Patent claims. While Jin discusses purity at a general level, it is completely silent with respect to the specific level of host cell protein (HCP) in its purified I2S composition. *See generally* Ex. 1002; *see also* Petition at 25.

[2] Jin uses "IDS" as an abbreviation of iduronate-2-sulfatase in its specification. "IDS" and "I2S" are used inter-changeably in this response.

In Experimental Example 2, Jin discloses clinical studies testing the therapeutic effect of its I2S composition in 31 patients with Hunter syndrome. Ex. 1002, Experimental Example 2. However, Jin does not disclose the purity of the I2S composition administered to the patients and does not mention, let alone provide data concerning, the specific HCP level. Jin also does not disclose where this clinical study was conducted and which regulatory agency's guidelines, if any, may have been followed. There is no indication whatsoever that this clinical study was conducted in the United States or whether Green Cross followed FDA guidelines.

C. PERSON OF ORDINARY SKILL IN THE ART

Patent Owner does not contest the Petitioner's definition of a person of ordinary skill in the art ("POSITA") for the purposes of this Preliminary Response. However, Patent Owner reserves its right to offer a different alternative definition in the event *inter partes* review is instituted against the '556 Patent and reserves its right to offer a different definition in any future proceedings involving the '556 Patent.

III. CONSTRUCTION OF THE CLAIMS

In its Petition, Green Cross stated that no terms or phrases require specific construction and requested all claim terms be given their plain and ordinary meaning. Petition at 24. Patent Owner does not contest the Petitioner's request

for the purposes of this Preliminary Response. However, Patent Owner reserves its right to offer different alternative claim constructions in the event *inter partes* review is instituted against the '556 Patent and reserves its right to offer different claim constructions in any future proceedings involving the '556 Patent.

IV. THE PETITION FAILS TO MEET PETITIONER'S BURDEN TO SHOW A REASONABLE LIKELIHOOD THAT GREEN CROSS WILL PREVAIL WITH RESPECT TO ANY OF THE CHALLENGED CLAIMS OF THE '556 PATENT

A. Legal standard

Pursuant to 35 U.S.C. § 314(a), "[t]he Director may not authorize an *inter partes* review to be instituted unless the Director determines that the information presented in the petition filed under section 311 and any response filed under section 313 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." The PTAB has consistently denied institution of *inter partes* review where the Petition failed to present information to meet Petitioner's burden to show a reasonable likelihood of prevailing with respect to at least one challenged claims.

For example, the PTAB recently denied institution in *Amgen, Inc. v. AbbVie Biotechnology Ltd.*, because Amgen failed to establish "a reasonable likelihood of prevailing with respect to at least one challenged claim . . ." IPR2015-01514, Paper 9, at 2 (P.T.A.B. Jan. 14, 2016). Noting that the petitioner also bears the burden of persuasion as to the teachings of the prior art, the PTAB stated it was

"not persuaded that the prior art provided sufficient guidance such that a skilled artisan would have a reasonable expectation of success" at arriving at the claimed pharmaceutical composition, given the "high degree of unpredictability" in the relevant science. *Id*. at 14-15. In doing so, the PTAB criticized the petitioner for relying solely on the declaration of its expert, and presenting arguments that were "too general to be persuasive." *Id*. at 17-18.

Similarly, in *Shopkick, Inc. v. Novitaz, Inc*., the PTAB was "not persuaded that the information presented in the Petitions demonstrates a reasonable likelihood that Petitioner will prevail in proving that at least one challenged claim would have been obvious." IPR2015-00277, Paper 7, at 3 (P.T.A.B. May 29, 2015). The PTAB denied institution because the petitions did not "set forth a meaningful obviousness analysis over the prior art cited because they do not adequately explain the significance of the evidence and do not direct us to persuasive evidence to support a rational for the particular combination of references identified." *Id.* at 23.

In *Endo Pharmaceuticals, Inc. v. Depomed, Inc.*, the PTAB denied the petition because the petitioner did not demonstrate a reasonable likelihood it would prevail in showing that the challenged claim was anticipated. IPR2014-00651, Paper 12, at 6 (P.T.A.B. Sept. 29, 2014). Specifically, the PTAB agreed with the patent owner that the petitioner did not show sufficiently "that

hydroxyethyl cellulose and HPMC are the same compound or are interchangeable." *Id*. at 9. In doing so, the PTAB noted that "the declaration evidence upon which Petitioner relies includes no objective support of such a proposition," and that "based on the information presented, the [cited reference] does not disclose every limitation of the challenged claims in the same way as recited in the claims." *Id.* at 10.

In *3D-Matrix, Ltd. v. Menicon Co., Ltd.*, the PTAB denied the petition to institute, stating "[b]ased on the information presented in the Petition, Preliminary Response, and cited exhibits, we are not persuaded there is a reasonable likelihood that Petitioner would prevail with respect to at least one of the claims challenged in the Petition." IPR2014-00398, Paper 11, at 2 (P.T.A.B. Aug. 1, 2014). Specifically, the PTAB found that the record before it (unsupported by any declaration, affidavit or further explanation) did not "contain sufficient evidence to support Petitioner's assertion . . ." and "Petitioner's argument is conclusory and lacks persuasive detail, evidentiary citations, and analysis." *Id*. at 10, 11.

In its Petition, Green Cross identifies the following two grounds as the purported basis for its request for review: (1) Claims 1-3 and 16-17 are obvious over Jin, certain guidelines, the general knowledge of those in the art, and the expectation of success; and (2) Claims 9-13 are anticipated by and/or obvious in view of Jin. As demonstrated below, Green Cross has failed to show in its

Petition that there is a reasonable likelihood that it will prevail with respect to either of those grounds. On the contrary, Green Cross's Petition relies entirely on conclusory attorney argument and unsubstantiated expert assertions. Indeed, with respect to several key issues, Green Cross's expert, Dr. Sands, does not identify *any* underlying facts, data, or other evidence on which he is relying and, in turn, Green Cross relies entirely on Dr. Sands' say-so.

Because Dr. Sands does not disclose any facts or data on which he is relying, his testimony should be given little weight. *See* 37 C.F.R. § 42.65(a) ("Expert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight."); *see also ActiveVideo Networks, Inc. v. Verizon Commc'ns, Inc.*, 694 F.3d 1312, 1327 (Fed. Cir. 2012) (discrediting expert testimony consisting only of "a conclusory statement that a person of ordinary skill in the art would have known how to combine any number of references to achieve the claimed inventions."); *Purdue Pharma L.P. v. Boehringer Ingelheim GmbH*, 98 F. Supp.2d 362, 388 (S.D.N.Y. May 16, 2000) (rejecting inherent anticipation argument based solely on testimony of expert without supporting documentary evidence); *Kinetic Techs., Inc. v. Skyworks Sols., Inc.*, IPR2014-00529, Paper 8, at 15 (P.T.A.B. Sept. 23, 2014) ("Merely repeating an argument from the Petition in the declaration of a proposed expert does not give that argument enhanced probative value."); *Wowza Media Sys., LLC v. Adobe*

Sys. Inc., IPR2013-00054, Paper 12, at 12 (P.T.A.B. Apr. 8, 2013) ("The Declaration . . . appears, for the most part, simply to track and repeat the arguments for unpatentability presented in the Petition [and] . . . is therefore no more helpful tha[n] the Petition in determining where the challenged recitation is found in the references."). Perhaps even more egregiously, in the few instances where Dr. Sands does cite to published literature (rather than solely relying on his own opinion), he mischaracterizes that literature in critical ways. *See discussion infra* at Pages 28 and 29. For this additional reason, his testimony must be disregarded.

