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Paper 60
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

APOTEX INC. and APOTEX CORP.,
Petitioner

v.

AMGEN INC. and AMGEN MANUFACTURING LIMITED,
Patent Owner.

Case IPR2016-01542
Patent 8,952,138 B2

Before JAMES T. MOORE, MICHAEL J. FITZPATRICK, and CHRISTOPHER G. PAULRAJ, *Administrative Patent Judges.*

MOORE, *Administrative Patent Judge.*

FINAL WRITTEN DECISION
35 U.S.C. § 318(a)

INTRODUCTION

Petitioner, Apotex, Inc. and Apotex Corp.[1] (hereinafter jointly "Petitioner") filed a Petition requesting institution of an *inter partes* review of claims 1–24 of U.S. Patent No. 8,952,138 B2 ("the '138 patent"). Paper 2 ("Pet."). Patent Owner, Amgen Inc. and Amgen Manufacturing Corp. (herein collectively "Patent Owner") filed a Preliminary Response. Paper 9 ("Prelim. Resp."). We instituted trial to determine whether the challenged claims were patentable. Paper 10. Patent Owner filed a response. Papers 14/15.[2] ("Resp."). Petitioner filed a reply. Papers 25/26. ("Reply"). Oral Argument was heard on December 13, 2017, and a transcript of the record has been made of record. Paper 59. Multiple unopposed motions to seal and multiple opposed motions to exclude and submit supplemental information are pending in this proceeding. See, *e.g.* Papers 16, 27, 33, 31, 37, 40, 43/44, 47, and 50.

For the reasons that follow, and based upon the totality of evidence in the record, we determine that Petitioner has carried its burden of persuasion that claims 1–17 and 19–24 of this patent are unpatentable. We also

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[1] Apotex Pharmaceuticals Holdings, Inc., Apotex Holdings, Inc., and ApoPharma USA, Inc., and Intas Pharmaceuticals Limited are said to be additional real parties in interest. Pet. 2.

[2] As we grant certain of the motions to seal, we use this designation to indicate the paper numbers of the unredacted and redacted (public) versions of the same document where applicable.

determine that Petitioner has not carried its burden of persuasion that claim 18 of this patent is unpatentable

A. Related Matters

Petitioner asserts that the '138 patent is the subject matter of district court litigation in the United States District Court for the Southern District of Florida.[3] Pet. 2. Petitioner further cites to related administrative matters, including nonprovisional patent applications, as related.[4] Pet. 2. Patent Owner points out that the district court litigation concerning Petitioner's invalidity defenses was resolved in its favor. Prelim. Resp. 4, Ex. 2004, 4–5. ("The Court finds that Apotex failed to meet its burden of establishing by clear and convincing evidence that the '138 patent is invalid for obviousness. The Court thus finds that each of the asserted claims 1-3, 6, 7, 13, 15-17, 22-23 of the '138 Patent is not invalid for obviousness under 35 U.S.C. § 103.") *Id*. at 5. While informative, the standards are different between the two proceedings, and the district court's decision is not binding upon this board.

B. The '138 Patent (Ex. 1001)

The '138 patent is entitled "Refolding Proteins Using a Chemically Controlled Redox State." Ex. 1001, (54). The '138 patent issued on

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[3] *Amgen Inc. et al. v. Apotex Inc. et al.*, No. 0:15-CV-61631-JIC/BSS (S.D. Fla.).

[4] U.S. Patent Application Serial Numbers 14/611,037 and 14/793,590.

February 10, 2015, from an application that was filed June 21, 2010. *Id.*, (22), (45). The '138 patent describes that the expression of recombinant proteins in the prior art prokaryotic systems is problematic in that the expressed proteins have limited solubility precipitates called inclusion bodies, which are improperly folded proteins. *Id.* at 1:18–33. According to the specification of the '138 patent:

> [V]arious methods have been developed for obtaining correctly folded proteins from bacterial inclusion bodies. These methods generally follow the procedure of expressing the protein, which typically precipitates in inclusion bodies, lysing the cells, collecting the inclusion bodies and then solubilizing the inclusion bodies in a solubilization buffer comprising a denaturant or surfactant and optionally a reductant, which unfolds the proteins and disassembles the inclusion bodies into individual protein chains with little to no structure. Subsequently, the protein chains are diluted into or washed with a refolding buffer that supports renaturation to a biologically active form.

Id. at 1:34–47.

According to the Specification, a problem existing until the present invention is said to be that "[m]ore complex molecules, such as antibodies, peptibodies and other large proteins, are generally not amenable to detergent refold conditions and are typically refolded" in so-called chaotropic refold solutions. *Id.* at 2:10–13. "These more complex molecules often have greater than two disulfide bonds, often between 8 and 24 disulfide bonds, and can be multi-chain proteins that form homo- or hetero-dimers." *Id.* at 13–16.Until the present invention, the specification states that "these types of complex molecules could not be refolded at high concentrations, i.e., concentrations

of 2.0 g/L and higher, with any meaningful degree of efficiency on a small scale, and notably not on an industrial scale." *Id.* at 2:17–21.

Thus, the invention of the '138 patent is said to be a method of refolding a protein expressed in a non-mammalian expression system (e.g. bacterial or viral) and present in a volume at a concentration of 2.0 g/L or greater comprising:

> (a) contacting the protein with a refold buffer comprising a redox component comprising a final thiol-pair ratio having a range of 0.001 to 100 and a redox buffer strength of 2 mM or greater and one or more of: (i) a denaturant; (ii) an aggregation suppressor; and (iii) a protein stabilizer; to form a refold mixture; (b) incubating the refold mixture; and (c) isolating the protein from the refold mixture.

Id. 2:52–61.

C. Illustrative Claim

All of the patent claims are challenged. In particular, they are claims 1–24. Pet. 3. Of these challenged claims, claim 1 is independent. Claims 2–24 depend, either directly or indirectly, from claim 1.

Claim 1 is illustrative, and reproduced below:

> 1. A method of refolding a protein expressed in a non-mammalian expression system and present in a volume at a concentration of 2.0 g/L or greater comprising:
>
> (a) contacting the protein with a refold buffer comprising a redox component comprising a final thiol-pair ratio having a range of 0.001 to 100 and a redox buffer strength of 2 mM or greater and one or more of:
>
> (i) a denaturant;
>
> (ii) an aggregation suppressor; and

(iii) a protein stabilizer;

to form a refold mixture;

(b) incubating the refold mixture; and

(c) isolating the protein from the refold mixture.

Ex. 1001, 17:47–59.

D. Prior Art Relied Upon

This proceeding utilizes the following prior art references:

Reference		Date	Exhibit
Schlegl	US 2007/0238860 A1	Oct. 11, 2007	Ex. 1003
Hevehan	"Oxidative Renaturation of Lysozyme at High Concentrations," *Biotechnology and Bioengineering,* 1996, 54(3):221-230	1996	Ex. 1004
Hakim[5]	"Inclonals" *mAbs*, 1:3, 281-287	June 2009	Ex. 1006

Petitioner also relies on the Declarations of Anne S. Robinson, Ph. D. ("Dr. Robinson"). Exs. 1002; 1056. Dr. Robinson's *curriculum vitae* is Exhibit 1049.

[5] Referred to throughout the Petition as "Inclonals." We use the first author's name, for consistency.

E. Instituted Grounds of Unpatentability

We instituted trial as to claims 1–24 of the '138 patent based on the following two grounds (Pet. 37–38):

Challenged Claim(s)	Basis	Reference(s)
1–11 and 13–24	§ 103(a)	Schlegl and Hevehan
12	§ 103(a)	Schlegl, Hevehan, and Hakim

II. ANALYSIS

The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). One seeking to establish obviousness based reference combination of teachings also must articulate sufficient reasoning with rational underpinnings to combine teachings. *See KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 418 (2007).

