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

INTER PARTES REVIEW OF U.S. PATENT NO. 9,051,556
Case IPR No.: 2016-00258

PETITIONER'S REPLY BRIEF

UPDATED LIST OF EXHIBITS

Exhibit 1001	U.S. Patent No. 9,051,556
Exhibit 1002	U.S. Patent Application Publication No. 2014/0242059
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Exhibit 1004	May 23, 2014 Restriction Requirement ('556 Prosecution History)
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Exhibit 1010	Declaration of Dr. Mark Sands in Support of Green Cross' Petition
Exhibit 1011	Wolter *et. al.*, *Assays for Controlling Host-Cell Impurities in Biopharmaceuticals,* BioProcess International, February 2005
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Exhibit 1013	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, *Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*, March 10, 1999

Exhibit 1014	Champion *et. al.*, *Defining Your Product Profile and Maintaining Control Over It, Part 2,* BioProcess International, 2005
Exhibit 1015	Wang *et. al.*, *Host Cell Proteins in Biologics Development: Identification, Quantitation and Risk Assessment,* Biotechnology and Bioengineering, Vol. 103, No. 3, June 15, 2009
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INTRODUCTION

Shire's Patent Owner Response ("POR") rests on two flawed premises, both of which are completely unsupported by scientific evidence.

First, with respect to priority date, Shire contends that it has "demonstrated reduction to practice prior to Jin's earliest effective date." POR at 3. If Shire were confident in its evidence of this prior reduction to practice, it would not have waited until page 64 of its response to present it. In fact, when one peers behind the conclusory statements in Shire's response and the equally conclusory supporting declarations of its current and former employees, one quickly realizes that Shire had not reduced its alleged invention to practice prior to June 2011 (the filing date of the Jin Provisional), nor even prior to June 2012 (the PCT filing date of Jin).

The challenged claims of the '556 patent require three things: (1) an I2S composition having a specific amino acid sequence known as "SEQ ID NO:1", (2) an I2S composition having a minimum cysteine to formylglycine conversion ratio at the 59-position (either 70%, 75%, or 85%), and (3) an I2S composition having a maximum host cell protein ("HCP") content (either 150 ng/mg, 100 ng/mg, or 80 ng/mg). Shire's evidence falters already on the first element. Shire provides no evidence whatsoever that it had reduced to practice the required SEQ ID NO:1 at any time, let alone prior to the filing and priority dates of Jin *et al*. US

2014/0242059 A1 ("Jin"). Shire's various declarations are devoid of any test data showing the amino acid sequence of the recombinant I2S ("r-I2S") enzyme Shire alleges to have possessed prior to the filing of Jin. Instead, Shire relies on incomplete documents coupled with what are admittedly attorney-generated "demonstratives." Such evidence is flatly insufficient to meet Shire's burden to show an actual reduction to practice of the challenged claims. Shire's alleged "evidence" is also completely disconnected – both temporally and as a matter of basic science – from the testimony of Mr. Dave Nichols, the sole inventor of the '556 patent.

Second, with respect to obviousness, Shire contends that purification of its I2S composition was difficult "due to the direct tension between how high FGly and low HCP levels are achieved during the production process." POR at 1. Shire further contends that "enzymes such as I2s were notoriously difficulty to purify compared to other proteins, due to their unusual complexity." *Id*. Shire's declarants, however, completely fail to provide support for either of these contentions. There was no evidence in the prior art that I2S was a particularly difficult enzyme to purify, or that the "complexity" of I2S in any way contributed to difficulties in purifying or removing HCPs from it. Quite to the contrary, all of the evidence indicates that I2S was an entirely unremarkable protein from a purification standpoint, and that industry-standard HCP levels of less than 100 ppm

were routinely achievable using different numbers and combinations of commonly available chromatography columns.

In response to Shire's allegations that Green Cross did not have its own r-I2S HCP data, *see* POR at 3, Green Cross has submitted the declarations of Doo-Hong Park, Ph.D. ("Park")(Ex.1035) and Chul-Soo Cheong ("Cheong")(Ex.1039) which conclusively establish that is not the case.

ARGUMENT

I. SHIRE'S PURPORTED ANTEDATION EVIDENCE IS INSUFFICIENT.

Petitioner proffered Jin, which constitutes prior art under pre-AIA 35 U.S.C. §102(e) because it issued from the U.S. national stage entry of PCT application No. KR2012/004734, filed on June 15, 2012. Jin was filed before the June 29, 2012 filing date of U.S. Provisional Application No. 61/666,733, which represents the earliest effective filing date for the '556 patent. *See* Paper 12 at 7.[1] The Board granted an *inter partes* review with regard to claims 1-3 and 16-17 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

[1] Jin additionally claims priority to U.S. Provisional Application No. 61/500,994, filed on June 24, 2011.

in the art as reflected in Jin and any one of Wolter, Champion, Wang, and Mihara. *Id.* at 22.

In order to antedate Jin, Shire bears the burden to produce evidence supporting, at a minimum, a date of invention before Jin's filing date of June 15, 2012. *See Neste Oil Oyj v. Reg Synthetic Fuels, LLC,* IPR2013-00578, Paper 54 at 17 (PTAB Mar. 12, 2015)("[T]he burden of production on antedation lies with [Patent Owner]."); *see also Dynamic Drinkware, LLC v. National Graphics, Inc.,* 800 F.3d 1375, 1380 (Fed. Cir. 2015).