As demonstrated further below, because Green Cross's stated grounds rely entirely on unsupported attorney argument and expert opinions, Green Cross fails to meet its threshold burden to establish a reasonable likelihood that it will prevail in demonstrating that any of the challenged claims are unpatentable. *See, e.g.*, *Gracenote, Inc. v. Iceberg Indus. LLC*, IPR2013-00552, Paper 6, at 21-22 (P.T.A.B. Mar. 7, 2014) (refusing to institute review based, in part, on the failure of the Petition to set forth evidence sufficient to support its burden of showing a reasonable likelihood of prevailing as to any of the challenged claims).

B. Green Cross Fails to Meet Its Burden to Show A Reasonable Likelihood That Claims 1-3 and 16-17 Are Obvious Over Jin, in View of the Cited Guidelines, the General Knowledge of Those in the Art, and the Expectation of Success

One of the two grounds asserted by Green Cross in the Petition is that Claims 1-13 and 16-17 of the '556 Patent are "obvious over Jin, guidelines advising that HCP content be minimized (as reflected by any one of Ex. 1011-1015), 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 Ex. 1011 and 1014-16)." Petition at 36. As set forth further below, however, each of Green Cross's purported obviousness arguments regarding Claims 1-3 and 16-17 of the '556 Patent fails for lack of sufficient objective evidence to support Petitioner's assertion.

An invention is obvious when "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." *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 13 (1966). Obviousness "cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *Oxford Nanopore Techs., Ltd. v. Univ. of Washington*, IPR2014-00512, Paper 12, at 13-14 (Sept. 15, 2014) (*citing KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 418 (2007)). "A party who petitions the Board for a determination of obviousness must show that 'a skilled artisan would have been motivated to

combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so." *3D-Matrix, Ltd., v. Menicon Co., Ltd.*, IPR2014-00398, Paper 11, at 15 (Aug. 1, 2014) (*quoting Proctor & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (citations omitted)).

Here, for the reasons set forth further below, Green Cross has not met its burden.

1. *The Petition does not present any objective evidence that Host Cell Protein content in Jin is less than 150 ng/mg as claimed in the '556 Patent.*

Claims 1-3 and 16-17 of the '556 Patent each require, *inter alia*, the claimed purified recombinant I2S to contain less than a specified amount of Host Cell Protein (HCP) – *i.e.*, "less than 150 ng/mg Host Cell Protein" (claims 1-3), "less than 100 ng/mg HCP" (claim 16), and "less than 80 ng/mg HCP" (claim 17). *See* '556 Patent, at 49:20-35 and 51:1-4. Green Cross acknowledges, as it must, that Jin does not quantify the amount of HCP remaining in its preparation after purification. *See, e.g.,* Petition at 3, 25, 27 and 40. Green Cross, however, appears to assert that: (1) Jin discloses highly pure I2S; (2) under guidelines for HCP content in medicinal treatments, it would have been obvious to a POSITA "to reduce the host cell protein content so that it could be used for medical treatment;" (3) "[m]ethods for removing HCP were well known in the art; and (4)

"based on the teachings of Jin, a POSITA would have had a reasonable expectation of successfully achieving low HCP content in compositions of purified I2S by simply employing routine experimentation." Petition at 40. As explained more fully below, Green Cross fails to provide sufficient evidence in its Petition to support these assertions.

a. *The Petition does not provide sufficient evidence to show that Jin discloses highly pure I2S.*

Green Cross first argues that, although Jin does not quantify the amount of HCP remaining in its preparation after purification, it "discloses highly pure I2S." Petition at 40-45. Green Cross's unsupported attorney argument in this regard is insufficient to meet its burden. Moreover, several of Green Cross's additional statements regarding the purity of the I2S disclosed in Jin are similarly speculative and simply not supported by the Jin disclosure.

For example, Green Cross relied on a single elution peak from size exclusion chromatography to assert that Jin's I2S "eluted with 100% purity". Petition at 41. Green Cross further asserts "[t]he single, sharp peak in the elution profile of the SEC indicates no impurities – and thus no host cell protein – in the I2S sample of Jin." Petition at 42. As any POSITA would appreciate, there is no such recombinantly produced protein composition that is "100% pure" and contains "no impurities" or "no host cell protein". Green Cross clearly did not take into consideration the fact that elution peaks from size exclusion

chromatography are highly diluted and impurities in a single peak may not be detectable. Green Cross also did not provide any evidence or explanation that size exclusion chromatography is a reliable and commonly accepted method for determining purity in a recombinant protein composition.

Green Cross also argues that the SDS-PAGE results in Figure 11 of Jin support the high purity of the I2S disclosed in Jin. Petition at 42-43. Yet, nothing in Jin indicates that that image of the SDS-PAGE gel in Figure 11 actually represents results from experimental conditions that would allow one to assess purity. On the contrary, Jin only discusses Figure 11 in the context of analyzing glycosylation pattern:

> "FIG. 11 is a photograph showing IDS run by SDS-PAGE after treatment with various glycoside hydrolase enzymes **to examine the glycosylation of the IDS** of the present invention." Jin at ¶ 65 (emphasis added).
>
> ***
>
> An assay was performed **to examine whether the IDS of the present invention is glycosylated and to identify the glycosylation pattern if any**. To this end, IDS was treated with various glycoside hydrolase enzymes, the digests were separated on SDS-PAGE and their motility patterns were analyzed. …As can be seen in FIG. 11, the IDS of the present invention was cleaved by PNGaseF and Endo H, but not by O-glycosidase, indicating that the IDS of the present invention is an N-glycosylated protein." Jin at ¶¶145-147 (emphasis added).

Nothing in Jin states that Figure 11 should be used to assess purity. Nor does Jin provide any experimental details that would allow one to reasonably conclude that Figure 11 even could be used to reliably assess purity. Jin simply does not

provide any details whatsoever as to what staining or visualization procedures were used or whether all proteins in the sample would even be visible in Figure 11.