A. The Person of Ordinary Skill In the Art at the Time of Invention

Petitioner proposes that the person of ordinary skill in the art to which the '138 Patent is directed "would have had at least a Bachelor's degree (or the equivalent) in Biochemistry or Chemical Engineering with several years' experience in biochemical manufacturing, protein purification, and protein refolding, or alternatively, an advanced degree (Masters or Ph.D.) in Biochemistry or Chemical Engineering with emphasis in these same areas."

Pet. 18. "This person may also work in collaboration with other scientists and/or clinicians who have experience in protein refolding or related disciplines." Pet. 18–19 Finally, Petitioner asserts that this person "would have easily understood the prior art references referred to herein and would have had the capacity to draw inferences from them." *Id.*

Patent Owner asserts that a person of ordinary skill in the relevant art, (the art of protein refolding in June of 2009, the priority date of the '138 Patent) "would have had a Ph.D. degree in biochemistry, biochemical engineering, molecular biology, or a related biological/chemical/engineering discipline, or a master's degree in such disciplines and several years of industrial experience producing proteins in non-mammalian expression systems." Prelim. Resp. 18; Resp. 14.

These two descriptions are mostly consistent, but we adopt the slightly higher level recited by Patent Owner, requiring a graduate level of education and experience. Ex. 2001, ¶ 17. This is due to the sophistication and complexity in the area of protein refolding. Ex. 2001, ¶ 16. A person of ordinary skill in the art would have an advanced degree in biochemistry with an engineering component and significant experience in protein production, including refolding. *Id.* ¶ 17. This is also the level of ordinary skill in the art reflected by the prior art of record. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001); *In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995); *In re Oelrich*, 579 F.2d 86, 91 (CCPA 1978).

B. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are interpreted according to their broadest reasonable construction in light of the

specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142–46 (2016). Consistent with that standard, claim terms also are given their ordinary and customary meaning, as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *See In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007).

There are, however, two exceptions to that rule: "1) when a patentee sets out a definition and acts as his own lexicographer," and "2) when the patentee disavows the full scope of a claim term either in the specification or during prosecution." *See Thorner v. Sony Computer Entm't Am. LLC*, 669 F.3d 1362, 1365 (Fed. Cir. 2012).

If an inventor acts as his or her own lexicographer, the definition must be set forth in the specification with reasonable clarity, deliberateness, and precision. *Renishaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1249 (Fed. Cir. 1998). Although it is improper to read a limitation from the specification into the claims, (*In re Van Geuns*, 988 F.2d 1181, 1184 (Fed. Cir. 1993)) claims still must be read in view of the specification of which they are a part. *Microsoft Corp. v. Multi-Tech Sys., Inc.*, 357 F.3d 1340, 1347 (Fed. Cir. 2004).

Only terms which are in controversy need to be construed, and only to the extent necessary to resolve the controversy. *See Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011); *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999). In view of the arguments made in the Response and Reply, we have altered some of the constructions adopted in the institution decision, as discussed below.

protein

Petitioner argues that "protein" should not be construed as a "complex protein." Pet. 20.

The following passage of the Specification, which defines "protein" gives us a clear definition:

> As used herein, the terms "protein" and "polypeptide" are used interchangeably and mean any chain of at least five naturally or non-naturally occurring amino acids linked by peptide bonds.

Ex. 1001, 5:47-50.

Accordingly, guided by the express definition in the Specification, we adopt the above-described minimum of five amino acids as the construction of "protein." Prelim. Resp. 12–13. This construction has not changed from the institution decision.

Final thiol-pair ratio "TPR"

The term "final thiol-pair ratio" is interpreted to mean the relationship of the reduced and oxidized redox species used in the redox component of the refold buffer as defined by the equation

$$\frac{[\text{reductant}]^2}{[\text{oxidant}]}$$

Ex. 1001, 6:20-27, Resp. 18, fn. 4. This construction has changed from that in the institution decision to reflect the claim language more accurately. *See* Response 18, n. 4.

Redox buffer strength "RBS"

The term "Redox buffer strength" is interpreted to mean the following:

2[oxidant] + [reductant].

Ex. 1001, 6:29-38. Resp. 20–21, fn. 5. This construction also has changed from that in the institution decision to reflect the claim language more accurately. *See* Response 18, n. 5.

refold mixture

The broadest reasonable interpretation for "refold mixture" is "a mixture formed from contacting (1) the protein with (2) a refold buffer." Ex. 1001, 17:50–57. We find that the protein volume and refold volumes combine to form the refold mixture volume. Resp. 16.

complex protein

Patent Owner argues that the specification defines complex protein. Prelim. Resp. 16.

> The protein can be a complex protein, i.e., a protein that (a) is larger than 20,000 MW, or comprises greater than 250 amino acid residues, and (b) comprises two or more disulfide bonds in its native form

Ex. 1001, 12:58-61. A similar statement is found at 5:64–69 as regards a "complex molecule."

We also observe that the specification also provides a slightly different description in a different location.

> The method can be applied to any type of protein, including simple proteins and complex proteins (e.g., proteins comprising 2-23

> disulfide bonds *or* greater than 250 amino acid residues, *or* having a MW of greater than 20,000 daltons)

Ex. 1001, 4:23–27 (emphases added). There was discussion at the oral argument as to which of these descriptions was the broadest reasonable definition. Paper 59, 13–14 and 31–35. Dr. Robinson testifies that the single use of the broader description is correct. Ex. 1056, ¶¶ 5–7. Patent Owner urges otherwise. Resp. 17, citing Ex. 2020 ¶ 9.

We agree with Patent Owner that the evidence of record in the specification is more persuasive. The specification has set forth a definition multiple times, and that it is the definition is evidenced by the use of "i.e." (*id est*, or "that is"). In contrast, "e.g." (*exempli gratia*, or "for example") does not indicate a definition. We also observe that the use of the "e.g." appears intended to exemplify both the simple protein and complex protein antecedents expansively defining how the method may be applied. Ex. 1001, 4:23–27.

We need not expressly interpret any additional terms.

C. Obviousness Grounds – The Prior Art

Petitioner asserted, and we instituted trial upon, two obviousness grounds of unpatentability that rely on Schlegl, combined with two other discrete references. A short summary of these references, Dr. Robinson's testimony, and our analysis of these grounds follow.

(1) Schlegl (Exhibit 1003)

Schlegl, U.S. Patent Application Publication 2007/0238860 A1, is a publication of application 11/695,950, filed April 3, 2007 and published

October 11, 2007, and entitled "Method for Refolding a Protein." Ex. 1003 (10), (21), (22), (43), (54). Based on its publication date, Schlegl is prior art.

Schlegl describes methods for protein refolding, including the refolding and production of recombinant proteins. Ex.1003 at Abstract, ¶ 4. Schlegl utilizes a dilution method of protein refolding that results in a protein concentration up to 10 mg/ml. *Id*. ¶¶ 4–8, 16.

Schlegl delineates a continuous process that optimizes flow rate by keeping the concentration of unfolded proteins low and adding the protein solution at a flow rate that gives the unfolded protein time to properly fold. *Id.* ¶¶ 33–61. Before mixing, Schlegl starts with a high concentration of unfolded protein. *Id*. at ¶ 40.

Schlegl further describes a refolding buffer with a redox system having a defined thiol-pair ratio and redox buffer strength. *Id.* ¶¶ 36, 41, 75. The refolding buffer also contains a denaturant, an aggregation suppressor, and/or a protein stabilizer. *Id.* ¶¶36, 41, 74-75.

(2) Hevehan (Ex. 1004)

Hevehan is prior art to the '138 Patent. Ex. 1004

Hevehan describes refolding proteins from inclusion bodies at high concentrations. Using multiple dilution profiles, Hevehan created an experimental matrix to investigate different effects and the relationship between variables to optimize yields at higher concentrations, arriving at concentrations higher than 2 g/L. *Id.* at 5–6, Figure 4.