Shire states in its response that "Mr. Nichols' invention was conceived and reduced to practice even before Jin's provisional filing date [of June 24, 2011]." POR at 65 n.7 (emphasis added). The same statement is made by Nichols himself: "[A]s of April, 2011, I and my team had purified a number of batches of recombinant I2S that met all of the limitations of these claims . . . . In other words, the invention as claimed in claims 1-3, 16, and 17 of the '556 patent was reduced to practice at least as of April, 2011." Ex.2014 ("Nichols Decl.") ¶5 (emphasis added); *see also id*. ¶27. As explained below, however, Shire's self-supporting and conclusory evidence fails to meet its burden to show an actual reduction to practice

of its purported invention before any date, let alone the filing date (June 15, 2012) or provisional date (June 24, 2011) of Jin.[2]

A. Legal Standard

In order to establish an actual reduction to practice, a party must establish three things: "(1) construction of an embodiment that met all the claim limitations; (2) . . . determination that the invention would work for its intended purpose, and (3) the existence of sufficient evidence to corroborate inventor testimony regarding these events." *K-40 Electronics, LLC, v. Escort, Inc.*, IPR2013–00240, Paper 37 at 11 (PTAB Sep. 29, 2014) (citing *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1169 (Fed. Cir. 2006)). The key to this test is objective, corroborative evidence, which provides a check against an inventor's temptation to "remember" facts favorable to his or her case. *See Mahurkar v. C.R. Bard, Inc.,* 79 F.3d 1572, 1577 (Fed. Cir. 1996); *see also In re NTP, Inc.*, 654 F.3d 1279,1291 (Fed. Cir. 2011). In assessing corroboration, this tribunal applies a "rule of reason analysis" analysis, in which "an evaluation of all pertinent evidence must be made so that a sound determination of the credibility of the inventor's story may be reached." *Sensio,*

[2] Shire's response is premised exclusively on a purported actual reduction to practice prior to the earliest possible filing date of Jin. Shire makes no argument or showing that there was conception, followed by diligence leading to a constructive reduction to practice.

Inc. v. Select Brand, Inc., IPR2013-00580, Paper 31 at 13 (PTAB Feb. 9, 2015)(quoting *Mahurkar*, 79 F.3d at 1577).

B. Shire failed to prove <u>any</u> actual reduction to practice of the challenged claims, let alone one prior to June 15, 2012.

1. Shire failed to demonstrate that it possessed an I2S composition having the required amino acid sequence SEQ ID NO:1.

Both Nichols, the sole inventor of the '556 patent, and Shire's in-house patent attorney responsible for prosecution of the '556 patent, admit that all of the challenged claims require, as a first element, an I2S protein having a <u>specific</u> 525-amino acid sequence known as SEQ ID NO:1. Nichols Decl. ¶5; Ex.2018 ("Morin Decl.") ¶7; *see also* '556 patent, cols. 39-42. The claims as drafted do not permit any variation in this specific sequence.[3]

[3] During prosecution, Shire amended the sequence language in claim 1 from "an amino acid sequence <u>at least 90% identical to</u> SEQ ID NO:1" to "<u>the</u> amino acid sequence of SEQ ID NO:1" in order to overcome a rejection under 35 U.S.C. §112. *See* Ex.1007 (Feb. 23, 2015 Response to Non-Final Office Action at 2) (emphasis added). This was a clear disavowal of claim scope. *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.,* 535 U.S. 722, 737 (2002).

Shire summarizes its alleged proof of reduction to practice of the SEQ ID NO:1 element of the challenged claims in a chart beginning on page 87 of Shire's response. This "proof" consists of the following items:

- ¶¶11 and 13 of the Nichols Declaration (Ex.2014);
- ¶11 of the Yang Declaration (Ex.2017);
- Ex.2115; and
- Ex.2111

POR at 87. The insufficiency of each of these pieces of evidence is addressed below.

a. Paragraphs 11 and 13 of the Nichols Declaration (Ex.2014)

Nichols states that the allegedly antedating batches of I2S purified by his team at Shire were "produced by an engineered human recombinant cell line, referred to as '2D'." Ex.2014, ¶11. Nichols further states that this 2D cell line contained an expression cassette for I2S named "pXI2S6." *Id*. In support, Nichols attached Exhibit 2117 (which is simply a screenshot of a Microsoft Word folder) and Exhibit 2115 (which is a research report).

Shire's Exhibit 2117 is proof of nothing. Nichols admitted that he never looked at a computer containing the screenshot, never attempted to find the folder allegedly represented in the screenshot, and has no idea who did so, or who found

any of the documents allegedly contained in the folder. *See* Nichols Dep. 123:11-124:4. Thus, Exhibit 2117 has an evidentiary value of zero.

Shire's Exhibit 2115 is not much better. On its face, it purports to be a report from Transkaryotic Therapies, Inc. ("TKT") entitled [redacted] expression plasmid pXI2S6 – the same plasmid referenced by Nichols in his declaration. Yet Exhibit 2115 contains no information whatsoever regarding the amino acid sequence of the protein <u>actually produced</u> by the plasmid pXI2S6.

At his deposition, [redacted] devoid of any details regarding its transfection into any host cell. Nichols Dep. 117:5-118:10. [redacted] and he had no idea what amino acid sequence would have resulted had the plasmid actually been transfected into host cells, expressed, and purified. *Id*. 142:15-20;143:4-16. Thus, Nichols had no idea if a complete and functional I2S protein amino acid was ever produced in connection with Exhibit 2115. In fact, Nichols had no idea who created Exhibit 2115 – nor could he have, because he was not involved with any cell-line work at TKT, and never worked in the TKT department that created the report. *Id*. 116:3-

15;119:11-13.[4] Evidence of a DNA sequence in a plasmid, without more, is not evidence of the amino acid sequence of the protein supposedly produced by that plasmid. *See* Webb Decl. ¶22. It also falls woefully short of establishing an actual reduction to practice of I2S. *See*, *e.g.*, *Purdue Pharma LP v. Boehringer Ingelheim GmbH*, 237 F.3d 1359, 1365 (Fed. Cir. 2001) ("To prove actual reduction to practice, an inventor must establish that he actually prepared the composition and knew it would work.").