Similarly, Green Cross represents that "[t]he SDS-PAGE gel in Figure 4 of Jin . . . also shows a single molecular weight band with no other impurities at high or low molecular weights." Petition at 44, n.5. Yet, Jin does not indicate what experiment Figure 4 relates to and it is not actually described in the Examples. In fact, the only mention of Figure 4 is in the "Description of the Drawings" section, which states: "FIG. 4 is a photograph showing an SDS-PAGE result of IDS for analyzing the N-terminal sequence where a marker was run on lane M, glycosylated IDS on lane 1, PNGase F on lane 2, and deglycosylated IDS on lane 3." Jin at ¶ 58. That description indicates that, like Figure 11, Figure 4 relates to glycosylation pattern analysis of I2S. Nothing in Jin suggests that the experimental design and condition is suitable for purity determination and Green Cross did not provide any evidence or explanation in its Petition to prove otherwise. Therefore, a person of ordinary skill in the art would not have concluded that Figure 4 could be used to reliably assess purity.

Finally, Green Cross argues that Jin's disclosure that its I2S was injected into human patients in clinical trials suggests that its I2S was highly pure, "as it is unlikely that any regulatory agency would have allowed clinical testing to go

forward had HCP content exceeded a level that would have rendered the protein composition unsafe." Petition at 44-45. Furthermore, Green Cross appears to assert that because in the Jin clinical trial, "patients that received Jin's I2S experienced a reduction in urinary GAG levels and an improvement in the 6-minute walk test as compared to patients treated with the FDA-approved drug Elaprase®," it must mean that Jin's I2S has a low HCP level. Petition at 45. This is pure speculation on the part of Green Cross. First, Green Cross provides no evidence whatsoever of the actual HCP levels in the Jin composition. Also, Green Cross provides no evidence of where or under what regulatory requirements, if any, Jin's clinical study was conducted. Instead, Green Cross exclusively relied on the unsupported say-so of its expert Dr. Mark Sands that, "if 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." Petition at 27, 45 (both citing Sands Decl., ¶ 45). Neither Green Cross nor Dr. Sands provided any supporting evidence or explanation as to why and how the patients' response to the treatment is necessarily related to the specific HCP level in the drug product. Petitioner also presented no evidence to show that the clinical trial described in Jin was conducted in the United States under the FDA guidelines. In fact, according to Green Cross's own press release from 2011, Hunterase clinical trials were carried out by Samsung Medical Center in Seoul, South Korea, on 31

patients suffering from Hunter Syndrome. Ex. 2003. The clinical trial described in the 2011 press release is consistent with the clinical study disclosed in Experimental Example 2 of Jin. Thus, Jin does not appear to describe a clinical trial conducted in the United States and therefore, the FDA guideline Green Cross now cites is irrelevant and cannot be used to establish HCP level in I2S disclosed in Jin.

In footnote 6 of its petition, Green Cross appears to further assert that *merely* because Jin also mentions that I2S is "safer" than Elaprase® in its abstract, the I2S of Jin must have "lower HCP contamination than a related, FDA-approved drug product." Petition at 45, n.6. Yet, there is no data whatsoever disclosed in Jin or provided by Green Cross in its Petition demonstrating that Jin's I2S is actually "safer" than Elaprase®. Green Cross also did not provide any evidence or explanation that the safety of a drug production is directly related to the specific HCP level in the drug product.

The entirely speculative and conclusory statements of Green Cross and its expert should be entitled to little or no weight. *See* 37 C.F.R. § 42.65(a) (an expert opinion "that does not disclose underlying facts or data on which an opinion is based is entitled to little or no weight"); *see also 3D-Matrix, Ltd., v. Menicon Co., Ltd.*, IPR2014-00398, Paper 11, at 8, 10 (P.T.A.B. Aug. 1, 2014) (reiterating that an expert who gives opinion testimony in an *inter partes* review

must "disclose the underlying facts or data on which the opinion is based"); *Daicel Corp. v. Celanese Int'l Corp*., Case IPR2014-01514, Paper 11, at 20-21 (P.T.A.B. Apr. 1, 2015) (finding experts' declarations lacked "persuasive merit" in showing that asserted claim was inherently anticipated by the cited reference) (*citing In re Am. Acad. of Sci. Tech. Ctr.*, 367 F.3d 1359, 1368 (Fed. Cir. 2004); *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 294 (Fed. Cir. 1985)). Without sufficient data and objective evidence underpinning Green Cross's arguments or its expert Dr. Sands's "opinions", Green Cross has not met its threshold burden to show that Jin's I2S preparation was of high purity with HCP level less than a specified amount.

b. *The Petition failed to present sufficient information to show that a POSITA would have been motivated to lower HCP content to 1-100 ppm.*

Green Cross next argues that a person of ordinary skill in the art would have been motivated "to reduce host cell protein to the lowest level possible, or even remove it entirely." Petition at 45-46, *citing* Sands Decl., ¶ 78. Green Cross further asserts that "[f]urther motivation is provided by guidelines advising that host cell protein impurities should be in the range of 1-100 ppm". Petition at 46. Significantly, Green Cross cited the disclosure in Patent Owner's '556 Patent (Ex. 1001 at 31:66-32:2) as the primary support for its assertion. In obviousness inquiry, the Supreme Court specifically warned against a "temptation to read into

the prior art the teachings of the invention in issue". *See KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 421 (2007) (*citing Graham v John Deere Co. of Kan. City*, 383 U.S. 1, 36 (1966)).

In an attempt to justify its assertion, Petitioner cited a number of additional documents, *i.e.*, Ex. 1012, Ex. 1013, Ex. 1014, and Ex. 1015, as purported support, including FDA's guidance document entitled "Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use" (Ex. 1012). However, Green Cross not only does not provide the relevant language from the cited documents in its Petition, it fails to even provide a page citation. For this reason alone, the Board should disregard these references entirely. *See* 37 C.F.R. § 42.104(b)(5) ("The Board may exclude or give no weight to the evidence where a party has failed to state its relevance or to identify specific portions of the evidence that support the challenge.").

Also, the various "guidance" documents relied on by Green Cross for the proposition that a POSITA would have been motivated to lower HCP content to 1-100 ppm belies Green Cross's contention. For, while the cited "guidance" generally describes "typical" HCP ranges, the cited references also consistently note that the appropriate level of HCP must be evaluated on a case-by-case basis. *See, e.g.*, Ex. 1011 (Wolter) at 40 ("[N]o exact limit is set for proteins; therefore, the specification for proteins must be determined case by case."); Ex. 1012 at 21

(FDA guidance document setting no specific limit for **host cell proteins**: "Tests for detection and quantitation of potential contaminants or additives (e.g., antibiotics, other media components, **host cell proteins** . . .)). Whenever possible, contaminants introduced by the recovery and purification process **should be below detectable levels using a highly sensitive analytical method**.") (emphasis added); Ex. 1013 at 9 ("**The absolute purity of biotechnological and biological products is difficult to determine** and the results are method-dependent."); Ex. 1014 (Champion) at 53, 54 ("Setting an acceptable level for residual host cell protein impurities is complicated by the different assays as well as the complexity of these impurity populations. . . These, and other variables, have resulted in the **'case-by-case' model** for regulatory assessment of impurities to be specified and acceptable limits for control. The absence of clear guidance contributes to uncertainty in the fitness of product development plans . . . **regulatory authorities have not set a global limit on host cell protein levels**.") (emphasis added); Ex. 1015 at 447 ("Because there is no universally available and accepted testing modality, and **a generalized lack of standardization in the industry**, there is currently **not a single test or absolute control limits required by regulators** during clinical trials and at registration.").