By varying the concentrations of reducing agent dithiothreitol ("DTT") and oxidizing agent oxidized glutathionone ("GSSG") in the redox

mixture, the *Hevehan* authors observed that renaturation yields were "strongly dependent on thiol concentrations in the renaturation buffer." *Id.* at 5.

The refold buffer used in *Hevehan* also included two folding aids, GdmCl (a denaturant) and L-arginine (a protein stabilizer and aggregation suppressor). *Id.* at Abstract. The authors found that such folding aids present in low concentrations during refolding can limit aggregation resulting in reactivation yields as high as 95%. *Id.* Finally, the authors of *Hevehan* incubated the refold mixture. *Id.* at 3.

(3) Hakim (Ex. 1006)

Hakim was published online on May 1, 2009. Ex. 1006, 1. Thus, Hakim is prior art to the '138 Patent under 35 U.S.C. § 102(a). Patent Owner attempts to antedate Hakim, which is discussed in more detail *infra*.

Hakim describes the production of fusion proteins. *Id.* at 4. Specifically, it describes the production of "PE38" fusions of the heavy chain or the light chain. *Id*. The bacterial expression system developed by Hakim allowed the production of antibodies in 8-9 days, instead of the eight weeks required when expressed in mammalian cells. *Id.* Hakim is pertinent to the proposed ground involving claim 12.

(4) Dr. Robinson's Initial Testimony Concerning the Combination

Dr. Robinson testifies that Hevehan explains the viewpoint of one of skill in the art looking to tackle the known problems of refolding proteins in 2009. Ex. 1002, ¶ 112. According to Dr. Robinson, Hevehan shows the systematic approach that those skilled in the art would take to refold a protein of interest. *Id.*, citing Ex. 1004 at 1–2. Specifically, Dr. Robinson

testifies that Hevehan considered conditions known to successfully refold proteins at low concentrations, minimizing aggregation, and applied those techniques to higher concentrations. Ex. 1002, ¶ 112, citing Ex. 1004 at 2.

Dr. Robinson further testifies that Hevehan authors found optimal refolding of proteins expressed in a non-mammalian expression system at higher concentrations is related to the thiol-pair ratio and redox buffer strength. Ex. 1002, ¶ 113, citing Ex. 1004 at 5. Hevehan concluded that yields are "strongly dependent" on thiol concentrations in the renaturation buffer. Ex. 1004 at 5. The optimum thiol-pair ratio was between 0.57 and 2.3 (DTT/GSSG). Ex. 1004 at Fig. 4 and ¶ 67, fn 5.

According to Dr. Robinson, one of ordinary skill would also be motivated to use the teachings of Schlegl and Hevehan to refold a "complex" protein, and would have a reasonable expectation of success in doing so. This is said to be so because both references teach the refolding of "complex" proteins by a dilution refolding method. Ex. 1002, ¶ 117.

(5) Analysis

a. Obviousness of Claims 1-11 and 13–24 in View of Schlegl and Hevehan

(i) Overview – Motivation to Combine

Petitioner asserts that one of ordinary skill in the art would have been motivated to combine Schlegl and Hevehan and would have had a reasonable expectation of success in doing so. Pet. 38. Specifically, Petitioner urges that the authors of Hevehan considered conditions already known to successfully refold proteins at low concentrations, minimizing aggregation. Pet. 39, citing Ex. 1004 at 2; Ex. 1002 at ¶ 112.

This position is supported by the testimony of Dr. Robinson, as noted above. We find Dr. Robinson is qualified to testify to the subject matter of this proceeding. Ex. 1002 ¶¶ 3–11; Ex. 1049. She testifies that one of ordinary skill in the art would look to Hevehan to solve the problem of refolding proteins at higher concentrations, and would have known the methods of Hevehan could apply to the dilution refolding methods of Schlegl. Ex. 1002, ¶ 115.

Petitioner is of the view that a person of ordinary skill in the art would have known that the refolding methods of Hevehan and Schlegl would be just as applicable to the refolding of proteins in inclusion bodies as to the proteins in denatured native proteins. Pet. 40.

Patent Owner, on the other hand, assert that Schlegl and Hevehan are fundamentally different and incompatible approaches to protein refolding. Resp. 2–3. Schlegl's method is said to be a "mechanical approach" to achieve protein refolding at dilute protein concentrations. *Id*.

We are provided with the declaration testimony of Richard C. Willson, Ph. D. ("Dr. Willson") as Exhibits 2001 and 2020. We find Dr. Willson qualified to testify to the subject matter of this proceeding. Ex. 2001, ¶¶ 7–14, Ex. 2002. His testimony is the basis for Patent Owner's contrary assertions.

According to Patent Owner, Hevehan's method is a different approach – a chemical approach (focused on denaturant and oxidant, but not reductant, in the refold buffer) to achieve protein refolding at high protein concentrations. Ex. 2001, ¶111. In Schlegl, protein aggregation is avoided by physically separating the protein molecules by dilution. *Id*. ¶112. In

Hevehan, refolding proteins at high concentrations necessarily reduces or eliminates such physical separation; chemicals are necessary to avoid aggregation and to achieve proper refolding. *Id*.

Dr. Willson further testifies that the equations involving the reactants (thiol pair ratio and redox buffer strength) are significant – reflecting the indiscovery that the refold efficiency is mostly impacted by the redox state of the refold system. Ex. 2001, ¶ 58.

Dr. Robinson responded to these positions in her second declaration. Ex. 1056. According to her testimony, the two approaches of protein refolding in Schlegl and Hevehan's refolding complement each other and Hevehan optimizes the refolding conditions. Ex. 1056, ¶ 18. She testifies that "Hevehan considered conditions known to successfully refold proteins at low concentrations, and applied those conditions to refolding of proteins expressed in a non-mammalian expression system at higher concentrations." *Id.* (citingEx.1004, 2). "Hevehan found that optimal refolding of proteins expressed in a non-mammalian expression system at higher concentrations is related to the thiol-pair ratio and redox buffer strength." *Id.* (citing Ex.1004, 5). "By varying the conditions of a reductant (DTT) and an oxidant (GSSG) and recording the outcomes, Hevehan concluded that yields are "strongly dependent" on thiol concentrations in the renaturation buffer." *Id.* (citing Ex.1004, 2.) *Id.*

Dr. Robinson also testifies that Schlegl has a clear indication of the use of redox chemistry. Ex. 1056, ¶ 22. She points to Schlegl claim 9 in her testimony, which recites "wherein the protein solution obtained after mixing is collected in a tank and incubated until the protein is completely present in

its biologically active form." Ex. 1056 ¶24 (citing Ex. 1003, 13). She testifies that it is her view that "the method of claim 9 of Schlegl cannot be practiced without redox chemistry for proteins with disulfide bonds in the native state. If one is working with a protein with disulfide bonds, it is unlikely that one can obtain a biologically active form without the use of redox components." Ex. 1056, ¶ 24.

Dr. Willson testified in his second declaration that Schlegl and Hevehan, alone or in combination, do not teach elements of claim 1; a person of ordinary skill in the art would not combine the references; and the art does not render the claims obvious. Ex. 2020*, passim*.

Dr. Robinson was cross-examined on May 8, 2017, in Washington, DC. A transcript of that deposition testimony is in the record as Exhibit 2019. Dr. Willson likewise was cross-examined, on August 9, 2017, in New York, NY. A transcript of that deposition testimony is in the record as Exhibit 1055. Subsequent to her second declaration, Dr. Robinson was again cross-examined on September 26, 2017, and a transcript of that cross-examination is in the record as Exhibit 2059. We have carefully reviewed the testimony provided by both witnesses.

