UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIALS 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.: Unassigned

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 9,051,556 UNDER 35 U.S.C. §§ 311-319 AND 37 C.F.R. §§ 42.1-80, 42.100 *et seq*.

LIST OF EXHIBITS

Exhibit 1001	U.S. Patent No. 9,051,556
Exhibit 1002	U.S. Patent Application Publication No. 2014/0242059
Exhibit 1003	June 20, 2013 Preliminary Amendment
Exhibit 1004	May 23, 2014 Restriction Requirement
Exhibit 1005	July 14, 2014 Response to Restriction Requirement
Exhibit 1006	August 21, 2014 Office Action
Exhibit 1007	February 23, 2015 Amendment and Response
Exhibit 1008	Nichols Declaration
Exhibit 1009	March 25, 2015 Notice of Allowance
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
Exhibit 1012	U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, *Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use*, Docket No. 94D-0259, February 28, 1997
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
Exhibit 1016	International Patent Publication Number WO 2012/101671
Exhibit 1017	United States Patent Application Publication No. 2012/0189605
Exhibit 1018	U.S. Patent Application Publication No. 2013/0195888
Exhibit 1019	Alfredo Uribe, *Selective Screening for Lysosomal Storage Diseases with Dried Blood Spots Collected on Filter Paper in 4,700 High-Risk Colombian Subjects*, JIMD REPORTS, Apr. 23, 2013

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I. INTRODUCTION

U.S. Patent No. 9,051,556 ("the '556 patent") describes its purported invention as providing "improved methods for purifying I2S protein produced recombinantly for enzyme replacement therapy." Ex. 1001 (the '556 Patent), at Abstract. The improved methods are based on the allegedly "surprising discovery that 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." *Id.* More specifically, the invention involves "purifying recombinant I2S protein from an impure preparation using a process based on one or more of anion-exchange chromatography, cation-exchange chromatography, mixed-mode chromatography, and hydrophobic interaction chromatography." *Id.* at 2:16-21.

The claims of the '556 patent are directed to the purified recombinant I2S that may be produced by the purportedly inventive method. More specifically, the '556 patent includes claims directed to a composition comprising recombinant I2S with a specific amino acid sequence and a specific percentage conversion of cysteine to Cα-formylglycine at the Cys59 position of the amino acid sequence. Certain of the claims require that the I2S composition have additional characteristics, including less than a stated amount of host cell protein ("HCP") contamination (claims 1-3 and 16-17), more than a stated amount of bis-

phosphorylated oligosaccharides (claims 4-5), more than a stated specific activity level as measured using a "sulfate release" assay (claims 6-8), more than a stated specific activity level as measured using a "4-MUF conversion" assay (claims 9-13), more than a stated sialic acid content (claim 14), and a glycan mapping profile having seven or fewer peaks selected from seven peak groups (claim 15).

Prior art U.S. Patent Application Publication No. 2014/0242059 ("Jin") discloses I2S sharing the same amino acid sequence and the same or substantially the same percentage conversion of cysteine to Cα-formylglycine at the Cys59 position as is claimed in the '556 patent. Ex. 1002 (Jin) at ¶ [0013] and pp. 11-12.[1] Moreover, the purification method used to obtain I2S in Jin overlaps significantly with that used in the '556 patent. Both methods use anion-exchange chromatography, cation-exchange chromatography, and hydrophobic chromatography to purify I2S. *Compare* Ex. 1001 at 2:16-21 *with* Ex. 1002 at ¶ [0005]. The methods differ principally in that Jin additionally uses affinity

[1] Jin abbreviates iduronate-2-sulfatase as "IDS". The '556 patent abbreviates iduronate-2-sulfatase as "I2S". Both IDS and I2S refer to the same enzyme. This Petition abbreviates iduronate-2-sulfatase as "I2S" unless it is quoting directly from Jin.

chromatography while the ‘556 patent additionally uses mixed-mode chromatography. *Compare* Ex. 1001 at 2:16-21 *with* Ex. 1002 at ¶ [0005].

Given the identity of amino acid sequence and the similarity in purification methods, a person of ordinary skill in the art (“POSITA”) would have expected the I2S of Jin and of the ‘556 patent to share similar characteristics. It is thus not surprising that Jin reports that the specific activity level of purified I2S protein (measured using a 4-MUF conversion assay) overlaps with the specific activity levels claimed in the ‘556 patent, anticipating claims 9-13. Accordingly, this petition challenges these claims as invalid over Jin.

This petition also challenges the claims requiring that host cell protein contamination be below a specific threshold (claims 1-3 and 16-17). While Jin includes several disclosures evidencing that its I2S has very low levels of host cell protein content – including SDS Page test results, size exclusion chromatography test results, and the fact that Jin’s I2S was safely injected into human patients – Jin does not quantify the amount of host cell protein remaining in its preparation after purification. At the time of the alleged invention of the ‘556 patent, however, there were well-known and generally-accepted guidelines advising that host cell protein in medicinal treatments should be kept well below the thresholds recited in the claims. To the extent the quantity of host cell protein remaining in Jin’s I2S exceeded the generally accepted guidelines for medicinal protein preparations, it

would have been obvious for a POSITA to remove that host cell protein from the preparation of Jin so that it could be used safely for its intended purpose – i.e., as a treatment for people with Hunter syndrome. Doing so would have required nothing more than the application of routine purification methods.

While it is possible (indeed likely) that the I2S protein of Jin shares other of the characteristics recited in the claims of the '556 patent, the Jin reference is silent as to these characteristics. Accordingly, the current petition does not challenge claims requiring a bis-phosphorylation content (claims 4-5), a specific activity level measured using a sulfate release assay (claims 6-8), a sialic acid content (claim 14), or a glycan mapping profile (claim 15).

II. STATEMENT OF MATERIAL FACTS

1. 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).

2. Jin discloses recombinant purified I2S having the amino acid identified in the '556 patent as SEQ ID NO:1.

3. Jin discloses recombinant purified I2S having "80% or higher" conversion of cysteine to formylglycine at Cys59 of the amino acid sequence identified as SEQ ID NO:1 in the '556 patent.

4. Jin discloses that its purified I2S has a specific activity level of 19-55 U/mg when measured using a 4-MUF conversion assay with 4-methylumbelliferyl-L-iduronide-2-sulfate Na_2 (MU-IdoA-2S) as a substrate.

5. If the specific activity of I2S disclosed in Jin were measured using a 4-MUF conversion assay with the generic sulfatase substrate 4-methylumbelliferyl sulfate, it would necessarily have the same or higher specific activity as is reported in Jin.

6. It has long been known in the art that host cell protein impurities are undesirable in proteins intended as medical treatments.

7. Well accepted guidelines suggest that host cell protein impurities should be less than 100 ppm in approved drug products containing recombinant proteins.

8. Jin discloses that its I2S preparation was injected into humans in a clinical trial.

9. Jin discloses I2S that was measured using size exclusion chromatography. The I2S sample that was measured was disclosed to be 100% pure. No other proteins, including host cell proteins, were reported to be present at detectable levels.

10. Jin discloses I2S that was measured using SDS Page. The sample tested showed a single band of protein corresponding to I2S. No other proteins, including host cell proteins, were present at detectable levels.

11. If the I2S of Jin were determined to have host cell protein content above the level suggested by well-accepted guidelines, a POSITA would have been motivated to remove as much host cell protein as possible from the I2S preparation so that it could be used for medical treatments.

12. It was known in the art prior to the alleged invention of the '556 patent that the host cell protein of a recombinant enzyme preparation could be reduced using column chromatography, including anion-exchange chromatography, cation-exchange chromatography, hydrophobic chromatography, and affinity chromatography.