Therefore, Green Cross failed to present sufficient information to show that a POSITA would have been motivated to lower HCP content in a protein drug product specifically to 1-100 ppm for therapeutic use.

c. *The Petition does not provide sufficient evidence to demonstrate that removal of HCP during protein purification was routine and well-known.*

Green Cross next argues that HCP can be removed using well-known and routine purification methods. *See* Petition at 46-48; *see also* Petition at 27-28 (*citing* Sands Decl., ¶¶ 46-48). Once again, neither Green Cross, nor its expert, presented any data or objective evidence to support this contention. Rather, Green Cross asserts (without basis) that the purification method described in Jin is as an "excellent starting point" for removing host cell protein "because, as discussed above, it would be expected to remove the vast majority of host cell proteins from an enzyme preparation." Petition at 47 (*(quoting* Sands Decl., ¶ 47, which states the same assertion verbatim without providing any explanation, objective evidence or supporting data) ("Jin . . . provides an excellent starting point . . . because, as discussed above, it would be expected to remove the vast majority of host cell proteins from an enzyme preparation.").

The only references cited by Dr. Sands in his declaration to support his opinion on HCP removal are (1) the '556 Patent; (2) Jin; and (3) Ex. 1018 (U.S.

Patent Publication No. 2013/0195888 ("Wang")).[3] Notably, however, Ex. 1018 does not actually disclose any steps that can be used to remove host cell protein impurities. On the contrary, Ex. 1018 only discusses use of ultrafiltration and diafiltration to remove salts, solvents or exchange buffer in samples in which HCPs have already been removed. Specifically, it states:

> Generally, diafiltration is a technique that uses membranes to remove, replace, or lower the concentration of salts or solvents from solutions containing proteins, peptides, nucleic acids, and other biomolecules. Protein production operations often involve final diafiltration of a protein solution into a formulation buffer *once* the protein has been purified from impurities resulting from its expression, e.g., host cell proteins.

Ex. 1018 at [0073], emphasis added.

Thus, Dr. Sands's testimony on removal of HCP should be given no weight because it is not supported by relevant extrinsic objective evidence. *See Dell, Inc. v. Electronics & Telecomm. Research Inst.*, IPR2014-00152, Paper 12, at 19 (P.T.A.B. May 16, 2014) ("Dr. Mercer's testimony on this point, which is not

[3] Neither the '556 Patent, nor Ex. 1018 is cited (let alone discussed) in the Petition itself in support of this argument and, therefore, should be disregarded. *See* 37 C.F.R. § 42.104(b)(5).

supported by underlying facts or data, is not persuasive.") (*citing* 37 C.F.R. § 42.65(a)); *Moses Lake Indus., Inc. v. Enthone, Inc.*, IPR2014-00246, Paper 6, at 18 (P.T.A.B. June 18, 2014) ("Nothing in the Federal Rules of Evidence or Federal Circuit jurisprudence requires a fact finder to credit the unsupported conclusions or assertions of an expert witness.") (citations omitted); *3D-Matrix, Ltd. v. Menicon Co., Ltd.*, IPR2014-00398, Paper 11, at 8 (P.T.A.B. Aug. 1, 2014) (without disclosure of facts or data upon which the opinion is based, an expert opinion is entitled to "little or no weight.").

Green Cross then argues that "[t]o the extent the I2S obtained from Jin exceeds guidelines for medicinal use, a person of ordinary skill in the art would have been motivated to determine how much target protein is present relative to contaminating host cell proteins at each step in the purification process." Petition at 48. The only reference cited by Green Cross in support of this argument is Ex. 1014.[4] Petition at 48. Yet, Ex. 1014 only teaches that "immunoassays can aid in development and optimization of purification processes," but does not provide any instruction to a POSITA that would enable him or her to "devise a rational purification scheme with a reasonable expectation of removing the vast majority of host cell proteins," as Green Cross asserts in its Petition. Petition at 48.

[4] Again, the Board should disregard this citation as no specific pincite is provided. *See* 37 C.F.R. § 42.104(b)(5).

Finally, Green Cross alleged that "[t]he patentee's silence regarding any inventive significance attributed to HCP purification is also telling." Petition at 48, citing *Cubist Pharms., Inc. v. Hospira, Inc.* 75 F. Supp. 3d 641, 669 (D. Del. 2014) (noting that "at no point during the lengthy prosecution" of the patent at issue did the patentee allege that eliminating impurities (as claimed) distinguished the alleged invention from the prior art). However, here, in sharp contrast to *Cubist*, the file history of the '556 Patent is unusually short. The inventive significance attributed to HCP purification was explained to the examiner during the interview conducted on January 27, 2015 (*see*, the Interview Summary (Ex. 2004)) and submitted in the response to Office Action filed on February 23, 2015 (Ex. 2005 at 13). Indeed, it is now Petitioner's burden to produce evidence to show otherwise. Green Cross's allegation is an attempt to shift the burden to Patent Owner and should not be allowed. *Cf. Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1380-81 (Fed. Cir. 2015) (noting that Petitioner's burden of proving unpatentability by a preponderance of the evidence "never shift[s]" to the patentee.)

In view of the above, it is clear that Green Cross has failed to present sufficient evidence to show that removal of HCP during protein purification was routine and well-known.

d. *The Petition does not present sufficient evidence to show that a POSITA would have a reasonable expectation of*

> *success in isolating I2S with HCP content less than 80 ng/mg.*

Finally, Green Cross asserts that a POSITA "would have fully expected to be able to successfully remove host cell protein contaminants following the method described in Jin." Petition at 49. To support its assertion, Green Cross cites the purported "multiple teachings of Jin that its I2S has a high degree of purity." *Id*. However, the only "teachings" in Jin is the size exclusion chromatography and SDS-PAGE analysis to determine glycosylation pattern of I2S. Ex. 1002 at ¶¶ 155-157 and ¶¶ 144-148. As described above (*see*, pages 20-22, *supra*), Green Cross has failed to establish that either size exclusion chromatography or SDS-PAGE described in Jin can be used to assess purity. Green Cross further relies on "[t]he expectation that most FDA-approved biological drug product[s] on the market today. . . likely fall within the guidelines advising that host cell protein content be below 100 ppm." Petition at 49 (*citing* Exs. 1014 and 1015). However, as also discussed above (*see* pages 26-28, *supra*), the references relied on by Green Cross do not provide a specific limit on HCP level and in fact teach that acceptable levels of HCPs will only be determined on a *case-by-case* basis. *See*, *e.g.*, Ex. 1011 at 40; Ex. 1013 at 9; Ex. 1014 at 53-54; Ex. 1015 at 447.

Green Cross then relies on alleged "[r]eports that others have achieved HCP content below the claimed thresholds using methods similar to those used in Jin."