Exhibit 2115 should be disregarded for a second, equally fundamental reason. Nichols stated that the allegedly antedating batches of I2S were purified from the "2D" cell line. Nichols Decl. ¶¶11, 13, 16 (describing "Run 80"), 24 (describing "Run 92"); Nichols Dep. 70:15-25. Nichols further admitted that this "2D" cell line was transfected with not just the I2S gene, but also one for formylglycine generating enzyme ("FGE") required to activate the key cysteine residue in I2S. Nichols Dep. 71:6-10. This is consistent with the '556 patent disclosure. Example 1 of the '556 patent discloses that "[a] cell line stably expressing an iduronate-2-sulfatase enzyme (I2S) and formylglycine generating enzyme (FGE) was developed." '556 patent, col. 30:26-28. And Example 3

[4] This begs the question of how Exhibit 2115 could have been created "at [the] direction and under [the] supervision" of Nichols, as he stated in his declaration. *See* Nichols Decl. ¶35; Nichols Dep. 120:11-14.

discloses that "[t]he I2S material was produced from cell line 2D expressing I2S and formylglycine generating enzyme (FGE) as described in Example 1." *Id*. col. 33:50-52. Nichols provided further confirmation of this during his deposition:

> **Q:** Is all the data in this patent with respect to the I2S that's been expressed, is all that data from a cell line that was transfected -- that was transfected with an I2S gene and an FGE gene?
>
> **A:** Yes.
>
> [. . .]
>
> **Q:** Well, I think I asked you earlier, this cell line 2D, we know that you testified that cell line is a cell line in which I2S and FGE were transfected into it, right?
>
> **A:** Yes.
>
> [. . .]
>
> **Q:** You said that the data for the cell lines in your '556 patent is from a cell line 2D?
>
> **A:** Yes.

Nichols Dep. 55:4-13;71:6-10;75:21-23.

These admissions are significant because Exhibit 2115 does not describe <u>any</u> vector containing the FGE gene. Moreover, Nichols admitted at his deposition that plasmid pXI2S6 does not have a gene encoding FGE, and that nowhere in Exhibit 2115 is any FGE gene, or any FGE-containing vector, described. Nichols Dep. 118:11-25;122:17-123:6. Thus, Exhibit 2115 <u>cannot</u> provide evidence of Shire's

I2S and FGE-containing "2D" cell line that was purportedly the genesis of the I2S compositions claimed in the '556 patent.[5]

Shire attempts to shore up these glaring deficiencies by pasting into Nichols' declaration what is referred to as "Figure 1," a figure which purports to show the amino acid sequence of I2S. Nichols Decl. ¶¶12-13. Nichols admitted at his deposition, however, that he has no idea where this figure came from. Nichols Dep. 135:17-21. He further admitted that Figure 1, as reproduced in his declaration, does not appear in any supporting exhibits. *Id*. 138:13-140:16. At best, Figure 1 is simply a demonstrative, untethered to any of Shire's data. *See* Nichols Dep. 137:14-19 (counsel for Shire admitting that Figure 1 is a demonstrative). The same is true of Exhibit 2111, also referenced by Nichols at ¶13 of his declaration, which is labeled in Shire's response as a "DEMONSTRATIVE EXHIBIT." *See* POR at 73,98. Shire lays no foundation for this document, nor for the underlying data from which it could plausibly be derived.

[5] Tellingly, Nichols admitted at his deposition that he had nothing to do with the design of the 2D cell line. Nichols Dep. 55:4-56:11;116:3-15. That was instead the work of Ferenc Boldog, ultimately resulting in U.S. Patent No. 9,150,841. *See* Ex.1025; *see also* '556 patent, col. 30:26-36 (referencing the provisional application of same).

b. Paragraph 11 of the Yang Declaration (Ex.2017)

Paragraph 11 of the Yang Declaration does nothing to cure Shire's lack of proof that it actually possessed SEQ ID NO:1 as claimed. Yang merely reiterates statements made at ¶¶11-13 of the Nichols declaration, provides even less firsthand testimony regarding any supporting documentation, and ultimately relies exclusively on Shire's admitted demonstrative, Exhibit 2111, as alleged "proof" of the SEQ ID NO:1 amino acid sequence. If anything, the Yang Declaration supports the disconnect between the I2S produced in cell line "2D" (as described in the '556 patent) and the I2S-containing plasmid described in Exhibit 2115, which cannot be related to cell line "2D" (because it does not describe both I2S and FGE constructs).

c. Shire Exhibit 2115

As discussed above, Exhibit 2115 is critically deficient on two fronts. First, it nowhere supplies evidence of the amino acid sequence of the r-I2S actually obtained by Shire/TKT. [redacted] Was it was transfected into cells, and if so, which ones? Was the transfection successful, and if so, under what conditions? Once transfected, was the protein successfully overexpressed, and under what conditions? Webb Decl. ¶¶34-36. A "predicted" amino acid sequence

is meaningless if one has no understanding of what was actually done with the plasmid. Webb Decl. ¶¶22,35.

Second, Exhibit 2115 is completely untethered from the "2D" cell line expressing both the I2S and FGE genes as disclosed in the '556 patent. Webb Decl. ¶¶36,38. Equally bizarre is the fact that Nichols stated in his declaration that Exhibit 2115 is a report from the year 2004, and yet Nichols testified at his deposition that his alleged invention was not "done and locked" until April 2011. *Compare* Nichols Decl. ¶11 n.3 *with* Nichols Dep. 157:18-20. If Exhibit 2115 is "proof" of Shire's '556 invention, what happened in the intervening seven years?[6] Shire "should not expect the Board to search the record and piece together what

[6] In addition to the substantive problems with Exhibit 2115, it is unsigned and quite evidently incomplete. T

may support [Patent Owner]'s arguments." *Nichia Corporation v. Emcore Corporation*, IPR2012-00005, Paper 68 at 63 (PTAB Feb. 11, 2014).

d. Shire Exhibit 2111

As discussed above, Exhibit 2111 is merely a demonstrative exhibit. *See* POR at 73, 98. Standing alone, it has no evidentiary value, and cannot be used to support Shire's case for antedation.

e. The consequences of Shire's lack of evidence for the alleged date of reduction to practice

Shire's evidentiary failings reveal a simple truth: Shire did not reduce to practice the I2S amino acid sequence claimed in the '556 patent prior to June 15, 2012. If Shire had possessed this evidence, it undoubtedly would have produced it. After all, obtaining the amino acid sequence of a recombinantly produced protein is not a difficult exercise. Webb Decl. ¶21. Companies sequence proteins, or have them sent to third parties for sequencing, all the time. *Id.* The exact amino acid sequence of a recombinantly produced protein may be determined by a variety of techniques that all were well-known by 2010-2011. *Id.* Yet Shire provides no evidence that it conducted any of these techniques on its allegedly antedating I2S preparations.