13. It was also known in the art prior to the alleged invention of the '556 patent that host cell proteins could be further removed from a protein preparation by ultrafiltration and diafiltration.

III. NOTICE OF LEAD AND BACKUP COUNSEL

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Pursuant to 37 C.F.R. § 42.10(b), a Power of Attorney accompanies this Petition.

IV. NOTICE OF EACH REAL PARTY-IN-INTEREST

The real parties-in-interest for this petition to institute *inter partes* review are Green Cross Corporation and Green Cross Holdings Corporation.

V. NOTICE OF RELATED MATTERS

Pursuant to 37 C.F.R. § 42.8(b)(2), Petitioner is not aware of any judicial proceedings involving U.S. Patent No. 9,051,556.

VI. NOTICE OF SERVICE INFORMATION FOR PETITIONER

Please address all correspondence to Lead Counsel at the address shown above. Petitioner also consents to electronic service by email at: dcotta@mintz.com; kkim@mintz.com; sashraf@mintz.com; twintner@mintz.com; pjcuomo@mintz.com.

VII. SERVICE ON THE PATENT OWNER

Pursuant to 37 C.F.R. § 105(a), service of this Petition has been made simultaneously with this filing to the current correspondence address for the '556 patent.

VIII. GROUNDS FOR STANDING

Petitioner hereby certifies that the patent for which review is sought is available for *inter partes* review and that Petitioner is not barred or estopped from requesting an *inter partes* review challenging the patent claims on the grounds identified in this Petition.

IX. THRESHOLD REQUIREMENT FOR *INTER PARTES* REVIEW

A petition for *inter partes* review must demonstrate "a reasonable likelihood that the Petitioner would prevail with respect to at least one of the claims challenged in the petition." 35 U.S.C. § 314(a). This Petition meets that threshold. All of the elements of claims 1-3, 9-13, and 16-17 of U.S. Patent No. 9,051,556 are taught and/or disclosed in the prior art as explained below, and reasons to combine

the prior art teachings and/or disclosures, where necessary, are established for each proposed ground under 35 U.S.C. §§ 102 and 103(a).

X. SUMMARY OF THE '556 PATENT

A. Overview of the '556 Patent

The '556 patent resulted from U.S. Patent Application No. 13/829,706 ("the '706 Application") filed on March 14, 2013, claiming priority from U.S. Provisional Patent Application No. 61/666,733 filed on June 29, 2012. The '556 patent includes 17 claims directed to compositions comprising purified recombinant I2S. The challenged claims can be divided into two groups: claims requiring that HCP content be less than a specified threshold (claims 1-3 and 16-17), and claims requiring that the I2S composition have a particular specific activity (claims 9-13). The challenged claims read as follows:

> 1. A composition comprising purified recombinant iduronate-2-sulfatase (I2S) having the amino acid sequence of SEQ ID NO:1, wherein the purified recombinant I2S comprises at least 70% conversion of the cysteine residue corresponding to Cys59 of SEQ ID NO:1 to Cα-formylglycine (FGly), wherein the purified recombinant I2S contains less than 150 ng/mg Host Cell Protein (HCP).
>
> 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-formylglycine (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-formylglycine (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 specific activity of at least 20 U/mg as determined by an in vitro 4-MUF-SO_4 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.

B. Summary of the Prosecution History

The '706 Application, as filed, included 67 claims. In a June 20, 2013 Preliminary Amendment, the patentee cancelled certain claims, and amended others. *See* Ex. 1003 at 4. On May 23, 2014, the examiner issued a restriction requirement identifying three groups of claims: claims drawn to iduronate-2-sulfatase, claims drawn to a method of purifying iduronate-2-sulfatase, and claims drawn to a method of treating Hunter syndrome by administering iduronate-2-sulfatase. *See* Ex. 1004 at 2. In response to this restriction requirement, on July 14, 2014, patentee elected the composition claims. *See* Ex. 1005 at 6. The patentee also filed an amended claim set with the response, by amending claim 1, canceling claims 2-67, and adding new claims 68 – 90. *See* Ex. 1005 at 2 – 5.

After patentee's election, the examiner rejected claims 1, 68-70, and 72-90 as not enabled under 35 U.S.C. § 112 (pre-AIA) and all of the pending claims (claims 1 and 68-90) as not sufficiently described under 35 U.S.C. § 112 (pre-AIA) and as obvious over U.S. Patent No. 8,128,925 in view of WO2011/044542. *See*

Ex. 1006 at 2 – 6. With respect to obviousness, the examiner found that the claimed limitations regarding bis-phosphorylated oligosaccharide content, sialic acid content, glycan mapping profile, and enzyme activity level were the product of routine optimization. *Id.* at 6 – 7.

In a February 23, 2015 Amendment and Response, the patentee amended the claims to address the examiner's written description and enablement rejections and to add limitations regarding host cell protein content (current claim 1) and glycan mapping profile (current claim 15). *See* Ex. 1007 at 2, 4. Patentee also submitted the declaration of the inventor, David Nichols, to counter the examiner's routine optimization arguments. *See* Ex. 1008. The Nichols Declaration focused on the alleged difficulty of obtaining I2S with high sialic acid content and high bis-phosphorylated oligosaccharide content, and the allegedly unexpected properties of compounds having such high sialic acid and bis-phosphorylated oligosaccharide content. *Id.* at 2 – 3, 6. The Nichols Declaration did not address whether the claimed host cell protein content and/or specific activity could be obtained through routine optimization. *Id.*

The examiner issued a notice of allowance on March 25, 2015, *see* Ex. 1009, and the '556 patent issued on June 9, 2015.

XI. STATEMENT OF PRECISE RELIEF REQUESTED

Petitioner respectfully requests that claims 1-3, 9-13, and 16-17 of the '556 patent (Ex. 1001) be canceled based on the following grounds of unpatentability, explained in greater detail (including relevant claim constructions) below.

Ground 1	Claims 9-13 are anticipated by or obvious over Jin.
Ground 2	Claims 1-3 and 16-17 are obvious over Jin and in view of guidelines advising that HCP content be minimized (as reflected in, e.g., 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).

XII. BACKGROUND REGARDING THE STATE OF THE ART

A. Hunter Syndrome

Lysosomal storage diseases or disorders ("LSDs") result from a deficiency of certain lysosomal enzymes that are critical for the degradation of cellular waste. A deficiency of these enzymes causes an accumulation of material that has not been properly degraded which results in the swelling and malfunction of lysosomes, and ultimately cellular and tissue damage. *See* Ex. 1010 (Declaration of Dr. Mark Sands) (hereinafter "Sands") at ¶ 14.

In some cases, lysosomal storage diseases can be treated by identifying the enzyme that is correlated with the disease, and delivering recombinant enzyme to affected tissues of patients. This is called enzyme replacement therapy. *Id.* at ¶ 15.

Hunter syndrome is a lysosomal storage disorder that results from a deficiency in the enzyme iduronate-2-sulfatase ("I2S"). *See* Ex. 1001, at 1:23-26. A deficiency in the activity and/or expression of I2S in humans leads to an accumulation of glycosaaminoglycans ("GAGs") in a variety of cell types. *Id.* at 1:28-32. This leads to cellular engorgement, organomegaly, tissue destruction, and organ system dysfunction. *Id.* People with Hunter syndrome may suffer from developmental delays and nervous system problems. *Id.* at 1:33-36. As the '556 patent explains:

> While the non-neuronal symptoms of Hunter syndrome are generally absent at birth, over time the progressive accumulation of GAG in the cells of the body can have a dramatic impact on the peripheral tissues of the body. GAG accumulation in the peripheral tissue leads to a distinctive coarseness in the facial features of a patient and is responsible for the prominent forehead, flattened bridge and enlarged tongue, the defining hallmarks of a Hunter patient. Similarly, the accumulation of GAG can adversely affect the organ systems of the body. Manifesting initially as a thickening of the wall of the heart, lungs and airways, and abnormal enlargement of the liver, spleen and kidneys, these profound changes can ultimately lead to widespread

> catastrophic organ failure. As a result, Hunter syndrome is always severe, progressive, and life-limiting.