Petition at 49 (*citing* Ex. 1016[5] at ¶ [0070] as "teaching isolation of I2S by a purification method including cation and anion exchange chromatography steps that resulted in only 12 ppm (equivalent to 12 ng/mg) of HCP.").[6] At minimum, however, Green Cross does not establish that the methods used in Ex. 1016 are sufficiently similar to that disclosed in Jin. Ex. 1016 discusses a lengthy purification process that includes a total of five column purification steps. In

[5] Exhibit 1016 is not prior art under §102(a). Ex. 1016 was published August 2, 2012, which is after the priority date of Jun. 29, 2012 for the '556 Patent. Nor has the Petition established that Ex. 1016 could be considered § 102(e) prior art. In any case, Ex. 1016 could not be considered to anticipate the challenged claims of the '556 Patent, as Ex. 1016 does not disclose all of the limitations of claims 1-3, 9-13, and 16-17. For example, Ex. 1016 does not disclose that the I2S compositions mentioned therein have any percentage conversion of the cysteine corresponding to Cys59 in SEQ ID NO:1 of the '556 Patent (Ex. 1001) to formylglycine.

[6] Patent Owner does not contest the Petitioner's characterization of Ex. 1016 for the purposes of this Preliminary Response; however, Patent Owner reserves its right to offer a different characterization of Ex. 1016 in the event *inter partes* review is instituted against the '556 Patent and in any future proceedings involving the '556 Patent.

contrast, Jin discloses four. Green Cross appears to suggest that two out of those five steps (*i.e.*, cation and anion exchange chromatography) are common between the methods used in Ex. 1016 and in Jin. That is not enough. In addition, Ex. 1016 discloses two types of columns that are not even used in Jin – fluorapatite column ("CFT type 40 um column"; *see* Table 1 and paragraph 006) and gel filtration column ("Superdex 200 pg"; *see* Table 1 and paragraph 62). The order of the steps taken in Ex. 1016 also differs from those taken in Jin, and Green Cross does not establish that the conditions employed in Ex. 1016 and Jin are the same.

For at least these reasons, Green Cross clearly has failed to present sufficient information to establish that a POSITA would have a reasonable expectation of success in isolating I2S with HCP content less than 80 ng/mg.

"Predictability is a touchstone of obviousness." ***DuPuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.***, 567 F.3d 1314, 1326 (Fed. Cir. 2009); *see* ***Amgen v. AbbVie***, IPR2015-01514, Paper 9, at 15 (P.T.A.B. Jan. 14, 2016). ("Although the Wang article indeed provides general guidance, the Wang article also underscores the unpredictability of the undertaking."); ***Moses Lake Indus., Inc. v. Enthone, Inc.***, IPR2014-00246, Paper, at 18 (P.T.A.B. June 18, 2014) ("To the extent an art is unpredictable, as the chemical arts often are, [the Petitioner's] focus on these 'identified, predictable solutions' may present a difficult hurdle

because potential solutions are less likely to be genuinely predictable.") (citations omitted). Because Green Cross has failed to present any objective evidence to show that the HCP content recited in the challenged claims of the '556 Patent can be predictably achieved using routine methods, it cannot meet its burden of showing a reasonable likelihood that it will prevail in its arguments that Claims 1-3 and 16-17 of the '556 Patent are obvious over Jin.

C. Green Cross Fails to Meet Its Burden to Show That There Is a Reasonable Likelihood That Claims 9-13 Are Anticipated by and/or Obvious in View of Jin

In the Petition, Green Cross also asserts that claims 9-13 of the '556 Patent are anticipated and/or obvious in view of Jin. Again, however, Green Cross fails to meet its threshold burden of showing a reasonable likelihood that it will prevail on this ground because, as explained more fully below, Green Cross relies solely on attorney argument and the unsupported assumptions and unsubstantiated "opinions" of its expert.

Each of claims 9-13 requires, *inter alia*, that "the recombinant I2S protein has a specific activity" of a particular level as determined by an "*in vitro* 4-MUF-SO4 to 4-MUF conversion assay." The required specific activity for each claim is: at least 20 U/mg (claim 9), at least 30 U/mg (claim 10), at least 40 U/mg (claim 11), at least 50 U/mg (claim 12), and at least 60 U/mg (claim 13). Ex. 1001 at 50:20-45. Green Cross acknowledged that Jin discloses I2S composition

with a specific activity of 19-55 nmol/min/µg, which, Green Cross asserts, corresponds to 19-55 U/mg. Significantly, however, the specific activity disclosed in Jin is measured using a different assay than the assay required by the claims. Jin measures activity using 4-methylumbelliferyl-L-iduronide-2-sulfate Na2 (MU-IdoA-2S) as a substrate, and not the 4-MUF-SO4 to 4-MUF conversion assay required by claims 9-13.

In order to justify its assertion that the specific activity range disclosed in Jin inherently anticipates claims 9-13 of the '556 Patent, Green Cross makes the following convoluted argument based on various unfounded assumptions: First, despite the fact that Jin and the '556 Patent use completely different methods, Green Cross contends, without providing any empirical support, that because MU-IdoA-2S is specific to I2S, "the I2S of Jin must necessarily have a specific activity level of 19-55U/mg or higher when measured using an enzyme-generic 4-MUF SO4 to 4-MUF assay." Petition at 30 (*citing* Sands Decl., ¶ 40). Green Cross then points to the ranges of specific activity disclosed in the '556 Patent and asserts that "the range of specific activity disclosed for I2S [in Jin] is substantially identical to that disclosed for the embodiment of the '556 patent." Petition at 31-32. In an inappropriate attempt to equate what is disclosed in the specification with what is claimed in claims 9-13 of the '556 Patent, Green Cross asserts that "the '556 patent does not ascribe any particular criticality to any of the specific activity levels

recited in the specification or the claims"; therefore, "a POSITA would find no reasonable difference in how the I2S having the claimed activity as compared to the I2S of Jin," without providing any evidence or data. *Id.* at 32, 34. Green Cross further asserts:

> "[t]his is true whether the claimed range is 'at least 20 U/mg,' 'at least 30 U/mg,' 'at least 40 U/mg,' 'at least 50 U/mg,' or 'at least 60 U/mg,' *Id.*, and it is particularly true given that Jin's use of an enzyme-specific substrate means the specific activity levels reported in Jin could have been higher had they been measured using a substrate – like that used in the '556 Patent – that is generic to all sulfatases. *Id.* at ¶ 40. Accordingly, the range of '19-55' U/mg in Jin anticipates the 4-MUF specific activity levels recited in claims 9-13 of the '556 patent."

Petition at 34.

This attempt by Green Cross to correlate two distinct assays in order to assert inherent anticipation without any actual supporting evidence does not withstand scrutiny.

To demonstrate inherent anticipation, "[t]he extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999); *3D-Matrix,*

Ltd., v. Menicon Co., Ltd., IPR2014-00398, Paper 11, at 6 (Aug. 1, 2014). "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *In re Robertson*, 169 F.3d at 745. Moreover, an expert's conclusory testimony, unsupported by the documentary evidence, cannot supplant the requirement of anticipatory disclosure in the prior art reference itself." *Purdue Pharma L.P. v. Boehringer Ingelheim GmbH*, 98 F.Supp. 2d 362 (S.D.N.Y. May 16, 2000).