We credit the testimony of Dr. Robinson on this point over that of Dr. Willson. We are especially persuaded by the fact that simply diluting the protein concentration will not necessarily result in refolding. Reply, 5. Dr. Robinson also makes a compelling point that using a dilution technique to contact a protein-containing volume with a refold buffer does not exclude the use of redox agents. Ex. 1056, ¶ 15.

She further testifies that Schlegl teaches the use of redox chemistry and a customized refold buffer. *Id.* at ¶ 17, citing Ex. 1003, ¶ 36. Paragraph 36 is reproduced below:

> The refolding buffer used for a given protein of interest is customized to the refolding requirements/kinetics of that protein. Refolding buffers are known in the art and commercially available; typical buffer components are guadinium chloride, dithiothreitol (DTT) and optionally a redox system (e.g. reduced glutathione GSH/oxidized glutathione GSSG), EDTA, detergents, salts, and refolding additives like L-arginine.

Ex. 1003, ¶ 36. It appears to us that glutathione discussed in Schlegl is also listed as an exemplary redox component in the optimized refold buffer of the '138 patent. Ex. 1001, 10:53–54.

Dr. Willson, on the other hand states that Schlegl "does not focus on" the use of redox chemicals. Ex. 2001, ¶ 93. The Response then asserts that because Schlegl's example was a well-known model protein and easy to refold, that "redox chemicals do not play a role in Schlegl's refolding method." Resp. 36. Focusing on the sole example, the Response notes that protein was simple to refold and uses calcium. *Id.*

This testimony of Dr. Willson, while literally true, cannot in our view be reconciled with Schlegl's express teaching of a customizable refolding buffer with a redox buffer option. We further find that the discussion in Schlegl does not support the Patent Owner's assertion that these references are "incompatible." Resp. 23.

Patent Owner also asserts that redox systems used for refolding at low protein concentrations "are inappropriate" when refolding at high protein

concentrations. *Id.* at 26(citing Dr. Willson's second declaration, Ex. 2020, ¶ 22). Dr. Willson makes the statement that "[a]cknowledging that what worked at low protein concentrations 'might not be appropriate when folding a protein at 1 mg/mL or higher concentrations,' *Hevehan* reports the use of a trial-and-error matrix approach to find appropriate conditions." Ex. 2020(citing Ex. 1004, 5).

The problem with this analysis is that, like that with respect to Schlegl above, it strays by incremental degrees from the original evidence of record, and it goes too far. According to Hevehan:

> The above thiol concentrations were optimized for oxidative renaturations at low protein concentrations (0.01–0.1 mg/mL) and might not be appropriate when folding a protein at 1 mg/mL or higher concentrations.

Ex. 1004, 5.

We read this paragraph, contained in a section headed *Thiol Concentration Dependence on Renaturation,* and sandwiched between a discussion of the prior art thiol concentrations in the renaturation buffer and empirical studies of different ranges as suggesting quite the opposite – as teaching that one of ordinary skill in the art could find workable ranges by routine experimentation.

Patent Owner also asserts that host-cell contaminants would lead one of ordinary skill in the art not to have an expectation of success as model proteins are not predictive of or applicable to recombinant proteins expressed in mammalian expression systems. Resp. 2–3 and 27–32. The evidence relied upon for this proposition is a publication originating from

the same laboratory that the authors of Hevehan occupied. *Id.* (citing Ex. 2033).

Again, the weakness in this position is that the authors of the relied upon exhibit(*i.e.* Ex. 2033) came to no such conclusion themselves. Patent Owner selectively relies upon a single example to state: "It decreased by 40% to 50%." Resp. 30. While this again may be literally true, and Patent Owner includes a chart referencing what appears to be the single worst example in the reference, we reproduce the abstract of the reference below to provide additional context:

> The effect of typical contaminants in inclusion body preparations such as DNA, ribosomal RNA, phospholipids, lipopolysaccharides, and other proteins on renaturation rate and yield of hen egg white lysozyme was investigated. Separate experiments were conducted in which known amounts of individual contaminants were added to test their effect on renaturation kinetics. **On the basis of a simplified model for the kinetic competition between folding and aggregation, it was found that none of the above contaminants had an effect on the rate of the folding reaction, but some of them significantly affected the rate of the aggregation reaction and, thus, the overall renaturation yield**. **While ribosomal RNA did not seem to affect the aggregation reaction, plasmid DNA and lipopolysaccharides increased the aggregation rate, resulting in a decrease of about 10% in the overall renaturation yield. Phospholipids were found to improve refolding yields by about 15% by decreasing the overall rate of the aggregation reaction without affecting the rate of the folding reaction.** Proteinaceous contaminants which aggregate upon folding, such as β-galactosidase and bovine serum albumin, were found to significantly decrease renaturation yields by promoting aggregation. The effect was strongly dependent on the concentration of the proteinaceous impurity. **On the other hand, the presence of refolding ribonuclease A, which does**

> **not significantly aggregate upon folding under the conditions tested in this work, did not affect the renaturation kinetics of lysozyme, even at concentrations as high as 0.7 mg/ml.**

Ex. 2033, Abstract. (Emphases added).

Dr. Willson does not address adequately any of the content we have emphasized in the exhibit's Abstract, which observations either cause lesser overall losses or, in one case, increase yield. While we have no doubt contamination can result in some reduction, none of the highlighted portions, which would appear to somewhat undercut the testimony, are sufficiently acknowledged by or appear to be adequately discussed or countered in the testimony. Ex. 2020, ¶ 43.

Dr. Willson cites to additional references Georgiou (Ex. 2034, at 2) and Darby (Ex. 2035, at 1–2) as further support. Ex. 2020, ¶ 42–43. As above, the cited references do not provide support sufficient to establish that for which they are cited. For example, while Georgiou does state that the efficiency of refolding is inversely proportional to the level of contamination (Ex. 2034, 2), Georgiou also states "[n]onetheless, as was shown with β-lactamase, it is often possible to modify the expression conditions to reduce the amount of extraneous material incorporated within the inclusion bodies" (*Id.* at 4). (footnotes omitted). Likewise, Darby (a letter to the Editor of Nature Magazine) mentions losses but then also concludes with "[n]evertheless, awareness of the possible presence of complexes should suggest ways of resolving them as well as the stage in the purification process at which refolding of the protein should be attempted." Ex. 2035, 2.

We also are further persuaded of the appropriateness of the combination by Dr. Robinson's observation that Schlegl describes quenching of oxidative refolding, and her view that claim 9 could not be practiced without redox chemistry. Ex. 1056, ¶¶ 23 and 24.

Patent Owner, on the other hand, through the testimony of Dr. Willson, asserts that one of ordinary skill in the art would not expect success for myriad reasons including Hevehan's kinetic model being inaccurate because: (1) the model incorrectly assumes that each step is irreversible and proceeds in only one direction (Ex. 2020, ¶74 citing Ex. 1004, 8, Figure 7); (2) the assumption in the model that the aggregation pathway follows third-order kinetics does not apply to all protein aggregation pathways(*id.* at ¶ 73 citing Ex. 2043, *passim*); (3) the model incorrectly assumes that only proteins in the intermediate state (between folded and unfolded) aggregate (*id.* at ¶ 74 citing Ex. 2046, 1, Ex. 2047, 1 6, and Fig. 7, and Ex. 2042 ("Buswell") at 1); and (4) the model incorrectly assumes that there is a single pathway for converting one protein state to another (*id.* at ¶75 citing Ex. 1004 at 8, Figure 7).

Relying on the above testimony and evidence, Patent Owner urges that it was known prior to Schlegl that Hevehan does not accurately predict refolding of its own model protein and therefore a person of ordinary skill in the art would not have applied Hevehan's teachings to refolding any other proteins. Resp. 39–42.