Id. at 1:37-51; *see also* Sands at ¶ 18.

B. Iduronate-2-Sulfatase ("I2S")

Sulfatases are a unique class of lysosomal enzymes that cleave esters from a number of substrates, including, for example, steroids, carbohydrates, proteoglycans and glycolipids. *See* Sands at ¶ 16. Iduronate 2-sulfatase ("I2S") is a sulfatase that cleaves sulfate moieties from GAGs. Ex. 1001 at 1:26-28. I2S is one of a family of at least 9 sulfatases that hydrolyze sulfate esters in human cells. *See* Sands at ¶ 17.

C. Enzyme Replacement Therapy

Enzyme replacement therapy is a therapeutic strategy for Hunter syndrome that can correct the enzymatic deficiency by administering exogenous I2S enzyme to a patient. *See* Sands at ¶ 19. After administration, the replacement enzyme is taken up by cells and transported to the lysosome. There, it begins to eliminate accumulated material (i.e., GAGs). *Id.*

D. Host Cell Protein ("HCP")

Recombinant proteins are typically produced by introducing DNA encoding the protein – i.e. the target protein – into a host cell and then causing the host cell to express the target protein. While the intent is to obtain a preparation including only the target protein, it is possible that impurities may be introduced. For

example, the preparation may include non-target protein derived from the host cell as well as other unwanted material (including, *e.g.*, partially processed cell medium, cell lysates and nucleic acids). *See* Sands at ¶ 21; *see also* Ex. 1001 at 8:16-20; 16:63-17:20; and 22:12-15.

It has long been known in the art – certainly before 2012 – that host cell protein impurities are undesirable in proteins intended as medicinal treatments. This is because any such impurities may provoke an undesired immune response in the patient, and thus affect both the safety and efficacy of a drug product. *See* Sands at ¶ 22; *see also*, Ex. 1011 at 40 ("Wolter") ("The downstream process must remove all contaminants, including host cell material such as DNA and cellular protein. … Such contaminants are obviously undesirable because of possible consequences if they are injected into patients along with it. They could potentially cause allergic reactions (proteins) or even transfection of cells (DNA) resulting in tumors."). Some host cell proteins can affect drug product stability and efficacy if not adequately removed and/or inactivated. *See* Sands at ¶ 22.

Given these concerns, the U.S. Food and Drug Administration ("FDA") and the International Conference of Harmonisation ("ICH") have issued guidance for biopharmaceutical products, advising that analytical methods demonstrate minimization of contaminant levels. *See* Ex. 1001 at 31:66-32:2 (noting that the claimed I2S meets "the <100 ppm specification required in many markets

including the US"); Ex. 1012 at 21 (Points to Consider in the Manufacture and Testing of Monoclonal Antibody Production for Human Use) ("Whenever possible, contaminants introduced by the recovery and purification process [identified to include host cell protein] should be below detectable levels using a highly sensitive analytical method."); Ex. 1013 at 9 (Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products Q6B) ("Process-related impurities (section 2.1.4 in the drug substance) may include … host cell proteins … These impurities should be minimized by use of appropriate well-controlled manufacturing processes.").

Multiple references quantify this guidance and advise that host cell protein impurities should be below 100 ppm in approved biological drug products. *See, e.g.*, Ex. 1001 at 31:66-32:2 (noting that the claimed I2S meets "the <100 ppm specification required in many markets including the US"); *see also*, Sands at ¶ 22; Ex. 1011 at 40 ("Host-cell proteins in the drug substance should be 'below detectable levels using a highly sensitive analytical method.' As a rule, that amount should not exceed a level of about 100 ppm. But no exact limit is set for proteins; therefore, the specification for proteins must be determined case by case."); Ex. 1014 at 54 ("Champion") ("Most biotechnology products reviewed by the FDA contain ELISA-based host cell protein levels of 1-100 ppm."); and Ex. 1015 at 447 ("Wang") ("Many biotechnology companies are using this range [1-

100 ppm] as a guideline for process development and for setting HCP specifications.").

E. Enzyme Purification

The efficacy of enzyme replacement therapy for lysosomal storage diseases using I2S is largely driven by the quality of the enzyme, including high activity, M-6-P modification, cellular uptake, and purity. Sands at ¶ 23; *See also*, *e.g.*, Ex. 1017 at ¶ [0007] ("Koppaka"). Generally speaking, these enzymes are purified using a process called column chromatography. *See* Sands at ¶ 23. Chromatography is a method of separating and isolating the parts of a sample mixture to remove the unwanted substances. *See id.* The system consists of a stationary phase and a mobile phase. The mobile phase consists of the sample diluted in a liquid. *Id.* The mobile phase is passed through the stationary phase, and then interactions between the two result in chromatographic separation. *Id.*

A number of different resins can be used as part of the stationary phase. *See* Sands at ¶ 24. Depending on the material used, the stationary phase can separate samples based on the interaction between charge groups (e.g., ion exchange chromatography), binding sites (e.g., affinity chromatography), hydrophobicity (e.g., hydrophobic interactions), and size (e.g., size exclusion chromatography). *Id.* As the enzyme undergoes multiple chromatography columns, it becomes more pure and free of unwanted substances. *Id.*

One of the main goals of column chromatography is to remove host cell proteins. *See* Sands at ¶ 25. It is nearly impossible for two different proteins to have the exact same size, charge, and affinity characteristics. *Id.* To remove host cell protein, one identifies a chromatography resin that will bind the protein of interest, but not the majority of other host cell proteins. *Id.* Once the contaminating host cell proteins flow through the column and are discarded, the protein of interest can be eluted with a specific buffer condition. *Id.*

Column chromatography can also be used in the reverse manner to separate host cell proteins from the protein of interest. *See* Sands at ¶ 26. In other words, conditions can be established whereby the protein of interest does not bind the column, but the majority of contaminating host cell proteins do bind the column resin. *Id.* In this scenario, the target protein flows through the column and is collected, whereas the contaminating host cell proteins are retained on the column, resulting in a significant purification of the protein of interest. *Id.*

There are a number of different types of column chromatography. The '556 patent discusses four types, including anion-exchange, cation-exchange, hydrophobic interaction, and mixed mode. Anion-exchange chromatography relies on charge-charge interactions between a negatively charged compound and a positively charged resin. *See* Ex. 1001 at 17:25-27. Cation-exchange chromatography relies on charge-charge interactions between a positively charged

compound and a negatively charged resin. *See id.* at 18:45-48. Hydrophobic interaction chromatography relies on hydrophobic properties to separate proteins from one another. *See id.* at 21:24-26. Finally, mixed-mode chromatography, also known as "pseudo-affinity" chromatography relies on multiple forms of interaction between the stationary phase and the mobile phase in order to separate and purify proteins. *See id.* at 20:4-6