Nor can the amino acid sequence of a recombinantly produced protein simply be "assumed" based on the DNA sequence of a vector, standing alone. Webb Decl. ¶22. Even if the vector is transfected into a host cell, without direct

sequencing of the protein itself there is no way to know if the DNA sequence was properly integrated into the cellular DNA and/or whether errors might have occurred during DNA transcription, mRNA translation, or at other points in the process by which the recombinant protein is produced. *Id.* Shire's own expert witness, Dr. Whitley, admitted this during his deposition:

> **Q:** Have you done any transfection experiments with plasmids?
>
> **A:** Yes.
>
> **Q:** And is that DNA necessarily incorporated into the chromosome?
>
> **A:** It might be integrated into the chromosome or it might not be integrated into the chromosome.
>
> ***
>
> **Q:** So you put the DNA into the cell. Let's assume translation takes place.
>
> **A:** Transfection or translation?
>
> **Q:** We transfect the cell, which ultimately results in translation.
>
> **A:** Okay.
>
> **Q:** The translation results in a polypeptide?
>
> **A:** Yes.
>
> **Q:** We don't know if that polypeptide is -- has the correct amino acid sequence as predicted by the DNA sequence unless we actually sequence that resulting polypeptide. Right?
>
> **A:** Yes.

Whitley Dep. 31:4-11;32:23-33:13.

Thus, without amino acid sequencing there would have been no way to confirm that the claimed I2S protein had been successfully obtained by transfection and translation of the pXI2S6 plasmid (even assuming that plasmid had been put into a host cell, a step which is completely missing from any of Shire's proffered exhibits). Webb Decl. ¶22. There would have been no way to rule out rearrangements during integration or errors in transcription, translation, or post-translational modification. *Id.* Notably, the '556 patent contemplates I2S protein variants. *See* '556 patent, col. 11:23-34 ("[T]he I2S protein may be a splice isoform and/or variant of SEQ ID NO:1, resulting from transcription at an alternative start site within the 5′ UTR of the I2S gene."). The '556 patent also warns that the obtained "recombinant I2S protein may be a homologue or an analogue of mature human I2S protein," including "a modified mature human I2S protein containing one or more amino acid substitutions, deletions, and/or insertions as compared to a wild-type or naturally-occurring I2S protein (e.g., SEQ ID NO:1)." *Id*. The '556 patent further notes that all of these variants of I2S could be produced "while retaining substantial I2S protein activity." *Id*. In other words, the mere fact that a protein obtained by Shire had a high FGly conversion ratio, or high enzymatic activity, cannot provide corroborative evidence that Shire actually possessed the specific amino acid SEQ ID NO:1 required by the challenged claims. Webb Decl. ¶¶27-29.

2. Shire failed to demonstrate that it possessed I2S having high FGly conversion as required by the challenged claims.

Shire provides various pieces of evidence of "peptide mapping" data that it obtained for its I2S preparations in order to show the percentage of cysteine to formylglycine conversion. *See* POR at 73,75,82; *see also* Nichols Dep. 151:19-152:3. This evidence, even if accurate, is irrelevant where Shire has no proof of the claimed amino acid sequence. *See* Webb Decl. ¶44.

3. Shire failed to demonstrate that it possessed I2S having low HCP impurities as required by the challenged claims.

Shire also provides various pieces of data regarding the HCP content of some of its I2S preparations. *See* POR at 61,70. Once again, this evidence, even if accurate, is irrelevant in light of the fact that Shire provides no proof of the amino acid sequence of the I2S protein for which it was allegedly measuring HCP. *See* Webb Decl. ¶44. Nor does Shire provide proof of the manner in which the pXI2S6 plasmid was transfected, details of the host cells into which it was transfected, or details of the way in which those host cells were grown and the target protein expressed. *Id*. ¶¶34-36.

II. SHIRE'S HCP CLAIMS ARE OBVIOUS.

The challenged claims are directed to I2S compositions having less than 150 (claims 1-3), 100 (claim 16) and 80 (claim 17) ng/mg HCP. *See* '556 patent, col. 49:20-35;51:1-5. None of these levels are new or non-obvious for a protein like I2S.

A. The '556 Patent and the Challenged Claims

It is important to put the challenged HCP claims in the context of the '556 patent as a whole, including its specification and file history. If one does this, it quickly becomes clear that r-I2S enzyme is not difficult to separate from HCPs, and that low levels of HCP for r-I2S can be achieved by using routine column chromatography steps.