Petitioner asserts in reply that Patent Owner has misapplied Buswell, which teaches that Hevehan's model does not work at low-protein concentrations (defined therein as 0.01-0.02 mg/L), which are not the

conditions Hevehan was using for its measurements. Reply, 10. Petitioner also observes that Buswell's theory has been discredited. *Id.* (citing Ex. 1056 ¶¶34-35, Ex. 1057, 91, 95).

We note that Ex. 1057 does expressly negate a principal conclusion of Buswell:

> Buswell and Middelberg (2003) reported that the presence of native lysozyme significantly decreased the effective refolding yield. This was because that native lysozyme was able to polymerize with aggregates (Buswell and Middelberg, 2002). We checked this possibility by adding pure native sGFPmut3.1 in our refolding buffer before refolding.
>
> In contrast to decrease in yields in the presence of native lysozyme (Buswell and Middelberg, 2003), refolding yields remained unaffected in the presence of pure native sGFPmut3.1 (Fig. 3).

Ex. 1057, 5.

Accordingly, while it is a close call with competing evidence, we find that a person of ordinary skill in the art would look to Hevehan to solve the problem of refolding proteins at higher concentrations, and would have known the methods of Hevehan could apply to the dilution refolding methods of Schlegl. We also find that a person of ordinary skill in the art (who would have been highly skilled as discussed above) would have had a reasonable expectation of success in combining Schlegl and Hevehan.

We next turn to comparison of the claimed subject matter against the prior art.

The Claimed Subject Matter vs. the Prior Art

Claim 1

> *1. A method of refolding a protein expressed in a non-mammalian expression system and present in a volume at a concentration of 2.0 g/L or greater comprising:*

Petitioner asserts that Schlegl describes refolding of recombinant proteins expressed using nonmammalian expression systems such as bacterial and yeast expression systems. Pet. 43. (citing Ex. 1003 ¶ 4). We find that Schlegl describes expression vectors including microorganisms such as bacteria. *Id.*

Schlegl is also said to describe protein present at a volume of 16.5 mg/mL (16.5 g/L) before being diluted by the refold buffer. Ex. 1003 at ¶ 75.

We find that Schlegl describes that denatured and reduced protein aliquots of 16.5 mg/ml are batch-diluted into a renaturation buffer. *Id.* While we observe that the end dilution is lower than 2.0 g/L, the protein is contained in a volume at an initial concentration greater than 2.0 g/L.

> *(a) contacting the protein with a refold buffer comprising a redox component comprising a final thiol-pair ratio having a range of 0.001 to 100 and a redox buffer strength of 2 mM or greater and one or more of:*
>
> *(i) a denaturant;*
>
> *(ii) an aggregation suppressor; and*
>
> *(iii) a protein stabilizer;*
>
> *to form a refold mixture;*

Ex. 1001, 17:47–59.

Petitioner asserts that the example in Schlegl discloses contacting bovine α-lactalbumin (a denatured model protein) with a refold buffer comprising a redox component as part of the dilution refold method of Schlegl to form a refold mixture. Pet. 44–45 (citing Ex. 1003 ¶ 75).

We find that, in the example, the protein is denatured and reduced in what Schlegl calls a refold buffer. Ex. 1003 ¶ 74. The Schlegl 'refold buffer' contains 0.1 M Tris-HCL, pH 8.0, 6 M GdmHCl, 1 mM EDTA and 20 mM DTT. *Id.*

We also find that the protein is rapidly diluted into a renaturation buffer containing 100 mM Tris-HCl, 5 mM $CaCl_2$, 2 mM cystine and 2 mM cysteine, pH 8.5. *Id.* ¶ 75.

Petitioner asserts that a person of ordinary skill in the art would understand that the addition of cystine and cysteine here serve as the redox system or redox component for bovine α-lactalbumin. Pet. 45 (citing Ex. 1002 at ¶ 124). We find this testimony to be credible. See also Ex. 2001, ¶ 53. (Dr. Willson testifying that cystine is the oxidant and cysteine is the reductant).

Petitioner asserts that this redox component has a thiol-pair ratio of 2 and a redox buffer strength of 6 mM. Pet. 45 (citing Ex. 1003 at ¶¶ 36, 0075). Dr. Robinson testifies to this fact. Ex. 1002 ¶ 124. She calculates the ratio at footnote 3 of paragraph 59 of her declaration (Ex. 1002). She states:

> Based upon the '138 patent, the thiol pair ratio (TPR) is defined by the equation $TPR = [reductant]^2/[oxidant]$, where the TPR is calculated in the redox component. Since these ratios will be the same in the refolding buffer, in this case, the

$$TPR = \frac{[cysteine]^2}{[cystine]} = \frac{[2\ mM]^2}{[2\ mM]} = \ 2\ mM$$

Ex. 1002, fn3.

Two is within the claimed ratio range of 0.001-100.

Dr. Robinson calculates the redox buffer strength as well:

> Based on the '138 patent, the redox buffer strength (BS) is defined by the equation, [R]BS=*2oxidant* + [*reductant*]. In this case, [R]BS=2[cysteine]+[cysteine]=6.[6]

Ex. 1002, fn4.

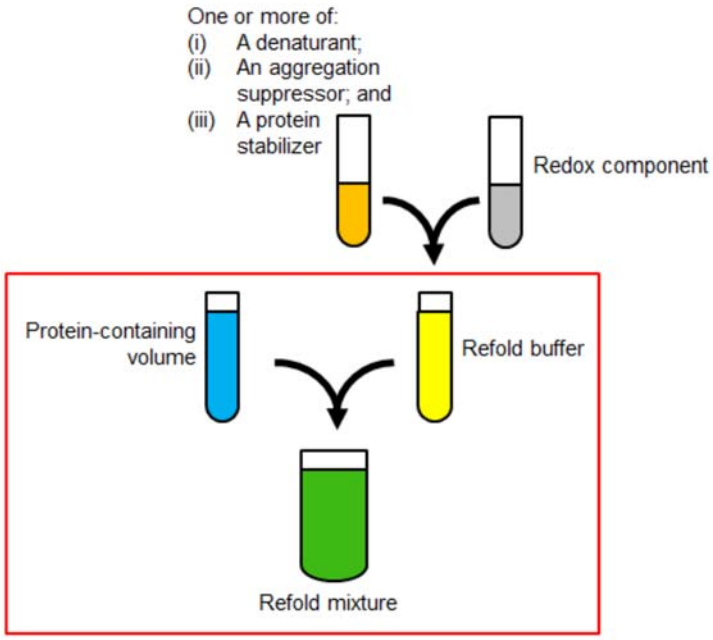
Six is within the claimed range of "greater than two."

Petitioner further asserts that Hevehan describes contacting a hen egg white lysozyme with a refold buffer comprising a redox component to form a refold mixture. Pet. 45 (citing Ex. 1004 at 6). Petitioner urges that the redox component "has a thiol-pair ratio of between 0.3 and 9 and a redox buffer strength of 5 mM to 19 mM, the optimum being between 10-16 mM." Pet. 45, citing Ex. 1003 at 5; Ex. 1002 ¶ 124.

Patent Owner urges that the above two assertions are incorrect.

Patent Owner has provided an illuminating diagrammatic representation of the claim to illustrate their point, which is reproduced below. The red box is said to indicate the "contacting" step.

[6] We observe that Dr. Robinson did not show all of her work; however, it is readily apparent to us that RBS=2[2 mM]+2 mM = 4+2 = 6 mM.



Resp. 15.

Patent Owner's first argument is that neither Schlegl or Hevehan describe the TPR and RBS equations. *Id.* at 22. According to Patent Owner, Dr. Robinson utilized the equations from the '138 Patent which is hindsight. *Id.* at 23.

While an interesting argument, we are not persuaded of its legal correctness. The TPR and RBS equations define ratios and concentrations of oxidant and reductant. In order to discern whether the claims are obvious, we of necessity must determine whether the prior art ratios and concentrations render the claimed range obvious. Petitioner is correct in observing that "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by

routine experimentation." Reply 3 (citing *In re Aller*, 220 F.2d. 454, 456 (CCPA 1955)).