The use of anion exchange, cation exchange, hydrophobic, and affinity columns takes advantage of the differential interaction of the protein of interest and host cell proteins, and provides comprehensive options for protein purification. *See* Sands at ¶ 27. Almost all host cell proteins will have some unique aspect that can be exploited by this array of columns such that they can be efficiently separated from the protein of interest. *See id.*

Although protein purification relies heavily on empirical experimentation, the basic approaches are routine. *See* Sands at ¶ 28. Therefore, with a relatively small amount of information about a given protein (e.g., a known glycosylation pattern or a specific enzyme assay), a rational and systematic purification scheme can be envisaged by a POSITA. *See id.* For example, a POSITA would have readily understood that a heavily glycosylated (i.e., sugar-containing) protein like I2S would bind an anion exchange column due to the negative charge on the sugar

molecules. It is thus not surprising that the '556 patent uses anion exchange chromatography as the first column chromatography step. *Id.*

Diafiltration and ultrafiltration were other techniques known in the art to remove host cell protein impurities at the time of the '556 patent. *See* Sands at ¶ 29. For example, the '556 patent references these techniques as "final concentration and filtration" steps, *see* Ex. 1001 at 31:22 and Fig. 1 (second to last box), and Jin references "ultrafiltration" and "nanofiltration." *See* Ex. 1002 at ¶¶ [0126] and [0128]. Diafiltration refers to a process in which the sample is diluted with a solvent and then re-filtered to reduce the concentration of soluble impurities. Ultrafiltration is a technique in which the sample is subjected to a semi-permeable membrane that retains macromolecules, but allows solvent and solute molecules to pass through. It is used to increase the concentration of protein in water. *See* Sands at ¶ 29; *see also*, *e.g.*, Ex. 1018 at ¶ [0038].

F. Specific Activity

Specific 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. The specific activity is a standard measure for enzymes and is measured in international units (U) per milligram (U/mg). *See* Sands at ¶ 30. When measuring the specific activity of a protein preparation, as the preparation becomes more pure, more of the total protein mass is made up of the

enzyme of interest, and thus the specific activity will continuously increase. *Id*. at ¶ 31.

One way the specific activity of a sulfatase like I2S can be measured is through use of an assay that employs a synthetic sulfate ester substrate, which, when cleaved by I2S, releases a fluorescent compound. The most generic of these synthetic substrates is known as 4-methylumbelliferyl-sulfate (4-MUF-SO_4). *See id*. at ¶ 32. When cleaved by a sulfatase, 4-MUF-SO_4 yields fluorescent 4-methylumbelliferone (4-MUF), the presence of which can be detected using a calibrated fluorimeter. *Id*; *see also* Ex. 1001 at Col. 23:20-25. The specific activity of the enzyme is then calculated by dividing the enzyme activity by the protein concentration. *See* Ex. 1001 at Col. 23:20-58.

In addition to using a generic substrate 4-methylumbelliferyl sulfate substrate that is capable of detecting any sulfatase enzyme, a 4-MUF assay may be designed that is capable of detecting only specific sulfatase enzymes. *See* Sands at ¶¶ 32-35; *see also* Ex. 1019 ("Uribe") at 107 and Table 1.

The specific 4-MUF assay for I2S also relies on the release of fluorescent 4-MUF (like the generic assay), but the starting material is 4-methylumbelliferyl-L-iduronide-2-sulfate (4-MU-IDU-sulfate). *See* Sands ¶ 34; *see also* Jin at ¶ [0159] (abbreviating the same as MU-IdoA-2S). Because 4-MU-IDU-sulfate contains the same sugar moiety (iduronide) recognized by I2S *in vivo*, it is highly specific for

I2S as opposed to other sulfatases (which recognize different sugar moieties). The use of the highly specific substrate 4-MU-IDU-sulfate ensures that the only enzyme that is being detected is the enzyme of interest, in this case I2S. *See* Sands at ¶ 34.

For 100% pure I2S preparations, there should be no difference between specific activity as measured by the enzyme-specific and enzyme-generic 4-MUF tests. However, if there are any contaminating sulfatases in the enzyme preparation being tested, the use of a generic substrate would result in an artificially high specific activity. *See* Sands at ¶ 36. The use of an enzyme-specific 4-MUF assay would produce a lower specific activity value, but that value would be a true reflection of I2S activity. For example, if one milligram of a preparation of recombinant enzyme contained 90 units of I2S and 10 units of arylsulfatase A, the specific activity using a generic substrate would be 100 U/mg. In contrast, if the same preparation were assayed with the 4-methylumbelliferyl-L-iduronide-2-sulfate substrate, the specific activity would be 90 U/mg, a lower but more accurate number. *See id*.

XIII. PERSON OF ORDINARY SKILL IN THE ART

A person of ordinary skill in the art ("POSITA") at the time of the alleged inventions claimed by the '556 Patent, would have a minimum of an M.D., Ph.D., or combined M.D./Ph.D. degree. *See* Sands at ¶ 10. This person would also have

experience with lysosomal storage diseases, either as a matter of basic research, as a clinician directly treating patients, or as a researcher using pre-clinical mammalian models of disease. In addition to the experience with patients or mammalian models of disease, this person would have first-hand experience with modern molecular biology and tissue culture techniques, as well as recombinant protein production and protein purification techniques. Finally, a POSITA would have at least some experience with in vitro and in vivo methods of characterizing recombinant enzymes implicated in lysosomal storage diseases. *See Id*.

XIV. CONSTRUCTION OF THE CLAIMS

A claim in *inter partes* review is given the "broadest reasonable construction in light of the specification of the patent in which it appears." *See* 37 C.F.R. § 42.100(b); *see also Office Patent Trial Practice Guide*, 77 Fed. Reg. 48756, 48766 (Aug. 14, 2012). Under this standard, no terms or phrases require specific construction for purpose of this Petition. All claim terms should be given their plain and ordinary meaning. 7 C.F.R. § 42.100(b). Because the legal standard for claim construction differs from the one applied in U.S. District Court litigation, *see In re Am. Acad. of Sci. Tech Ctr.*, 367 F.3d 1359, 1364, 1369 (Fed. Cir. 2004), Petitioner reserves the right to advocate a different construction in any subsequent litigation for any term found in the '556 patent.

XV. THE PRIOR ART JIN REFERENCE

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). Jin discloses recombinant purified I2S having the amino acid sequence identified in the '556 Patent as SEQ ID NO:1, *see* Jin at pp. 11-12, and having more than 80% conversion of cysteine to formylglycine at Cys59 of the amino acid sequence identified as SEQ ID NO:1 in the '556 Patent. *See id*. at ¶¶ [0020] and [0143].

Jin discloses that its purified I2S has a specific activity level of 19-55 U/mg when measured using a 4-methylumbelliferyl-L-iduronide-2-sulfate Na_2 (MU-IdoA-2S) to 4-MUF conversion assay. *See id*. at ¶ [0159]. For the reasons discussed *supra* pp. 22-23, 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. *See* Sands at ¶ 40.[2]

Jin does not quantify the amount of host cell protein remaining after its I2S has undergone purification. However, as described *supra* pp. 19-20, the

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[2] Jin provides specific activity measurements in nmol/min/µg. As Dr. Sands explains, when these units are converted to U/mg as recited in the claims of the '556 patent, 19-55 µmol/min/mg as disclosed in Jin translates to 19-55 U/mg. *See* Sands at ¶ 41.

purification steps described in Jin – which include anion exchange, cation exchange, hydrophobic and affinity chromatography – were known in the art to efficiently remove host cell protein. *See* Sands at ¶ 42. In fact, the purification scheme described by Jin is very similar to that described in the '556 patent. The only significant difference is that the '556 patent uses a hydroxyapatite column as the affinity chromatography step, whereas Jin uses a Blue Sepharose affinity column. *Id.* Even if those two columns rely on different characteristics of I2S, each still adds another level of purification vis-à-vis host cell proteins. *Id.*

Several aspects of Jin indicate that the I2S obtained was of high purity. First, Jin shows that there is only a single band of the correct molecular weight detected by SDS polyacrylamide gel electrophoresis. *See* Jin at Fig. 11. This assay is highly sensitive to contaminating protein and the presence of only a band corresponding I2S indicates that negligable host cell protein was detected. *See* Sands at ¶ 43. Jin also shows that there is a single discrete peak of protein from the final I2S preparation that elutes off a sepharose sizing column. *See* Jin at Fig. 13. Contaminating host cell proteins would appear as additional protein peaks on the chromatogram, and yet no such peaks exist. *See* Sands at ¶ 43.