Consider the breadth of the challenged claims as written. Claims 1-3 and 16-17 are all composition claims. They are agnostic as to the cells from which the r-I2S should be prepared, the medium in which those cells should be cultured, or the number or type of purification steps that should be used in order to achieve the claimed HCP limitations. The '556 patent allegedly enables r-I2S prepared from virtually any mammalian cell type. '556 patent, col. 13:45-14:26. It also allegedly enables r-I2S prepared from cells raised under virtually any cell culture conditions. *Id*. col. 16:1-43. And it allegedly enables r-I2S prepared from virtually any set of chromatography columns, under virtually any conditions, so long as they include "one or more of anion-exchange chromatography, cation-exchange chromatography, mixed-mode chromatography, and hydrophobic interaction chromatography." *Id*. col. 16:47-50. Moreover, the chromatography columns can be used in any order, and as few as 2 and as many as 5 columns can be used to achieve the claimed HCP levels. *Id*. col. 16:50-55. Shire's own expert (Dr. Zhou)

and the inventor of the '556 patent (Mr. Nichols) conceded this. Zhou Dep. 131:3-9;131:10-18;126:21-127:19; Nichols Dep. 11:6-9. Zhou went even further, stating that a 2-,3-,4-,5-,6-, or 7-column process could be used to obtain the claimed compositions of the '556 patent. Zhou Dep. 122:18-125:15;113:16-114:11. Viewing the challenged claims in light of these allegedly enabling disclosures, the notion that I2S would have been "notoriously difficult" to purify, *see* POR at 1, is simply untenable. *See* Declaration of Ruben Carbonell, Ph.D. (Ex.1051)("Carbonell") ¶¶40-42; *see also Purdue Pharma L.P. v. Epic Pharma, LLC*, 811 F.3d 1345, 1353 (Fed. Cir. 2016) (giving heightened scrutiny to, and finding obvious, claims to an "end product" having low impurities, when a "particular method for creating that product" is not claimed or specified).

Both Nichols and Zhou were unable to identify a single chromatography column used to purify I2S in the '556 patent, or a single condition for that chromatography column, that a POSITA would have considered to be out of the ordinary. They admitted that those columns – Capto Q, ceramic hydroxyapatite, SP Sepharose, and Phenyl Sepharose – were "commonly used," "commercially available" columns for protein purification. *See*, *e.g.*, Zhou Dep. 24:14-16;25:11-

19;29:6-16;30:13-23.[7] And they admitted that no conditions are described in the '556 patent that would suggest a difficult chromatographic purification. *Id.* at 69:9-25. If anything, the purification of the "I2S-AF" (I2S-"Animal Free") described in the '556 patent was easier than that for the prior art Elaprase® I2S product, because it was achieved with two fewer columns. *See* '556 patent, col. 1:61-2:1 (comparing the "[a]pproved existing process" for purifying r-I2S using 6 columns, with the "surprising discovery" that the same can be achieved with 4 columns); *see also id*. col. 2:11-13 ("[T]he present invention provides an effective, cheaper, and faster process for purifying recombinant I2S protein."); Nichols Dep. 35:12-36:11.

The '556 patent also discloses initial HCP loads – amounts of HCP from harvested cell culture before any chromatographic purification has taken place – that are remarkably low. Carbonell ¶¶23,51. Table 12 of Example 3 shows an initial HCP level of 46,292 ng/mg. '556 patent, col. 35:24-38; *see also* Zhou Dep. 74:2-6;118:16-20. A POSITA would have understood that the starting material used in Example 1 of the '556 patent was derived from the same cell culture as in Example 3. *See* '556 patent, col. 33:50-52 (in Example 3, "[t]he I2S-AF material

[7] The only column listed in the '556 patent that Zhou had not heard of was "Capto Q". Zhou Dep. 24:17-19. Carbonell confirmed, however, that Capto Q is a commonly use ion exchange column. Carbonell ¶45 n.3.

was produced from cell line 2D expressing I2S and formylglycine generating enzyme (FGE) as described in Example 1"); Carbonell ¶51. These low initial HCP loads are not entirely surprising given that the I2S described in the '556 patent is a secreted protein, and given that animal-free ("AF") cell culture medium was used. *Id.*; *see also* Nichols Dep. 35:12-36:11("admitting that "you wouldn't need a protein G column in order to purify something [animal serum] that's not there"); *id*. 36:5-11 (admitting that the 6th column did not remove HCPs but was instead just for buffer exchange). It was known to persons skilled in the art that initial HCP loads for recombinant proteins produced from mammalian cells could routinely be in the hundreds of thousands or millions of ng/mg, and yet even these initially high amounts could routinely be reduced to less than 100 ng/mg. Carbonell ¶¶23,51; *see also* Shire Ex.2037, at 1423 ("Typically, starting samples from the cell culture may have HCP levels ranging from several hundred thousand to several million ng/mg, and final products may have HCP levels ranging from <1 to 100 ng/mg (showing many logs of clearance)."). Thus, the disclosure in the '556 patent of a very low initial HCP load suggests an <u>easier</u> purification, not a harder one.

Finally, nothing in the '556 patent or file history talks about why removal of HCPs from I2S was thought to be particularly difficult, or why low HCP claims for that protein would have been remotely inventive. For example, removal of HCPs

to a particular level is not described as an object of the invention, nor are any such problems described as having existed with I2S preparations in the prior art.

The declaration filed by Mr. Nichols during the prosecution of the '556 patent is instructive. *See* Ex.1008. The declaration was submitted in order to overcome §103 rejections by the Examiner, and yet it never once mentions HCP removal as something that was difficult or hard to achieve in Shire's allegedly novel I2S preparations (let alone anything about the relationship between high formylglycine conversion levels and low HCP levels).[8] This glaring absence was confirmed by Nichols at his deposition. *See* Nichols Dep. 128:23-129:6. HCP-related statements provided by Nichols for purposes of this IPR are thus revealed for what they are: convenient hindsight reconstruction, completely unsupported by the specification and prosecution history of the '556 patent.

B. The Known Properties of the I2S Protein

Shire's non-obviousness expert repeatedly testified that even though he had no personal experience with I2S it was nevertheless "very close to [his] heart" and thus he had "monitored this literature and the development of this drug for years."

[8] This Nichols declaration was also filed in Korea in response to a rejection by the Korean Patent Office. Nichols Dep. 125:22-130:4 (referencing Office Action and response filed associated with Korean Patent Application No: 10-2012-0099511 which also claims priority to U.S. Provisional 61/666,733) (Exs.1026-1028).