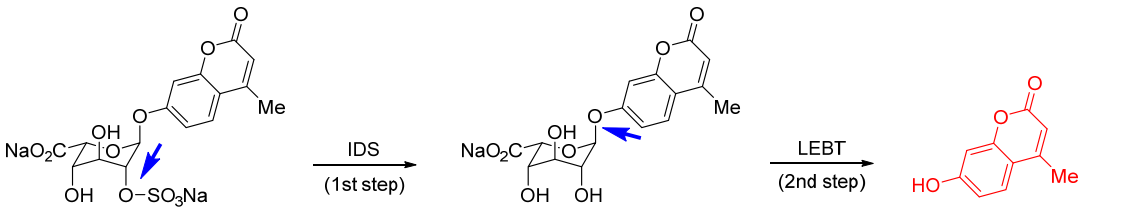
For the reasons enumerated below, Green Cross has not met its threshold burden to show that the specific activity range disclosed in Jin inherently anticipates claims 9-13 of the '556 patent.

1. *The Petition fails to present sufficient evidence that, if the specific activity of I2S disclosed in Jin were measured using the assay claimed in the '556 patent, it would necessarily have the same or higher specific activity as is reported in Jin.*

Green Cross's purported conclusion that "the I2S of Jin must necessarily have a specific activity level of 19-55U/mg or higher when measured using an enzyme-generic 4-MUF SO4 to 4-MUF assay" (Petition at 30 (*citing* Sands Decl., ¶ 40)) is based on the assumption that Jin's substrate MU-IdoA-2S is I2S

specific[7], therefore, only I2S can release 4-MUF from the MU-IdoA-2S substrate used in Jin, while any sulfatase can release 4-MUF from the enzyme generic 4-MUF-SO_4 substrate. Petition at 30.

Green Cross cannot, and does not, dispute that the MU-IdoA-2S based assay described in Jin is a completely different method than the 4-MUF-SO_4 assay described in the '556 Patent. Petition at 21-23. As illustrated below, the assay employed in Jin is a two-step assay that uses two different enzymes (I2S and Lysosomal Enzymes purified from Bovine Testes ("LEBT")) to release 4-MUF:



See Ex. 1002, ¶ 159. The assay required by claims 9-13 of the '556 Patent, in contrast, is a one-step assay that involves only the enzyme being tested (I2S), which cleaves the sulfate bond to release the 4-MUF fluorophore.

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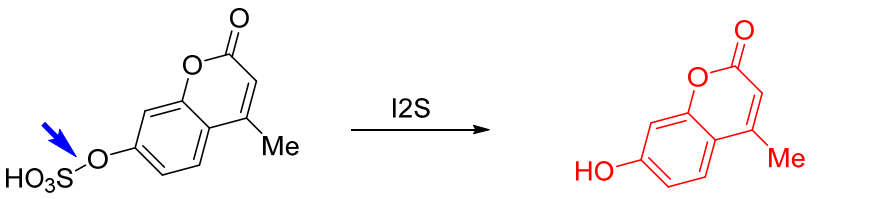
[7] For the purposes of this Preliminary Response, Patent Owner does not contest the Petitioner's assertion that Jin's substrate MU-IdoA-2S is I2S specific; however, Patent Owner reserves its right to do so in the event *inter partes* review is instituted against the '556 Patent and in any future proceedings involving the '556 Patent.



4-methylumbelliferyl-sulfate

4-methylumbelliferyl fluorophore (4-MUF)

See Ex. 1001 at 23:20-24, 23:43-45.

Clearly, these two assays are different. They involve different steps and different substrates. As a result, the outputs cannot be compared directly.

Indeed, Green Cross's own exhibits demonstrate that "specific activity" is necessarily linked to, and defined by, the assay chosen and, therefore, highly method-dependent. For example, Green Cross's Ex. 1013 states, "the relative purity of a biological product has been expressed in terms of specific activity (units of biological activity per mg of product) which is also ***highly method-dependent.***" Ex. 1013 at 4, section 2.1.4 (emphasis added). In addition, as Green Cross correctly acknowledged in the "Background Regarding the State of the Art" section of the Petition, "[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***." Petition at 21 (the first sentence of the subsection "F. Specific Activity", emphasis added). Thus, because determining specific activity is highly dependent on the assay employed and the conditions used, the specific activity of I2S disclosed in Jin measured using a

completely different assay simply cannot be compared to the specific activity assay disclosed or claimed in the '556 Patent, regardless of the specificity of the substrate used.

Green Cross has not provided any objective evidence to show otherwise. In fact, Green Cross' unfounded assumption is flatly contradicted by its own cited reference in the Petition. Nor has its expert Dr. Sands provided any experimental data or scientific paper which could prove a correlation between the assay performed in Jin and the assay claimed in the '556 Patent. Instead, Dr. Sands merely asserts, without support, the very same self-serving conclusion that appears in Green Cross Petition. For this reason alone, these arguments must be accorded little or no weight. *See* 37 C.F.R. § 42.65(a) ("Expert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight."); *Kinetic Techs., Inc. v. Skyworks Sols., Inc.*, IPR2015-00529, Paper 8, at 15 (P.T.A.B. Sept. 23, 2014) ("Merely repeating an argument from the Petition in the declaration of a proposed expert does not give that argument enhanced probative value."); *Wowza Media Sys., LLC v. Adobe Sys. Inc.*, IPR2013-00054, Paper 12, at 12 (P.T.A.B. Apr. 8, 2013) ("The Declaration . . . appears, for the most part, simply to track and repeat the arguments for unpatentability presented in the Petition [and] . . . is therefore no more helpful

tha[n] the Petition in determining where the challenged recitation is found in the references.").

Green Cross then argues that "if the specific activity of I2S disclosed in Jin were measured using a generic 4-MUF conversion assay, it would necessarily have the same or higher specific activity as is reported in Jin." Petition at 25. Green Cross's argument is simply wrong. As discussed above, the specific activity assay used in Jin is completely different than the 4-MUF conversion assay claimed in the '556 Patent. Because the specific activity measured is entirely dependent on the method employed and the set of conditions used, it would be hard to predict how the specific activity of I2S disclosed in Jin would be measured if a completely different assay disclosed in the '556 Patent were used. For the sake of argument, even if we assume that the specific activity disclosed in Jin could be converted by 1:1 ratio to the specific activity measured using a generic 4-MUF conversion assay claimed in the '556 Patent, Green Cross's argument still fails because it is inconsistent with its assertion that Jin's I2S is highly pure. The scenario that Green Cross argued would be true *only if* there are any contaminating sulfatases in Jin's I2S composition that would also release 4-MUF from a generic substrate, therefore resulting in an artificially high specific activity. *See* Petition at 23. Green Cross has not provided any evidence that Jin's I2S composition contains any such contaminating sulfatases. In fact, this is

inconsistent with Green Cross's assertion that Jin's I2S composition is highly pure (*see* pages 19-23, *supra*). In Material Fact No. 9, Green Cross asserts "Jin discloses I2S that was measured using size exclusion chromatography. The I2S sample that was measured was disclosed to be 100% pure."[8] Petition at 5. Thus, Green Cross cannot simultaneously argue that Jin disclosed a 100% pure I2S preparation and that Jin's I2S contains contaminating sulfatases that would give rise to artificially high specific activity using a generic substrate. Green Cross simply cannot have it both ways.