Second, as discussed above, the specific activity of the I2S purified by the method of Jin is 19-55 U/mg. This is nearly identical to the specific activity of I2S claimed in the '556 patent (20-60 U/mg). Therefore, the amount of I2S per

milligram of total protein (which includes any contaminating host cell protein) is the same as that claimed in the '556 patent. In fact, the use of an enzyme-specific substrate by Jin opens the possibility that Jin's method results in a preparation that is even more pure than the '556 patent. *See* Sands at ¶ 44.

Finally, treatment of patients with the enzyme preparation of I2S purified using the method described in Jin resulted in a reduction in urinary GAG levels and an improvement in the 6-minute-walk test in patients affected with Hunter syndrome, as compared to patients treated with the FDA-approved drug, Elaprase®. *See* Jin at ¶¶ [168]-[173]. 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. *See* Sands at ¶ 45.

While a POSITA would expect the I2S of Jin to be substantially free of host cell protein, Jin does not quantify the exact amount. To the extent the quantity of host cell protein present exceeded the generally accepted thresholds for medicinal protein compositions, however, it would have been obvious for a POSITA to have removed host cell protein using standard and routine methods to the point where it could be used safely for its intended use as a medical treatment for people with Hunter syndrome. *See* Sands at ¶ 46.

The purification method described by Jin (anion exchange chromatography, hydrophobic chromatography, cation exchange chromatography, affinity

chromatography) provides 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. *See* Sands at ¶ 47; *see also Cubist Pharms., Inc. v. Hospira, Inc.*, Appeal Nos. 2015-1197, -1204, -1259, 2015 U.S. App. LEXIS19662, at *41-2 (Fed. Cir. Nov. 12, 2015) (crediting the district court's findings, including that ion exchange chromatography was "one of the most common purification techniques" known in the art).

The availability of sensitive and specific enzyme assays for I2S greatly facilitates the purification process since the desired protein can be analyzed in the flow through and in specific eluted fractions. *See e.g.,* Ex. 1014 (discussing assays for quantifying HCP content). This allows for easy and rapid determinations of how much target protein is present relative to contaminating host cell proteins at each step in the purification process. With this information, and with a general knowledge of the properties of I2S, a POSITA would have been able to devise a rational purification scheme with a reasonable expectation of removing the vast majority of host cell proteins. *See* Sands at ¶ 48; *see also* Ex. 1014 at 56 ("immunoassays can aid in development and optimization of purification processes.").

XVI. CLAIM-BY-CLAIM EXPLANATION OF GROUNDS FOR UNPATENTABILITY

A. Ground 1: Claims 9-13 are anticipated by and/or obvious in view of Jin.

1. Limitation: amino acid sequence of SEQ ID NO:1

Each of claims 9-13 of the '556 patent requires a "composition comprising purified recombinant iduronate-2-sulfatase (I2S) having the amino acid sequence of SEQ ID NO:1." Jin anticipates this limitation by disclosing the amino acid sequence of SEQ ID NO:1. *See* Jin at pp. 11-12 (SEQ ID NO:1).

2. Limitation: cysteine residue conversion

Each of claims 9-13 of the '556 patent requires "70% conversion of the cysteine residue corresponding to Cys59 of SEQ ID NO:1 to Cα-formylglycine (FGly)." Jin anticipates this limitation by disclosing that "the IDS used in the composition … according to the present invention has an amino acid sequence of SEQ ID NO:1 with the conversion of cysteine at position 59 to formylglycine (FGly) at a molar ratio of 65% or higher, preferably at a molar ratio of 75% or higher, and more preferably at a molar ratio of 80% or higher…." Jin at ¶ [0020]. Jin further discloses an example of I2S with a percent formylglycine conversion of 80 +/- 15%. *Id*. at ¶ [0143].

3. Limitation: specific activity as measured by an in vitro 4-MUF-SO_4 to 4-MUF conversion assay

Each of claims 9-13 includes a limitation requiring that "the recombinant 12S protein has a specific activity" of a specified amount as determined by an "in vitro 4-MUF-SO_4 to 4-MUF conversion assay." The required specific activity for each of these claims 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).

The I2S of Jin is disclosed to have a specific activity of 19-55 nmol/min/μg, Jin at [0159], which corresponds to 19-55 U/mg. *See* Sands at ¶ 41. As discussed above, the specific activity level reported in Jin is measured using 4-methylumbelliferyl-L-iduronide-2-sulfate Na_2 as a substrate. *See* Jin at ¶ [0159]. This is a substrate that is specific to I2S. In contrast to an enzyme-generic 4-MUF SO_4 to 4-MUF assay, where any sulfatase can release 4-MUF, only I2S can release 4-MUF from the 4-methylumbelliferyl-L-iduronide-2-sulfate Na_2 substrate used in Jin. *See* Sands at ¶¶ 32-36. Thus, the I2S of Jin must necessarily have a specific activity level of 19-55 U/mg or higher when measured using an enzyme-generic 4-MUF SO_4 to 4-MUF assay. *Id*. at ¶ 40.

The disclosure of a range in the prior art is "anticipatory if it describes the claimed range with sufficient specificity such that a reasonable fact finder could conclude that there is no reasonable difference in how the invention operates over

the ranges." *Ineos USA LLC v. Berry Plastics Corp.*, 783 F.3d. 856, 869 (citing *Atofina v. Great Lakes Chemical Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006); *ClearValue, Inc. v. Pearl River Polymers, Inc.*, 668 F.3d 1340, 1345 (Fed. Cir. 2012). The Federal Circuit has found no reasonable difference in how an invention operates over claimed and prior art ranges where ***the patentee*** failed to provide evidence showing that the claimed range is critical to the operability of the invention. *Ineos*, 783 F.3d at 865 (affirming summary judgment of invalidity based on overlapping range "because [the patentee] failed to raise a genuine question of fact about whether the range claimed is critical to the operability of the invention."); *ClearValue, Inc.*, 668 F.3d at 1345 (reversing jury finding of no anticipation of overlapping ranges where "there [was] no allegation of criticality or evidence demonstrating any difference across the range").

Here, Jin discloses I2S having specific activity ranging from 19-55 U/mg, while the '556 patent claims I2S having specific activity of at least 20, at least 30, at least 40, at least 50, and at least 60 U/mg. The range recited in Jin is both relatively narrow and similar to the range of activity disclosed for embodiments of the '556 patent. *See, e.g.*, Ex. 1001 at 23:30-39 ("In some embodiments, a desired enzymatic activity, as measured by in vitro 4-MUF assay, of the produced recombinant I2S protein ranges from about 0-50 U/mg (e.g., about 0-40 U/mg, about 0-30 U/mg, about 0-20 U/mg, about 0-10 U/mg, about 2-50 U/mg, about 2-

40 U/mg, about 2-30 U/mg, about 2-20 U/mg, about 2-10 U/mg, about 4-50 U/mg, about 4-40 U/mg, about 4-30 U/mg, about 4-20 U/mg, about 4-10 U/mg, about 6-50 U/mg, about 6-40 U/mg, about 6-30 U/mg, about 6-20 U/mg, about 6-10 U/mg.")). As Dr. Sands explains, the range of specific activity disclosed for I2S is substantially identical to that disclosed for the embodiment of the '556 patent. *See* Sands at ¶¶ 41, 60-61.