Zhou Dep. 16:16-18; *see also id*. 151:18-153:4 ("I personally studied the literature" on I2S). Zhou also stressed the importance of having scientific data to support any expert's statements. *Id*. 233:16-18. Yet, despite all of his work monitoring the I2S literature, and the professed importance of backing up statements with scientific data, Zhou could not point to a single literature reference that would have suggested to a POSITA that I2S was a "difficult and challenging protein to purify." *Compare* Zhou Decl. ¶39 (making that assertion) *with* Zhou Dep. 180:9-15 (admitting that "[t]here's no literature on that").

The exact opposite is actually true. The I2S protein was first purified from natural sources in 1990, and had been thoroughly studied, described, and produced recombinantly as reported in dozens of publications since that time. Sands Decl. ¶¶12-15; Carbonell Decl. ¶33. Zhou admitted that by at least 2010, I2S was known by persons of skill in the art to have at least the following distinguishing characteristics:

- a size of 60-90 kilodaltons [Zhou Dep. 55:21-24];
- 2 disulfide bonds [*id*. 57:4-6];
- conversion of Cys59 to FGly for activity [*id*. 52:2-9];
- 8 N-linked glycosylation sites [*id*. 57:22-25];
- a high proportion of mannose-type sugars including, in particular, mannose-6-phosphate ("M6P") [*id*. 58:9-14;58:25-59:5]

- a high sialic acid content [*id*. 78:2-14]; and
- a particular isoelectric point [*id*. 79:12-14];

See also Jin ¶¶[0014]-[0018]. Recombinant I2S was also known to be secreted into the cell culture medium, thus making it, as a general rule, easier to purify. *Id*. ¶[0015]; *see also* Zhou Dep. 56:17-20; Carbonell ¶26; Ex.2026, at 29 (noting that secreted proteins are "normally much simpler to purify").

A POSITA would have understood these distinguishing properties to make I2S easier to purify from HCPs, not harder. Carbonell ¶¶28-39. For example, taking advantage of the glycosylation and sialylation patterns would have been an easy way to separate I2S from vast amounts of HCPs. *Id*. ¶¶37-38. Taking advantage of the M6P "handle" would have been similarly easy. *Id*. ¶35-36. Despite professing to be "an expert on enzymes," Zhou was unable to name a single enzyme or protein class, other than sulfatases, containing the M6P modification. Zhou Dep. 143:7-11. It is not surprising that scientists were able to use this knowledge to design a highly successful purification scheme for I2S. *See*, *e.g.*, Mihara, Ex.1016, ¶¶13,36 ([T]he present invention makes it possible to selectively purify hrI2S having mannose 6-phosphate residue in its oligosaccharide chain. … [t]he more mannose 6-phosphate residues hrI2S has in its oligosaccharide chain, the more selectively it is bound to fluoroapatite."); *see also* Carbonell ¶36.

As both Sands and Carbonell point out, a POSITA would know that there is a rational design that can be applied to protein purification, even if it is not an exact science. Sands Decl. #1 (Ex.1010) ¶28; Carbonell ¶¶24,32. A protein is only "difficult" to purify from HCPs if it departs from these design expectations, or has some "sensitivity" that makes purification difficult. Dr. Carbonell describes some of these potential difficulties. Carbonell ¶¶26-27. None apply to or were ever reported in the prior art for I2S. *Id*. There is no suggestion, for example, of a group of proteins that "frequently co-purif[ies]" with I2S, or of any instability issues with I2S. *Id*. (*cf*. POR at 7-8). Shire repeatedly points to the alleged "complexity" of the I2S protein, but this is simply a re-hash of properties that make I2S unique vis-à-vis other proteins, and thus easier to separate from them. Zhou Dep. 137:9-22;140:2-24.

C. Shire's unsupported "cell culture" theory regarding I2S, FGE, and HCPs must be rejected.

Shire emphasizes the purported difficulty in obtaining an I2S enzyme that has simultaneously a high percent conversion of Cys59 to FGly and a low HCP content. *See*, *e.g.*, POR at 5; Nichols Decl. ¶6. Yet, Shire is unable to identify a single disclosure in the '556 patent or prior art to support this theory. When Nichols filed his declaration during prosecution of the '556 patent, in which he discussed what was difficult and unexpected about his I2S purification, this alleged

problem was never identified. Nichols Dep. 128:23-129:6. It is an entirely *post-hoc*, IPR-inspired argument, and must be rejected.

If it were actually true that obtaining I2S with high %FGly conversion and low HCPs was "amongst the most challenging endeavors of [Mr. Nichols'] career," Nichols Decl. ¶9, then either Shire or Nichols would have provided some support for that statement. Without any direct proof, Shire is thus left to argue generalities, such as:

> Producing therapeutically active I2S in recombinant protein production systems poses unique challenges. To activate over-expressed recombinant I2S protein in host cells, the amount of FGE in the host cells also must be increased. The easiest way to increase the FGE level in host cells is to increase the expression of HCPs in host cells globally, which is ***typically*** accomplished by adjusting cell culture conditions. On the other hand, increasing the expression of HCPs in order to obtain increased FGE expression presents additional challenges for subsequent purification efforts, as a result of the higher HCP loads that must be removed.

Zhou Decl. ¶76 (emphasis added); *see also* Nichols Decl. ¶7.

There are three major problems with Shire's theory. First, it is unsupported by any citation to the '556 patent or other scientific literature. *See Mahurkar,* 79 F.3d at 1577 (rejecting uncorroborated inventor testimony); 37 C.F.R.§ 42.65(a) (same for unsupported expert testimony). Shire has presented no objective

evidence that (1) the only way to obtain high %FGly conversion in I2S is to overexpress HCPs globally (and not just FGE specifically), (2) increasing expression of a second protein (here, FGE) in addition to the target protein (here, I2S) would have made the HCP purification process more difficult, or (3) I2S would be a difficult protein to purify, with or without a high %FGly content. *See* Zhou Dep. 168:12-17 ("There's no citation here."); Nichols Dep. 60:23-61:6;65:10-24 (unable to explain where in the '556 patent there was any disclosure of globally increased HCPs due to overexpression of FGE); *see also* Carbonell ¶¶49-50.