Therefore, Green Cross fails to present sufficient evidence to show that, if the specific activity of I2S disclosed in Jin were measured using the assay claimed in the '556 Patent, it would necessarily have the same or higher specific activity as is reported in Jin.

2. *The Petitioner fails to meet its burden to show that Jin anticipates each and every limitations of claims 9-13 of the '556 Patent*

The only range of specific activity disclosed in Jin is 19-55 nmol/min/μg, using an *in vitro* MU-IdoA-2S assay, which is, as discussed above, a different

[8] Patent Owner does not concede to the assertion stated in Material Fact No. 9.

assay than the 4-MUF-SO_4 assay claimed in the '556 Patent. Green Cross asserts that 19-55 nmol/min/μg corresponds to 19-55 U/mg.[9]

In an attempt to justify that the single specific activity range 19-55 U/mg measured using a completely different assay disclosed in Jin is sufficient to anticipate each of claims 9-13 of the '556 patent, which requires a specific activity of "at least 20 U/mg," "at least 30 U/mg," "at least 40 U/mg," "at least 50 U/mg," or "at least 60 U/mg," respectively, as determined by an *in vitro* 4-MUF-SO_4 to 4-MUF conversion assay, Green Cross asserts that "the '556 patent does not ascribe any particular criticality to any of the specific activity levels recited in the specification or the claims"; therefore "a POSITA would find no reasonable difference in how the I2S having the claimed activity as compared to the I2S of Jin." Petition at 32, 34. "This is true whether the claimed range is 'at least 20 U/mg,' 'at least 30 U/mg,' 'at least 40 U/mg,' 'at least 50 U/mg,' or 'at least 60 U/mg,' *Id.*, . . . Accordingly, the range of '19-55' U/mg in Jin anticipates the 4-MUF specific activity levels recited in claims 9-13 of the '556 patent." *Id.* at 34. Again, Green Cross relies on a false assumption.

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[9] Patent Owner does not contest the Petitioner's assertion for the purpose of the Preliminary Response; however, Patent Owner reserves its right to do so in the event *inter partes* review is instituted against the '556 Patent and in any future proceedings involving the '556 Patent.

Contrary to Green Cross's assertion, the Patent Owner demonstrated the criticality of the specific activity levels recited in claims 9-13 during an interview with the Examiner on January 27, 2015, and summarized in the response to Office Action filed on February 23, 2015. See Ex. 2005 at 6 and 11-14. In particular, Shire explained to the Examiner that improvement on specific activity *directly and materially* impacts the safety and efficacy of the I2S protein, which can lead to a significantly improved therapeutic protein drug for Hunter patients. The Examiner considered Shire's explanation and allowed the case. It is now Green Cross's burden to prove otherwise. *See discussion infra* at Page 30 (discussion related to the burden of production of evidence). Green Cross makes no serious attempt to meet this burden.

Indeed, Green Cross has not presented any data or objective evidence to show that a POSITA would find no reasonable difference in the I2S having the claimed activity (*i.e.*, "at least 20 U/mg," "at least 30 U/mg," "at least 40 U/mg," "at least 50 U/mg," or "at least 60 U/mg") as compared to the I2S of Jin. Green Cross merely asserts without support that "the '556 patent does not ascribe any particular criticality to any of the specific activity levels recited in the specification or the claims." That is not enough. Without any real evidence to support its assertion, Green Cross fails to meet its burden.

3. *The Petitioner fails to present any evidence or rational to show that Jin would render claims 9-13 of the '556 Patent obvious*

Green Cross's entire obviousness argument constitutes two paragraphs in its Petition on pages 35 and 36 where Green Cross makes conclusory statements without any detailed supporting data, analysis or rational. Specifically, Green Cross asserts that "the overlap between the range disclosed in Jin (19-55 U/mg) and the ranges recited in claims 9-13 of the '556 patent (at least 20, 30, 40, 50, and 60 U/mg) creates a *prima facie* case that the limitations at issue are obvious." Petition at 35. As discussed above, the specific activity range disclosed in Jin (19-55 U/mg) was measured using a different assay; therefore, it cannot be directly compared to the ranges claimed in the '556 patent. Green Cross has not provided any data or evidence correlating the two different assays or proving any actual overlap between the range disclosed in Jin and the ranges recited in claims 9-13 of the '556 patent.

Green Cross further alleges that "Petitioner is not aware of any evidence that would rebut this *prima facie* case of obviousness" (Id. at 35) and "to the extent there is evidence that one of the claimed thresholds – at least 20, 30, 40, 50 or 60 U/mg specific activity as indicated in claims 9-13 – is critical to the clinical function of I2S, it would have been obvious to purify I2S as described in Jin, test it for specific activity, and select only the preparations at the higher end of the disclosed range. See Sands at ¶69." Petition at 36. Green Cross once again relies exclusively on the Sands declaration, which merely asserts, without support, the

very same contentions that are then repeated in the Petition. These arguments must be accorded little or no weight. *See, Kinetic Techs., Inc. v. Skyworks Sols., Inc.*, IPR2015-00529, Paper 8, at 15 (P.T.A.B. Sept. 23, 2014) ("Merely repeating an argument from the Petition in the declaration of a proposed expert does not give that argument enhanced probative value.").

Green Cross's allegation that "Petitioner is not aware of any evidence that would rebut this *prima facie* case of obviousness" is simply untrue. As discussed above, Shire presented evidence during prosecution showing that improvement on specific activity *directly and materially* impacts the safety and efficacy of the I2S protein and such improvement required real innovation and was not a result of mere routine optimization. See Ex. 2005 at 6 and 11-14; and Ex. 1008 at ¶ 5. Neither Green Cross nor its expert Dr. Sands addressed such secondary considerations of nonobviousness. Like in the Petition, Dr. Sands makes the conclusory assertion that he is "not aware of any objective indicia of non-obviousness or other evidence that would rebut a finding of obviousness." *See* Sands Decl. ¶ 82. Such blanket statements, without any supporting evidence are not enough to enable Green Cross to meet its burden. *See, e.g.*, *Dell, Inc. v. Electronics & Telecomm. Research Inst.*, IPR2014-00152, Paper 12, at 19 (P.T.A.B. May 16, 2014) ("Dr. Mercer's testimony on this point, which is not supported by underlying facts or data, is not persuasive.") (denying Institution)

(*citing* 37 C.F.R. § 42.65(a)); *Moses Lake Indus., Inc. v. Enthone, Inc.*, IPR2014-00246, Paper 6, at 18 (P.T.A.B. June 18, 2014) (denying Institution) ("Nothing in the Federal Rules of Evidence or Federal Circuit jurisprudence requires a fact finder to credit the unsupported conclusions or assertions of an expert witness.") (citations omitted).