To hold otherwise would eviscerate long-standing legal precedent and simply allow for the patenting of inventions whose only contribution was to quantify into a previously unwritten equation relationships that were discernible to one of ordinary skill in the art from the prior art. For example, if we were to follow Patent Owner's logic to its conclusion, and if another inventor calculated the TPS using a third order relationship, creating an even broader claim, we might be compelled to conclude that the new, broader claim was unobvious simply because the formula was not known. See., e.g. *Brown & Williamson Tobacco Corp. v. Philip Morris Inc*., 229 F. 3d. 1120 (Fed. Cir. 2000)(affirming judgment that patent claiming a reduced circumference cigarette was invalid as obvious over prior art cigarettes also with a different reduced circumference, despite argument that tobacco utilization efficiency "TUE" recited in the claim, defined by the formula TUE= amount of tobacco consumed/puff, was an unobvious advance and not known in the prior art).

Patent Owner's second argument, that one of ordinary skill would not combine Schlegl and Hevehan, has been addressed above and found to be unpersuasive. Resp. 23–31.

Patent Owner's third argument is that the combination of Schlegl and Hevehan does not teach the claimed TPR limitation. Resp. 32. More specifically, Patent Owner urges that the TPR of the combination of Schlegl and Hevehan is zero, and falls outside the claimed range. *Id.*

This argument was initially raised in passing in the Preliminary Response, page 26, citing to testimony of Dr. Willson that the addition of a reductant was not necessary. Ex. 2001, ¶ 109.

This argument was further developed in the Response, 32–35. More specifically Patent Owner amplifies:

> But *Hevehan* explicitly teaches that there is no reductant in the refold buffer. EX2020 at ¶54. *Hevehan* teaches two volumes: a protein-containing volume and a refold buffer (called the renaturation media). EX2019 at 74:20-75:3; EX2020 at ¶55; EX1004 at 2-3. *Hevehan*'s protein-containing volume contains, in relevant part, HEWL (the protein) and DTT (which Dr. Robinson identifies as the reductant). EX1004 at 2; EX1002 at ¶68, fn. 5; EX2020 at ¶55. *Hevehan*'s refold buffer contains Tris-HCl, EDTA, GSSG (the oxidant), and possibly some GdmCl and L-arginine—none of which are reductants. EX1004 at 2-3; EX2019 at 75:4-25 (GdmCl and L-arginine are not redox chemicals); EX2020 at ¶55 (Tris-HCl and EDTA are not redox chemicals).
>
> Critically, *Hevehan* explicitly teaches that the reductant is not necessary in the refold (renaturation) buffer:
>
> > Addition of GSSG's reducing partner, GSH, to the renaturation system was not necessary due to the DTT carried over from the denatured [protein] solution.
>
> EX1004 at 3; EX2019 at 77:8-16. And Dr. Robinson admitted at deposition that there is no DTT reductant in the refold buffer. EX2019 at 76:1-5; EX2020 at ¶56.

Response 33.

Were there a teaching of no reductant in the refold buffers in Hevehan, then it appears to us that the Patent Owner would prevail. However, Petitioner correctly observes that the very next sentence in Hevehan states:

> In a typical experiment, the refolding solution contained 5 mM GSSG and 2 mM DTT, resulting in a glutathione ratio [GSH]/[GSSG] of 1.33/1.

Reply 8 (citing Ex. 1004, 3).

Petitioner also observes that the TPR in Hevehan cannot be zero, as Hevehan states that protein yields are "strongly dependent" on thiol concentrations in the renaturation buffer. Reply 9 (citing Ex. 1004, 5). Petitioner asserts that this conclusion would not be possible if Hevehan were teaching a TPR of zero. Petitioner observes that Hevehan discloses that the optimum thiol-pair ratio is between 0.57 and 2.3 (DTT/GSSG). Ex. 1004, Fig. 4; Ex. 1002, ¶68; Ex. 1056, ¶¶31–33.

We find Petitioner's evidence more credible and compelling. Patent Owner appears to rely upon an isolated portion of evidence without considering the overall teachings of the Hevehan reference. The combination of Schlegl and Hevehan does not teach a TPR of zero; to the contrary, we find it teaches additional points within the broad range of claim 1.

(b) incubating the refold mixture; and

Petitioner asserts that Schlegl describes "[c]omplete refolding, including formation of disulfide bonds, proline isomerization and domain pairing may take hours and up to several days" of further incubation in the

refolding tank to allow complete refolding of the protein. Pet. 48 (citing Ex. 1003 ¶¶ 16, 60). Patent Owner does not significantly dispute this teaching.

(c) isolating the protein from the refold mixture.

Lastly, Petitioner asserts that Schlegl discloses isolation of the protein from the refold mixture as a final step in the disclosed refold method, including via dialysis, filtration, extraction, precipitation and chromatography. Pet. 48 (citing Ex. 1003 ¶¶ 39, 65). Patent Owner does not significantly dispute this teaching.

On consideration of the evidence presented at trial, including Patent Owner's evidence to the contrary, we find Petitioner to have met its burden of proof. We conclude that claim 1 is unpatentable as obvious over Schlegl and Hevehan.

Claim 2

Claim 2 depends from claim 1, and further recites that the final thiol-pair ratio is selected from the group consisting of 0.05 to 50, 0.1 to 50, 0.25 to 50, 0.5 to 50, 0.75 to 40, 1.0 to 50 and 1.5 to 50, 2 to 50, 5 to 50, 10 to 50, 15 to 50, 20 to 50, 30 to 50 or 40 to 50. Ex. 1001, 17:60–18:2.

Petitioner asserts that Schlegl describes contacting the protein with a refold buffer with a thiol-pair ratio of 2. Pet. 49 (citing Ex. 1003 at ¶ 75). Hevehan is said to describe a thiol pair ratio of 0.3 to 9. *Id.* (citing Ex. 1004, 5). Patent Owner does not separately argue claim 2.

As the evidence shows that the final TPR in Schlegl and Hevehan fall within several of the claimed ranges of claim 2, we are persuaded that Petitioner has demonstrated that challenged claim 2 is unpatentable as obvious over Schlegl and Hevehan.

Claim 3

Claim 3 depends from claim 1 and further recites that the thiol-pair buffer strength is selected from the group consisting of greater than or equal to 2.25 mM, 2.5 mM, 2.75 mM, 3 mM, 5 mM, 7.5 mM, 10 mM and 15mM. Ex. 1001, 18:3–6.

Petitioner asserts that the example in Schlegl describes a redox buffer strength of 6 mM. Pet. 49 (citing Ex. 1003 ¶ 75). Hevehan is also said to describe a redox buffer strength of 5 to 19 mM, with an optimum 10 to 16 mM. *Id.* (citing Ex. 1004, 5). Both disclosures are urged to fall within the scope of claim 3. Patent Owner does not separately argue claim 3.

As the final RBS in Schlegl and Hevehan appear to fall within the claimed range of claim 3, we are persuaded that Petitioner has demonstrated that challenged claim 3 is unpatentable as obvious over Schlegl and Hevehan.

Claims 4 and 5

Claim 4 depends from claim 1, and further recites that the protein is present in the volume in a non-native limited solubility form. Ex. 1001, 18:7–8. Claim 5 depends from claim 4, and further recites that the form is an inclusion body. *Id.* 18:9–10.

Petitioner asserts that Schlegl discloses that the protein is deposited in the cells in a paracrystalline form, in so-called "inclusion bodies," also termed "refractile bodies." Pet. 52–53 (citing Ex. 1003 ¶ 6). Hevehan is said to describe that the "[a]ctive protein can be recovered by solubilization of inclusion bodies followed by renaturation of the solubilized (unfolded)

protein." *Id.* (citing Ex. 1004, Abstract). Patent Owner does not separately argue claims 4 or 5.