Second, neither Nichols nor Zhou is an expert in cell culture. Nichols was in the purification process department at Shire, not the cell culture process department. Nichols Dep. 116:3-10; *see also id*. 169:24 ("I'm not a cell line expert."). He does not even recall who was in Shire's cell culture department at the time. *Id*. Zhou, for his part, admitted that he is "not an expert in cell culture area," and thus cannot tell any "meaningful difference" between various cell culture processes when presented with them. Zhou Dep. 132:17-18;133:2-6;133:24-134:7;135:5-7. Zhou did not even know the size or properties of the FGE enzyme, or whether it would be easy or hard to separate from I2S. *Id*. 159:23-160:4;162:3-9.

Third, Shire's theory is undermined by the '556 patent itself. If Shire's theory were accurate, one would expect a high initial HCP load in the '556 patent, not a low one. And yet exactly the opposite is disclosed. *See* Carbonell ¶51.

D. The Jin Reference

Jin undoubtedly discloses an extremely pure preparation of r-I2S. Jin's I2S is described as "safe and efficacious thanks to its purity of 99.99% or higher." Jin ¶[0053]. Other portions of Jin even describe it as "100% pure." *Id.* ¶[0157]. None of the purification procedures described in Jin would have been viewed by a POSITA as abnormal or difficult to carry out. Jin states, for example, that "[o]nce secreted into the culture medium, IDS may be used as a drug after going through typical isolation and purification processes." *Id.* ¶[0015] (emphasis added).[9] In fact, while the four chromatography steps disclosed in Jin differ somewhat from those in the '556 patent, they all still make use of "common," "commercially available" columns. *See* Zhou Dep. 68:14-69:8; Carbonell ¶¶44-47.

Zhou further criticizes Jin for only using SDS-PAGE and Size Exclusion Chromatography (SEC) to measure the purity of I2S. And yet these are precisely

[9] Zhou claimed at his deposition that a POSITA would not understand what the word "typical" means. Zhou Dep. 70:16-21. That statement is not credible given that Zhou used the word "typical" or "typically" at least a dozen times in his declaration. *See*, *e.g.*, Ex.2012 (Zhou) ¶¶21-22,25-26,46,76,etc.

the tools that were used to measure purity in the '556 patent, which states that "the level of host cell protein (HCP) may be measured by ELISA or SDS-PAGE." '556 patent, col. 22:12-19 (emphasis added). "In some embodiments," the patent goes on to say, "the purified recombinant I2S protein contains less than 150 ng HCP/mg I2S protein (e.g., less than 140, 130, 120, 110, 100, 90, 80, 70, 60, 50, 40, 30, 20, 10 ng HCP/mg I2S protein)." *Id*. Thus, the '556 patent effectively concedes that SDS-PAGE can be used to measure HCP levels down to as low as 10 ppm. Shire's own experts do not dispute that SDS-PAGE, used with a staining technique such as silver staining, is extremely sensitive to HCP levels. *See* Zhou Dep. 215:18-22 (agreeing that SDS-PAGE can be used to detect all the way down to 0.1 nanograms, or 100 picograms, of HCP).

The same disconnect exists for the testimony of Shire's "clinical" expert, Dr. Whitley. Whitley criticizes Green Cross for confusing "efficacy" (as shown by a clinical trial) with "purity" (as shown by HCP level). But it is clear that these two factors are interrelated. *See* Ex.2037, at 1416 ("Residual HCPs have the potential to affect product quality, safety, ***and*** efficacy.")(emphasis added)). Whitley also criticizes Jin for failing to disclose additional information about the patient population on which the various clinical studies were performed. Yet these are the same disclosures made in Green Cross's approved Hunterase® label in Korea, and indeed Shire's own Elaprase® label does not include the very information that

Whitley says is so important. Whitley Dep. 60:9-12 ("The [Elaprase®] label does not include a great deal of information about a clinical trial which may be relevant."); *see also* Ex. 1031 (Hunterase Label).[10]

It is telling that when asked whether "there is a single figure or a single disclosure in Jin that you can point to that shows evidence of a protein impurity in the I2S of Jin," Zhou answered "No." Zhou Dep. 237:25-238:5.

E. Reasonable Expectation of Success

The industry-wide motivation to reduce HCPs to levels as low as possible, preferably below 100 ppm, is confirmed by the '556 patent itself. '556 patent, col. 32:1-2 (acknowledging that for HCPs there is a "<100 ppm specification required in many markets, including the U.S."). This is corroborated by several other references, cited both by Green Cross and Shire. *See*

[10] Whitley does not define a POSITA anywhere in his declaration. Instead, his perspective is that of "one of the foremost experts in lysosomal storage enzymes in the world," at least with respect to "clinical applications," including "study design." Whitley Dep. 34:5-18. Thus, what Whitley is able to read into the clinical disclosures of Jin is not remotely representative of what a POSITA would understand. A POSITA would see the clinical and scientific disclosures in Jin, understand the 100 ppm HCP requirement for approved protein products, and conclude that Jin's I2S had a purity of 100 ppm or less. *See* Ex. 1010 (Sands) ¶45.

Ex.1011(p.40);Ex.1014(p.54);Ex.1015(p.447);Ex.2030(p.43);Ex.2040(p.1);Ex.2042(p.35);Ex.2048;(p.1732);Ex.2055(p.1128). There is no dispute, even from Shire's declarants, that a POSITA would have wanted to get HCPs to the lowest level possible in any final protein product. *See*, *e.g.*, Nichols Dep. 46:21-23 (the task of a protein purification group is "to make a product as pure as possible").