For at least the above reasons, Green Cross fails to meet its threshold burden to show that there is a reasonable likelihood that claims 9-13 are anticipated by and/or obvious in view of Jin.

V. THE JIN REFERENCE IS, AT BEST FOR GREEN CROSS, ONLY ENTITLED TO THE JUNE 15, 2012 PCT FILING FOR PURPOSES OF 35 U.S.C. 102(E)

As discussed above, each of Green Cross's asserted grounds of unpatentability relies on U.S. Patent Publication No. 2014/0242059 ("Jin") under Pre-AIA 35 U.S.C. 102(e). Jin claims priority to its PCT No. KR2012/004734, filed on June 15, 2012, which in turn claims priority to its U.S. Provisional Application No. 61/500,994, filed in Korean on June 24, 2011 (the '994 Provisional). Green Cross does not specifically identify in its Petition the actual § 102(e) date on which it purports to rely. Furthermore, Green Cross has not cited or referred to the provisional in the Petition and has not submitted it as an exhibit with the Petition. Finally, Green Cross has not asserted that or even discussed

whether the '994 Provisional discloses the subject matter recited in the challenged claims.

For all the reasons stated herein, Green Cross's Petition should be denied regardless of the actual 102(e) date of Jin. However, in the event *inter partes* review is instituted against the '556 Patent, Patent Owner respectfully requests the Board determine that Green Cross has not met its burden to establish that the Jin reference is entitled to its provisional filing date as its § 102(e) date and has waived its right to do so. In other words, at earliest, the Jin reference is only entitled to its PCT filing date June 15, 2012 as its § 102(e) date.

Globus Medical, Inc. v. DePuy Synthes Prods., LLC, IPR2015-00107, Paper 11 (P.T.A.B. May 1, 2015) is analogous. In *Globus Medical*, the petitioner challenged the patent owner's claims as unpatentable under 35 U.S.C. § 103 in view of two prior art references, one of which was a patent (the Panjabi patent) claiming priority to U.S. provisional application 60/581,716 (the '716 provisional). *Id.* at 2. The PTAB noted that the effective date of the reference was the date on which an application in the priority chain "disclose[d] the information *relied upon* to prove unpatentability of the challenged claims." *Id.* at 3, emphasis added. The petitioner *Globus* did not "state expressly the effective date" of the reference patent as prior art in its petition, however. *Id.* at 2. The petitioner likewise did not analyze whether the '716 provisional "disclose[d] the

subject matter recited in the challenged claims," and did not cite any portion of the provisional or submit it as an exhibit in its Petition. *Id.* at 3. As a result, the PTAB deemed that the Panjabi patent was not entitled to its provisional filing date and accorded the non-provisional filing date of the Panjabi patent as the actual 102(e) date for the purpose of *inter partes* review.[10] *Id.*

Like in *Globus*, Green Cross has not "state[d] expressly the effective date" of Jin as an alleged prior art reference in its Petition.[11] *See Globus*, IPR2015-

[10] In *Globus*, because the non-provisional filing date of the Panjabi patent post-dates the challenged patent, the PTAB declined to institute IPR on any of the challenged claims. *Id.* at 3-4.

[11] The facts here are distinguishable over *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375 (Fed. Cir. 2015), because Petitioner Green Cross makes no mention of the provisional application whatsoever in its Petition; nor does Petitioner attach it as an exhibit. *Compare Green Cross Corp. v. Shire Human Genetic Therapies, Inc.*, IPR2016-00258, Paper 2, at 2, 4, 25-28 ("U.S. Patent Application Publication No. 2014/0242059 ("Jin") is prior art with respect to the '556 patent under pre-AIA 35 U.S.C. § 102(e).") *with Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, IPR2013-00131 (Corrected Petition), at 4 ("U.S. Patent Publication No. 2004/0157011 by Raymond et al. . . published on

00107, Paper 11, at 2. Green Cross likewise has neither cited any portion of the provisional nor submitted it as an exhibit to its Petition. *See id.* Therefore, the Board should follow *Globus* to find that the Jin reference is not entitled to its provisional filing date and accord the PCT date June 15, 2012 of the Jin reference as the actual § 102(e) date for the purpose of *inter partes* review, should the *inter partes* review be ultimately instituted.[12]

VI. CONCLUSION

For all the reasons stated above, Patent Owner respectfully requests that the Board deny the Petition because the Petition failed to present sufficient information to meet the threshold burden of showing there is a "reasonable

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8/12/2004 and having a priority date of 2/15/2000 based on U.S. Prov. Pat. App. 60/182,490 filed on 2/15/2000.") (Feb. 14, 2013).

[12] Should this IPR ultimately be instituted, Shire intends to file a motion to antedate the Jin PCT filing date. However, the burden shifting process in *Dynamic Drinkware* should not apply in this case because Green Cross has waived its right to establish the provisional date as the § 102(e) date because it has failed to state Jin's effective prior art date, cite the provisional in its Petition, or attach the provisional as an exhibit to its Petition. *See Globus Medical, Inc. v. DePuy Synthes Prods., LLC*, IPR2015-00107, Paper 11 (P.T.A.B. May 1, 2015).

likelihood" that any of the challenged claims of the '556 Patent are unpatentable under 35 U.S.C. § 314(a).

Should the *inter partes* review be ultimately instituted, Patent Owner respectfully requests that the Board determine that the Jin reference relied upon by Petitioner is only entitled to the PCT filing date as the actual § 102(e) date for the purpose of this IPR.

Date: March 9, 2016

Respectfully submitted,

/ Fangli Chen /

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PATENT OWNER'S EXHIBIT LIST

Exhibit #	Document
2001	Affidavit of Eric J. Marandett in Support of Patent Owner's Motion for *Pro Hac Vice* Admission
2002	Affidavit of Margaret E. Ives in Support of Patent Owner's Motion for *Pro Hac Vice* Admission
2003	Green Cross Press Release, October 11, 2011
2004	Applicant initiated interview summary for USSN 13/829,706, February 3, 2015
2005	Response to Non-Final Office Action for USSN 13/829,707, submitted February 23, 2015
2006	Information Disclosure Statement (PTO/SB/08) for USSN 13/829,706, submitted February 23, 2015
2007	Initialed copy of Information Disclosure Statement (PTO/SB/08) for USSN 13/829,706, submitted February 23, 2015, initialed on March 25, 2015

CERTIFICATE OF SERVICE (37 C.F.R. § 42.6(e))

The undersigned hereby certifies that a copy of the attached PATENT OWNER'S PRELIMINARY RESPONSE and Exhibits 2003-2007 are being served via electronic mail on March 9, 2016, to dcotta@mintz.com; kkim@mintz.com; sashraf@mintz.com; twintner@mintz.com; and pjcuomo@mintz.com, as consented to on page 8 of the Petition, on November 25, 2015.

Respectfully submitted,

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