As the evidence of record establishes that the final inclusion bodies in Schlegl and Hevehan fall within the non-native limited solubility form of claim 4, and the inclusion body of claim 5, we are persuaded that Petitioner has demonstrated that challenged claims 4 and 5 are unpatentable as obvious over Schlegl and Hevehan.

Claim 6

Claim 6 depends from claim 1, and recites that the protein is present in the volume in a soluble form. Ex. 1001, 18:11–12.

Petitioner asserts that Schlegl describes a method of refolding a protein, where that protein before refolding is dissolved as a protein solution. Pet. 53 (citing Ex. 1003 ¶¶ 16, 63). Patent Owner does not significantly argue claim 6.

As the evidence of record establishes that the protein solution in Schlegl falls within the soluble form of claim 6, we are persuaded that Petitioner has demonstrated challenged claim 6 is unpatentable as obvious over Schlegl and Hevehan.

Claims 7-11

Claim 7 depends from claim 1, and further recites that the protein is recombinant. Ex. 1001, 18:13–14. Claim 8 depends from claim 1 and further recites that the protein is an endogenous protein. *Id.* 18:15–16. Claim 9 depends from claim 1, and further recites that the protein is an antibody. *Id.* 18:17–18. Claim 10 depends from claim 1, and further recites that the protein is a complex protein. *Id.* 18:19–20. Claim 11 depends from

claim 1, and further recites that the protein is a multimeric protein. *Id.* 18:21–22.

Petitioner asserts, alternatively, that Schlegl discloses a method of refolding the various proteins identified in claims 7-11, and that one of ordinary skill in the art would immediately recognize that the methods of Schlegl could be applied. Pet. 53–54. Petitioner points to Schlegl's description that the methods can be applied to "any protein, protein fragment or peptide that requires refolding upon recombinant expression in order to obtain such protein in its biologically active form" *Id.* (citing Ex. 1003 ¶ 31). Petitioner observes that Schlegl describes the refolding of bovine α-lactalbumin, a protein containing 123 amino acid residues and four disulfide bonds, while Hevehan describes refolding hen egg white lysozyme having 129 amino acids and four disulfide bonds. Pet. 54 (citing Ex., 1003, 1004).

Dr. Robinson testifies that a person of skill in the art would immediately recognize that the methods taught by Schlegl could be applied to each of these types of proteins, and in particular multimeric proteins, such as antibodies. Ex. 1002, ¶ 145 (citing Ex. 1006 at 281).

Patent Owner does not separately argue claims 7 and 8. Patent Owner, however, provides contrary arguments for claims 9, 10, and 11.

Patent Owner urges that none of the refolded proteins of Schlegl and Hevehan are complex proteins as recited in claim 10. Resp. 42–44. More specifically, Patent Owner asserts that there is no empirical evidence that a person of ordinary skill in the art would have had a reasonable expectation of success of refolding complex proteins, antibodies, or multimeric proteins. Resp. 43. Dr. Willson testifies that neither Schlegl nor Hevehan "teach or

suggest" the proteins required by claims 9, 10, and 11. Ex. 2020, ¶ 94. Dr. Willson concedes that Schlegl broadly states that its method can be used on "any protein, protein fragment or peptide that requires refolding upon recombinant expression in order to obtain such protein in its biologically active form." Ex. 1003, ¶ 31. However, he would require an experimental showing to support this assertion, not the model protein example actually conducted. Patent Owner also observes that refolding complex proteins can be "extremely difficult" and "challenging." Resp. 43.

We accept that refolding proteins is difficult and challenging. However, the person of ordinary skill in the art is highly skilled. The Petition asserts that one of ordinary skill in the art would immediately recognize that the methods of Schlegl could be applied to those types of molecules, and Dr. Robinson's testimony supports the statement made in Schlegl. Ex. 1002, ¶ 145.

Dr. Robinson relies in part on Ex. 1006, which is a publication from "mAbs" journal in 2009.[7] We also take into account her cross-examination testimony in which she stated:

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[7] Patent Owner asserts that Ex. 1006 is not prior art to their claims. They have provided the declaration testimony of Dr. Roger A. Hart (Ex. 2021), and internal Amgen presentations (Ex. 2022 and Ex. 2024) which are considered to be confidential and subject to protective order. Exhibits 2022 and 2024 discuss protein AMG 745 and Exhibits 2023 and 2025 indicate the documents were created in 2009 and 2008 However, other than the code names of the proteins, no real identification of the type of protein that designation reflects is made in the contemporaneous documents. Dr. Hart testifies that AMG 745 falls within the scope of, *e.g.,* claims 1, 7, 10, 11, and 12(Ex. 2021, ¶ 35) , identification would have been unnecessary on

> Q So let me ask the question this way:
> Generally speaking, would you expect the refolding of multimeric proteins, antibodies and FC-protein conjugates to be more complex than the refolding of hen egg white lysozyme?
>
> A So again, I think it's protein-dependent. I think some complex proteins refold easily and some -- some multimeric proteins refold readily, I guess I should say, and some don't. So I don't think there's a hard and fast rule.

Ex. 2019, 61:21–25, 62:1–5.

We accept her testimony such that, even not considering Ex. 1006, we find that one of ordinary skill would recognize that the methods of Schlegl could be applied to those and various types of protein molecules.

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internal documents (Ex. 1054, 68:13–20; 95:12–17; and 102:11–103:3), and as such the invention was reduced to practice prior to the publication of Ex. 1006(Ex. 2021, 16). However, the documentation relied upon to identify AMG 745 with reasonable precision is from 2014, as discussed infra. Ex. 2026. Our careful review of the evidence leads us to observe that about the closest the contemporaneous documents come is an undescribed molecular schematic labeled AMG 745 (Ex. 2022, 16) which Patent Owner characterizes as "resembl[ing] an antibody." Resp. 52. We therefore agree with Petitioner that documents relied upon to teach a specific type of protein should, in this instance, give a more credible identification of what the protein is if the antedating effort is to be persuasive. Reply 24–25. Testimony from 2017 and a document by others from 2014 are fairly well removed from the events of 2008 and 2009, and not sufficiently persuasive.

Consequently, as the proteins described in Schlegl fall within the types recited by these claims, Petitioner has demonstrated that challenged claims 7–11 are unpatentable as obvious over Schlegl and Hevehan.

Claim 13

Claim 13 depends from claim 1, and recites that "the non-mammalian expression system is one of a bacterial expression system and a yeast expression system." Ex. 1001, 18:24–26.

Petitioner asserts that Schlegl describes microorganisms such as bacteria, yeast or fungi, or from animal or plant cells to produce a protein of interest. Pet. 54–55 (citing Ex. 1003 at ¶ 4). Patent Owner does not separately argue claim 13

We find that Schlegl describes various conventional non-mammalian systems. Ex. 1003, *passim.*

Petitioner has demonstrated that challenged claim 13 is unpatentable as obvious over Schlegl and Hevehan.

Claim 14

Claim 14 depends from claim 1, and recites that "the denaturant is selected from the group consisting of urea, guanidinium salts, dimethyl urea, methylurea and ethylurea." Ex. 1001, 18:28–30.

Petitioner asserts, and we find, that Schlegl teaches the use of components that promote the solubilization of inclusion bodies, e.g. chaotropic agents such as urea, guanidinium chloride (GdmCl), sodium and/or potassium thiocyanate. Pet. 49 (citing Ex. 1003 ¶ 64). Patent Owner does not separately argue claim 14

Petitioner has demonstrated that challenged claim 14 is unpatentable as obvious over Schlegl and Hevehan.