Other than Humira®, approved by the FDA almost 20 years ago, Shire's experts were unable to identify a single FDA-approved protein with an HCP content greater than 100 ppm. Zhou Dep. 95:3-9;96:5-7. And even when Humira® was approved in 1998, more than a dozen years before the priority date in this case, HCP levels for Humira® were still very low (approximately 150 ppm). Zhou Dep. 96:8-9. The current, proposed biosimilar versions of Humira® appear to have had no difficulty obtaining much lower levels of HCP, typically on the order of 50 ppm. Zhou Dep. 96:21-25. This is consistent with the notion, discussed above, that the reduction of HCPs is an entirely routine process, unless there is evidence that a protein presents particular difficulties. Carbonell ¶¶20-27. Shire provides no evidence for why I2S fits into this "difficult" category, or why I2S could not be purified via routine optimizations of column chromatography conditions. *Id. See also In re Applied Materials,* 692 F.3d 1284, 1297-98 (Fed. Cir. 2012) (holding that absent a new and unexpected result, routine optimization is nothing more than the exercise of ordinary skill in the art).

Shire's three counterarguments do not withstand scrutiny. First, Shire contends that every protein is different, and thus every HCP profile is different, and thus HCP levels cannot be predicted in advance. This makes little sense in view of the clear teachings that HCP levels <100 ppm are readily obtainable – if not required by regulatory authorities – for most protein drugs. *See* '556 patent, col. 32:1-2. The trick with HCPs is not removing them to levels below those claimed in the '556 patent; the trick is understanding the effect, if any, that those very low levels of HCP might have on a patient, because each individual HCP is difficult to characterize. *See* Carbonell ¶25.

Second, Shire contends that I2S is different because it belongs to a select group of "enzyme replacement therapy" drugs which constitute only about 2% of all FDA-approved proteins. POR at 20; Zhou Decl. ¶168. This is a non sequitur. If anything, a POSITA would be motivated to make sure a protein for enzyme replacement therapy was more pure than one used for other clinical purposes. Moreover, the low number of enzyme replacement drugs is related to the fact that they are all used to treat relatively uncommon, "orphan" diseases. *See* Whitley Decl. ¶22 (and cited FDA labels). It is not related to any inherent difficulty in separating them from HCPs.

Third, Shire identifies numerous "countervailing considerations" that it contends would have undercut a POSITA's motivation to reduce HCPs in a r-I2S

preparation. All of these countervailing considerations, however, are legally irrelevant to the obviousness inquiry because they bear no relation to the challenged claims. There is nothing in the '556 patent, let alone the challenged claims, that says anything about the risk of "inactivating the target protein," or maintaining "stability," or "reducing product yield to unacceptably low levels," or "accidentally introducing undesirable chemical impurities and degradation products," or the "cost" of the purification process, or "speed to market." POR at 12-13,15,16; *see also* Zhou Dep. 201:22-202:2 (Zhou unable to point to any literature discussing I2S's "sensitivity to catalytic site inactivation"); *id*. at 101:2-6 (admitting claims say nothing about "yield"); *id*. at 101:21-25 (admitting claims say nothing about "cost"); *id*. at 102:24-103:4 (admitting claims say nothing about "speed to market"). Nor do the challenged claims say anything about "unnecessary additional purification" steps. POR at 13,15,16,18. The challenged claims place no limit on the number of purification steps: there could be 2, or 200, as Shire drafted them.

Removal of HCPs from therapeutic proteins with known properties, using orthogonal chromatography techniques, was and is standard practice in the industry. Carbonell ¶¶20-24. Thus, a POSITA working with r-I2S, whose properties were both known and in many respects unique relative to other proteins, would have had a reasonable expectation of success in achieving the HCP levels

claimed in the '556 patent. *Id*. ¶¶33-39;44-47. Obviousness does not require absolute predictability. *See In re Rinehart*, 531 F.2d 1048 (CCPA 1976).

F. Green Cross obtained recombinant I2S enzyme with HCP levels of less than 100 ppm.

Green Cross did not have difficulty achieving low HCP levels for its r-I2S.

[redacted]

Contrary to Shire's assertions, Green Cross did purify r-I2S with simultaneously high %Fgly conversion and low HCP levels. It was a routine and expected result.

CONCLUSION

Shire's response and supporting declarations are a house of cards. Shire's proffered "evidence" fails to show reduction to practice of Claims 1-3 and 16-17 of the '556 patent prior to any date, let alone the filing date of Jin. Moreover, in view of the disclosures in Jin, other supporting references, and general knowledge of

persons skilled in the art at the time, the challenged claims of the '556 patent are invalid as obvious under 35 U.S.C. §103 and should be cancelled.

Dated: November 9, 2016

Respectfully submitted,

/*John Bauer* /

John Bauer (Reg. No. 32,554)
Thomas Wintner (*pro hac vice*)
Peter J. Cuomo (Reg. No. 58,481)
Kongsik Kim (Reg. No. 63,867)
MINTZ, LEVIN, COHN, FERRIS, GLOVSKY AND POPEO, P.C.
One Financial Center
Boston, MA 02111
Phone: (617) 542-6000
Fax: (617) 542-2241

Counsel for Petitioner
Green Cross Corporation

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Pursuant to 37 C.F.R. §42.24(d), Petitioner hereby certifies, in reliance on the word count of the word-processing system (Microsoft Office Word 2010) used to prepare this **PETITIONER'S REPLY BRIEF**, that the number of words in this paper is **7,694**. This word count excludes the Tables of Contents, Tables of Authorities, Certificate of Word Count, Certificate of Service, and Updated List of Exhibits.

Dated: November 9, 2016

/*John Bauer* /
John Bauer (Reg. No. 32,554)

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The undersigned hereby certifies that a copy of the foregoing **PETITIONER'S REPLY BRIEF** was served pursuant to 37 C.F.R. § 42.6 electronically in its entirety on Patent Owner (by consent of the parties) to Attorneys for Patent Owner at:

Fangli Chen, Ph.D.	FChenPTABMatters@proskauer.com
Eric J. Marandett	emarandett@choate.com
Daniel Klein	dklein@proskauer.com

Date: November 9, 2016

/*John Bauer* /
John Bauer (Reg. No. 32,554)
Lead Counsel for Petitioner