Not only is the range of specific activity in the embodiments of the '556 patent substantially identical to that of Jin, but also the '556 patent does not ascribe any particular criticality to any of the specific activity levels recited in the specification or the claims. While the specification of the '556 patent identifies numerous ranges of specific activity, including ranges that are broader than that recited in Jin, it does not teach that any level of specific level of activity is necessary to practice the invention. *See, e.g.*, Ex. 1001 at 23:25-39 (providing ranges of specific activity levels, including 0-50 U/mg, but not identifying any criticality for any of these ranges). For this reason alone, the specific activity ranges of Jin anticipate the ranges in claims 9-13 of the '556 patent. *Ineos*, 783 F.3d at 865.

Moreover, to the extent the operation of the invention is considered to relate to the efficacy of I2S, nothing in the prior art or the '556 patent indicates that a protein preparation with a specific activity level of 60 U/mg would be efficacious

while one with an activity level of 20 U/mg would not be.[3] The closest the '556 patent comes to tying specific activity level to therapeutic efficacy is to state that the "amount of therapeutic agent (e.g. a recombinant lysosomal enzyme) administered to a patient in need thereof will depend upon the characteristics of the subject." *See* Ex. 1001, at 29:39-42. This statement does not suggest that any particular activity level is required for efficacy. Rather, it merely indicates that the

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[3] As discussed above, a prior art range that overlaps with a claimed range is anticipatory where there is no reasonable difference in how the invention operates over the two ranges. Here, however, it is not clear on what basis the "operation" of the invention is to be judged. The claims merely recite a "composition," without requiring that the composition have any particular use. The specification suggests that the "invention" lies in the ***method*** used to obtain the composition, not the composition (i.e., the enzyme preparation) obtained. *See,* Ex. 1001 at 2:11-13 ("Therefore, the present invention provides an effective, cheaper, and faster process for purifying recombinant I2S protein."); *see also generally, id.* at "Summary of the Invention." Moreover, while the '556 patent states that I2S obtained by the inventive method can be "adapted for administration to human beings," it provides no biological data by which one could judge the operation of the invention at specific activity levels. Indeed it provides no biological data at all.

amount of I2S required for efficacy in patients may change from patient to patient. Further, as Dr. Sands explains, "the therapeutic efficacy of a recombinant lysosomal enzyme like I2S is dependent not simply on it specific activity but also on other factors such as M-6-P modification and other factors." *See* Sands at ¶ 63. As a result, a preparation of I2S with a specific activity of 20 U/mg might turn out to be efficacious, while a preparation with an activity of 60 U/mg might not be. *Id.*

Given this, a POSITA would find no reasonable difference in how the I2S having the claimed activity levels operates as compared to the I2S of Jin. *See* Sands at ¶¶ 64-68. 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*., 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.

Jin also anticipates claim 13, which recites a specific activity of 60 U/mg. While the upper end of the range in Jin is disclosed to be 55 U/mg, this is within a 10-20% margin of error, *see* Sands at ¶¶ 60-61, rendering the claimed and prior art ranges virtually indistinguishable to a person of ordinary skill in the art. *Id; see*

also, id. at ¶ 41. Petitioner further notes that the highest specific activity disclosed in the '556 specification for the 4-MUF assay is 50 U/mg. *See* Ex. 1001 at 23:25-39. Thus, to the extent the 50 U/mg disclosure of the '556 patent supports a claim directed to 60 U/mg, there must not be any significant difference between the two.

In the event Jin is found not to anticipate these 4-MUF specific activity limitations, Jin would likely render them obvious. Overlap between a prior art range and a range recited in a patent creates a *prima facie* case of obviousness. *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003) ("[W]e and our predecessor court have consistently held that even a slight overlap in range establishes a *prima facie* case of obviousness."). Here, 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. Petitioner is not aware of any evidence that would rebut this *prima facie* case of obviousness.[4]

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[4] Notably, the purported unexpected results reported in the Nichols Declaration relate to sialic acid content and bis-phosphorylation, not to specific activity. *See* Ex. 1008, at ¶¶ 3, 5-6, 7, 11, 13-16 . Petitioner does not agree that the Nichols Declaration provides evidence of unexpected results. However, because the challenged claims in this petition do not include limitations related to sialic acid

Moreover, to the extent there is evidence that one of the claimed thresholds – at least 20, 30, 40, 50 and 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. This is nothing more than routine optimization of protein activity. *Id.* Accordingly, if Jin does not anticipate these limitations, it renders them obvious.

B. Ground 2: Claims 1-3 and 16-17 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).

1. Limitation: amino acid sequence of SEQ ID NO: 1

Claims 1-3 and 16-17 of the '556 patent require a "composition comprising purified recombinant iduronate-2-sulfatase (I2S) having the amino acid sequence of SEQ ID NO:1." Jin discloses this limitation by disclosing the amino acid sequence of SEQ ID NO:1. *See* Jin at pp. 11-12.

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content or bis-phosphorylation, there is no need to address the arguments set forth in the Nichols Declaration here.

2. Limitation: cysteine residue conversion

Claims 1-3 and 16-17 of the '556 patent also require a specified percentage "conversion of the cysteine residue corresponding to Cys59 of SEQ ID NO:1 to Cα-formylglycine (FGly)."

Claims 1 and 16-17 require at least 70% conversion of cysteine to formylglycine. Jin discloses this limitation by disclosing that "the IDS used in the composition … according to the present invention has an amino acid sequence of SEQ ID NO:1 with the conversion of cysteine at position 59 to formylglycine (FGly) at a molar ratio of 65% or higher, preferably at a molar ratio of 75% or higher, and more preferably at a molar ratio of 80% or higher…." *See* Jin at ¶ [0020]. Jin further discloses an example of I2S with a percent formyglycine conversion of 80 +/- 15%. *Id*. at ¶ [0143].

Claim 2 requires at least 75% conversion. Jin also discloses this limitation. *Id*. at ¶¶ [0020] and [0143].

Claim 3 requires at least 85% conversion. Jin's disclosure of I2S having "more preferably . . . 80% or higher conversion" and of I2S with a percent conversion of "80 +/- 15%" overlaps with the range of claim 3. As discussed *supra*, the disclosure of a range in the prior art is "anticipatory if it describes the claimed range with sufficient specificity such that a reasonable fact finder could conclude that there is no reasonable difference in how the invention operates over

the ranges." *Ineos*, 783 F.3d. at 869. As also discussed *supra*, the Federal Circuit has found no reasonable difference in how an invention operates over claimed and prior art ranges where ***the patentee*** failed to provide evidence showing that the claimed range is critical to the operability of the invention. *See, e.g., id.*

Here, the prior art and claimed ranges differ only slightly. While the '556 patent teaches the importance of a high content of Cα-formylglycine (*see* Ex. 1001 at 2:7-8 ("the present invention retains high percentage of Cα-formylglycine (FGly) (*e.g.*, higher than 70% and up to 100%), which is important for the activity of I2S enzyme")), there is no indication that the difference between 80% and 85% conversion is of particular significance. To the contrary, during prosecution of the '556 patent, patentee suggested that 70% was the threshold sufficient for high I2S potency. *See* Ex. 1007 at 13 (Response to Office Action filed on February 23, 2015 (stating that "high FGly conversion (e.g., >70%) is directly associated with high potency of I2S").

Moreover, as Dr. Sands explains, a POSITA would not have expected there to be any reasonable difference in how I2S works when Cα-formylglycine content is over 80% as compared to over 85%. *See* Sands at ¶¶ 73-75. Accordingly, Jin discloses the limitation of claim 3 requiring "at least 85%" cysteine to formylglycine conversion. *Cf. Ineos*, 783 F.3d. at 869 (citing *Atofina*, 441 F.3d at 999); *ClearValue*, 668 F.3d at 1345 .

To the extent Jin is found not to disclose the "at least 85%" limitation in claim 3, this limitation is obvious in view of the "80% or higher" or "80 +/- 15%" conversion range disclosed in Jin. As discussed above, an overlap between a prior art range and a range recited in a patent creates a *prima facie* case of obviousness. *In re Peterson*, 315 F.3d at 1329; *In re Geisler*, 116 F.3d 1465, 1469 (Fed. Cir. 1997) (overlap only at the end points). Petitioner is not aware of any objective indicia of non-obviousness or other evidence that would rebut this *prima facie* case of obviousness.

Moreover, if the difference between more than 80% and more than 85% cysteine to formylglycine conversion were found to be significant (for example, if it was known that I2S with 85% cysteine to formylglycine conversion was more efficacious or safer than I2S with 80% cysteine to formylglycine conversion), then it would have been obvious to purify I2S as described in Jin and select only the preparations with the highest level of formylglycine conversion. *See* Sands at ¶ 76. This is nothing more than routine optimization of protein activity. *Id.* Accordingly, if Jin does not anticipate claim 3 of the '556 patent, it renders claim 3 obvious.

3. Limitation: HCP content less than a specified amount

Claims 1-3 and 16-17 of the '556 patent also include limitations requiring that host cell protein ("HCP") content be less than a specified amount. Specifically,

these claims require that HCP content be less than 150 ng/mg (claims 1-3), less than 100 ng/mg (claim 16), and less than 80 ng/mg (claim 17).

Jin provides a method of purifying I2S that a person of ordinary skill in the art would expect to result in a preparation that is substantially free of HCP. *See* Sands at ¶ 46. While the Jin disclosure provides multiple indications that its enzyme preparation is highly pure, it does not quantify the exact amount of host cell protein remaining. There are, however, guidelines for host cell protein content in medicinal treatments. To the extent a POSITA were to have determined that the I2S of Jin exceeded those guidelines, it would have been obvious to reduce the host cell protein content so that it could be used for medical treatments. Methods for removing HCP were well-known in the art and, 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.

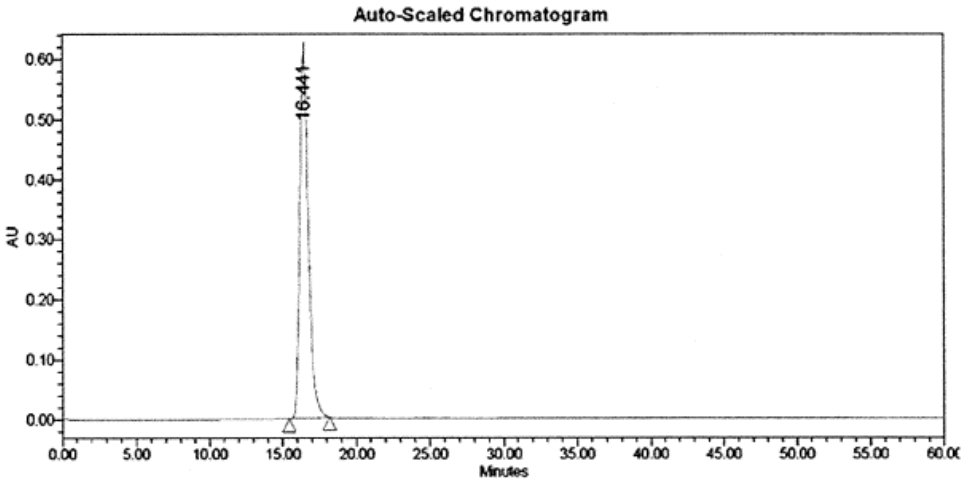
i. Jin discloses highly pure I2S.

Jin provides multiple indications that the I2S preparation disclosed is of very high purity. For example, after purifying I2S as described, Jin measured its purity using size exclusion chromatography ("SEC"). *See* Jin. at ¶¶ [0155]-[0157]. Jin explains how this process works:

> Size exclusion chromatography is a chromatographic method in which molecules in solution are separated by their relative molecular weight and shape. In size exclusion chromatography, proteins larger than the pore size of the column cannot penetrate the pore system and pass through the column at once. Subsequently, the analytes with smaller molecular weights or sizes elute later.

Id. at ¶ [0156]. After describing the general process, Jin describes the conditions under which its I2S sample was tested. Jin explains: "IDS, after being diluted to a concentration of 1.0 mg/mL in a formulation buffer, was loaded in a volume of 10 μL onto the column… [and] allowed to flow with mobile phase (20 mM sodium phosphate buffer, 200 mM NaCl, pH 7.0) at a flow rate of 0.5 mL/min for 60 min." *Id.* The sample that passed through the column was then measured using a UV/VIS detector, and it was determined that it "eluted with 100% purity." *Id.* at ¶ [0157]. This can be seen graphically in Figure 13 of Jin:

FIG. 13



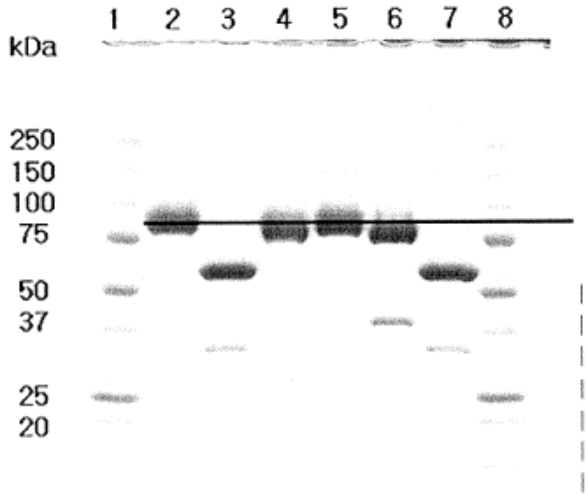
Peak Results

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

The chromatogram in Figure 13 of Jin shows a very narrow distribution of protein and consists of a single, sharp peak. Contaminating host cell proteins would appear as additional protein peaks on the chromatogram, and yet they are nowhere to be found. *See* Sands at ¶ 43. The 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. Furthermore, the percent area-under-the-curve of the peak was evaluated to be 100%, *see* Fig. 13, indicating that the peak (which represents I2S) contained all of the material detected.

The results of the SEC testing are consistent with other purity teachings of Jin. For example, Jin discloses that its I2S was tested using SDS-PAGE gel after treatment of I2S with various glycoside hydrolase enzymes. The results are provided in Figure 11, which is reproduced below:

FIG. 11



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

The band in lane 2 shows purified IDS with a molecular weight of at least 60-90 kDa. As is readily evident, there are no impurities at higher and/or lower molecular weights. The purity of Jin's IDS is thus further confirmed by the presence of this single, prominent band in the SDS-PAGE gel. *See* Sands at ¶ 43.

The absence of additional bands on the SDS-PAGE gel indicates that the sample does not contain impurities – including host cell proteins – at detectable levels.[5]

The high level of purity reflected in Jin's size exclusion chromatography and SDS-PAGE testing is further confirmed by the specific activity levels reported. The specific activity of the I2S purified by the method of Jin is 19-55 U/mg. Jin at ¶ [0159]. This is nearly identical to the specific activity claimed in the '556 patent (20-60 U/mg). Therefore, as Dr. Sands explains, the amount of I2S per milligram of total protein (which includes any contaminating host cell protein) is the same as that claimed in the '556 patent. *See* Sands at ¶ 44. In fact, as discussed above, the use of an enzyme-specific substrate by Jin opens the possibility that Jin's method results in an I2S preparation that is ***even more pure*** than that claimed in the '556 patent. *Id.*

Finally, the I2S disclosed in Jin was further disclosed to have been injected into human patients in clinical trials. This alone suggests that the I2S in Jin is 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

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[5] The SDS-PAGE gel in Figure 4 of Jin (which depicts glycosylated IDS in lane 1) also shows a single molecular weight band with no other impurities at high or low molecular weights.

rendered the protein composition unsafe. In this 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®. *See* Jin at ¶¶ [0167]-[0173]. As Dr. Sands explains, "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." *See* Sands at ¶ 45.[6]

ii. Motivation to lower HCP content to 1-100 ppm for therapeutic biologics.

The I2S of Jin is intended for use in treatment of patients with Hunter Syndrome. *See* Jin at ¶ ¶ [0012], [0013], [0018]-[0022]. "It was well known in the art that host cell protein impurities were undesirable because of their potential to provoke an immune response or otherwise interfere with the target enzyme." Sands at ¶ 78; *see also*, Ex. 1011 at 40. As Dr. Sands explains, "this alone would have provided motivation for a POSITA to reduce host cell protein to the lowest

[6] Jin also teaches that its I2S is "safer" than Elaprase®, *see* Jin at Abstract, suggesting that that the I2S of Jin has lower HCP contamination than a related, FDA-approved drug product.

level possible, or even remove it entirely." *See* Sands at ¶ 78.[7] Further motivation is provided by guidelines advising that host cell protein impurities should be in the range of 1-100 ppm. *See* Ex. 1001 at 31:66-32:2; Ex. 1012; Ex. 1013; Ex. 1014; Ex. 1015. Given this, it would have been obvious to purify the I2S of Jin to the point where host cell protein falls within these well-accepted guidelines. *See* Sands at ¶ 80.

iii. Removal of HCP during protein purification was routine and well-known

Having been motivated to remove any host cell proteins that would have rendered the I2S of Jin unsafe for injection into human patients, a POSITA could have removed such contaminants using routine methods. As Dr. Sands explains:

> Although protein purification relies heavily on empirical experimentation, the basic approaches are routine. Therefore, with a relatively small amount of information about a given protein (e.g., a known glycosylation pattern or a specific enzyme assay), a rational and systematic purification scheme can be envisaged by a POSITA. For example, a POSITA would readily understand that a heavily glycosylated (i.e., sugar-containing) protein like I2S would bind an

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[7] As discussed *infra* p. 48, the success of others in purifying their proteins suggests that the "lowest level possible" is well below even the lowest threshold recited in the claims (80 ng/mg).

> anion exchange column due to the negative charge on the sugar molecules.

Sands at ¶ 28. The purification method described by Jin (anion exchange chromatography, hydrophobic chromatography, cation exchange chromatography, affinity chromatography) provides 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. *See* Sands at ¶ 47.

Jin's I2S is obtained by following a four-step purification method followed by ultrafiltration and nanofiltration. More specifically, the I2S of Jin is purified by anion-exchange chromatography, cation-exchange chromatography, hydrophobic chromatography, and affinity chromatography.[8] As discussed above, these purification steps were known to remove host cell proteins from purified recombinant proteins. *See* Sands at ¶¶ 23-29, 42. In Jin, the chromatography steps were followed by ultrafiltration system using tangential flow filtration membrane system, including concentration and diafiltration. *See* Jin at ¶¶ [0126-0128]; *see also id*. at Fig. 3. These steps were also known to remove host cell proteins. *See* Sands at ¶ 29.

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[8] As previously noted, three of these four chromatography steps are common to the purification method of the '556 patent, and the fourth is very similar as well.

To 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. *See* Sands at ¶ 48; *see also,* Ex. 1014. This can be done easily and rapidly using existing assays. *Id.* With this information, and a general knowledge of the properties of I2S, a person skilled in the art would have been able to devise a "rational purification scheme with a reasonable expectation of removing the vast majority of host cell proteins." *See* Sands at ¶ 48; *see also Ex parte Stern,* 13 USPQ2d 1379, 1381-2 (BPAI 1987) (rejecting applicant's argument that the claimed degree of purification of interleukin-2 conferred patentability where the desirability and methods of purification were known in the art.). The patentee's silence regarding any inventive significance attributed to HCP purification is also telling. *See 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); *see also, Cubist Pharms., Inc. v. Hospira, Inc.,* Appeal Nos. 2015-1197, -1204, -1259, 2015 U.S. App. LEXIS19662, at *41-2 (Fed. Cir. Nov. 12, 2015) (affirming District Court's decision).

iv. A POSITA would have a reasonable expectation of success in isolating I2S with HCP content less than 80 ng/mg

The POSITA would have fully expected to be able to successfully remove host cell protein contaminants following the method described in Jin. This expectation would have arisen from:

- The multiple teachings of Jin that its I2S has a high degree of purity. *See supra* pp. 40-44;
- The expectation that most FDA-approved biological drug product on the market today, as well as almost every biological drug product that the FDA allowed to be tested in clinical trials, likely fall within the guidelines advising that host cell protein content be below 100 ppm. *See* Ex. 1014 at 54; Ex. 1015 at 447.
- Reports that others have achieved HCP content below the claimed thresholds using methods similar to those used in Jin. *See, e.g.*, Ex. 1016 at ¶ [0070] ("Mihara") (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).

Simply put, removing contaminating host cell proteins from a target enzyme preparation is a readily achievable goal. Indeed, as Dr. Sands opines, "a person of ordinary skill in the art would have had a very high degree of confidence,

bordering on certainty, that levels of host cell protein at or below those claimed in the '556 patents could be achieved using routine purification methods for I2S." *See* Sands at ¶ 81.

In sum, the host cell protein content limitations of claims 1-3 and 16-17 of the '556 patent are obvious in view of Jin because methods for removing host cell proteins were routine and well-known in the art; a POSITA would have been motivated to remove or lower the host cell protein content so that the enzyme obtained can be used in medicinal treatments; and, based on the teachings of Jin, a POSITA would have a high degree of confidence that they could successfully reduce host cell protein content below the claimed thresholds by routine experimentation.

Petitioner is not aware of any objective indicia of non-obviousness or other evidence that would rebut this *prima facie* case of obviousness. Accordingly, Jin renders claims 1-3 and 16-17 obvious.

XVII. CONCLUSION

In view of the foregoing, it is respectfully submitted here that there is a reasonable likelihood that Petitioner will prevail with respect to at least one of claims 1-3, 9-13, and 16-17 challenged in this Petition. Accordingly, Petitioner requests that this Petition be granted and that an *inter partes* review of the '556

patent be instituted. Claims 1-3, 9-13 and 16-17 should be found unpatentable and these claims should be cancelled.

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Respectfully submitted,

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CERTIFICATE OF SERVICE

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