Claim 15

Claim 15 depends from claim 1, and recites that "the protein stabilizer is selected from the group consisting of arginine, proline, polyethylene glycols, non-ionic surfactants, ionic surfactants, polyhydric alcohols, glycerol, sucrose, sorbitol, glucose, Tris, sodium sulfate, potassium sulfate and osmolytes." Ex. 1001, 18:31–35.

Petitioner asserts that Schlegl shows refolding buffers were known in the art and commercially available; typical buffer components are guadinium chloride, dithiothreitol (DTT) and optionally a redox system (e.g. reduced glutathione GSH/oxidized glutathione GSSG), EDTA, detergents, salts, and refolding additives like L-arginine. Pet. 50 (citing Ex. 1003 ¶¶ 36, 41). Patent Owner does not separately argue claim 15

As Schlegl describes arginine, which falls within the stabilizers recited by this claim, Petitioner has demonstrated that challenged claim 15 is unpatentable as obvious over Schlegl and Hevehan.

Claim 16

Claim 16 depends from claim 1, and further recites that "the aggregation suppressor is selected from the group consisting of arginine, proline, polyethylene glycols, nonionic surfactants, ionic surfactants, polyhydric alcohols, glycerol, sucrose, sorbitol, glucose, Tris, sodium sulfate, potassium sulfate and osmolytes." Ex. 1001, 18:36–41.

Petitioner asserts that Schlegl describes arginine. Pet. 50. Patent Owner has not separately challenged this.

As we find that Schlegl describes arginine, which falls within the aggregation suppressors recited by this claim, Petitioner has demonstrated that challenged claim 16 is unpatentable as obvious over Schlegl and Hevehan.

Claim 17

Claim 17 depends from claim 1, and recites that the thiol-pairs comprise at least one component selected from the group consisting of glutathione-reduced, glutathione-oxidized, cysteine, cystine, cysteamine, cystamine and betamercaptoethanol. Ex. 1001, 18:42–45.

Petitioner asserts Schlegl describes the use of a refold buffer containing refolding additives including as examples L-arginine, Tris, detergents, redox systems like GSH/GSSG, ionic liquids like N'-alkyl and N'-(omega-hydroxy-alkyl)-N-methylimidazolium chlorides. Pet. 51–52, citing Ex. 1003 ¶ 41. Patent Owner does not separately argue claim 17.

As Schlegl describes GSH, which is glutathione-reduced and GSSG, which is glutathione-oxidized arginine, it discloses a thiol pair that falls within that recited by this claim, Petitioner has demonstrated that challenged claim 17 is unpatentable as obvious over Schlegl and Hevehan.

Claim 18

Claim 18 depends from claim 1, and recites that "the incubation is performed under non-aerobic conditions." Ex. 1001, 18:46–47.

Petitioner asserts that one of ordinary skill knew at the time of the invention that aerobic conditions could impact the redox chemistry of the refolding reaction, as testified to by Dr. Robinson. Pet. 55, citing Ex. 1002 ¶ 148. Petitioner also observes that Hevehan describes solutions of reduced

DTT that were prepared immediately prior to each experiment to minimize air oxidation. Pet. 55 (citing Ex. 1004 at 2; Ex. 1028 (fermentation); Ex. 1020, 3 (also fermentation)).

Patent Owner urges that Petitioner incorrectly asserts that the combination of Schlegl and Hevehan teaches that "incubation is performed under non-aerobic conditions." Resp. 47. According to Patent Owner, Dr. Robinson testified during her deposition that Schlegl is "silent on the presence or absence of oxygen." *Id.* (citing Ex. 2019 at 54:20-55:2). Moreover, it is urged that Schlegl's figures make abundantly clear that the refolding tanks are open to air, i.e., under aerobic conditions. *Id.* (citing Ex. 1003 at Figures 1–3.

As for Hevehan, Patent Owner urges that the minimization of oxidation of DTT, a reductant, does not indicate that the refolding of the protein occurred under anaerobic conditions. Reply 47–48 (citing Ex. 2019 at 82:17-20). We agree with Patent Owner, the evidence cited in the Petition does not support a finding that Schlegl or Hevehan describe anaerobic conditions. In its Reply, Petitioner asserts that as DTT oxidation should be minimized, a person of ordinary skill in the art would have been motivated to eliminate oxygen from the refolding reaction. Reply 17. Petitioner fails however to address the open-tank reactors of Hevehan and Schlegl, which substantially undercuts its position.

Consequently, as Hevehan and Schlegl fail to describe anaerobic conditions for folding, we are not persuaded that Petitioner has demonstrated that challenged claim 18 is unpatentable as obvious over Schlegl and Hevehan.

Claims 19–24

Claim 19 depends from claim 1, and recites that the isolation comprises contacting the mixture with an affinity separation matrix. Ex. 1001, 18:48–49. Claim 20 depends from claim 19, and recites that the affinity separation matrix is a Protein A resin. Ex. 1001, 18:50–51. Claim 21 depends from claim 19, and further recites that the affinity resin is a mixed mode separation matrix. Ex. 1001, 18:52–53. Claim 22 depends from claim 1, and further recites that "the isolating comprises contacting the mixture with an ion exchange separation matrix." Ex. 1001, 18:54–56. Claim 23 depends from claim 1, and recites that "the isolating further comprises a filtration step." Ex. 1001, 18:57–58. Claim 24 depends from claim 23, and further recites that "the filtration step comprises depth filtration." Ex. 1001, 18:58–59.

Petitioner asserts that Claims 19–24 are directed to particular isolation methods, each of which were well known in the art at the time of the invention. . Pet. 55–56 (citing Ex. 1002 at ¶ 149). Petitioner urges that these standard methods and their usage are the result of routine optimization, and thus are not patentably distinguishing claim elements. *Id.* Additionally, Petitioner observes that Schlegl describes that protein is separated and purified according to methods known in the art, including, but not limited to, dialysis, filtration, extraction, precipitation and chromatography techniques. Pet. 56 (citing Ex. 1003 ¶ 65). Patent Owner does not meaningfully separately argue claims 19–24.

As Schlegl describes customary known isolation methods, which fall within the methods recited by these claims, and Dr. Robinson has testified to

these being known methods, we are persuaded that Petitioner has demonstrated that challenged claims 19–24 are unpatentable as obvious over Schlegl and Hevehan.

b. Obviousness of Claim 12 in View of Schlegl, Hevehan, and Hakim

Claim 12 depends from claim 1, and further recites that the protein is an Fc-protein conjugate. Ex. 1001, 18:23–24.

Petitioner asserts that a person of ordinary skill at the time the invention was made would have understood Hakim to teach that that the methods of Schlegl and Hevehan could be applied to an Fc-protein conjugate. Pet. 56–58, citing Dr. Robinson's testimony. Ex. 1002 ¶ 151.

Petitioner also observes that Hakim describes a method for producing a full-length antibody fusion protein using an E. coli expression system. Ex. 1006, Abstract.

Because Hakim was able to successfully obtain a full-length antibody fusion protein using an E. coli expression system, Petitioner concludes, based upon Dr. Robinson's testimony, that a person of ordinary skill in the art would have had a reasonable expectation of success in using the method described by Schlegl and Hevehan to produce a fusion protein with an antibody fragment because the Fc region is a smaller portion of a heavy chain, and an Fc-conjugate represents a polypeptide linkage between the Fc region and another protein. Pet. 57 (citing Ex. 1002 ¶ 152).

Patent Owner argues this ground separately. First, it urges that Patent Owner has antedated the Hakim reference. Resp. 50–60. Hakim is relied upon for the teaching of a fusion protein. Ex. 1006, Abstract. Thus, as Petitioner correctly observes, the Patent Owner's evidence of antedating

must credibly establish that AMG 745 is a fusion protein. We are told, that AMG 745 is an Fc protein conjugate. Resp. 52. We are pointed to a passage in Ex. 2026:

> Antimyostatin peptibody (AMG 745) is a novel antimyostatin peptibody. Structurally, it is a fusion protein with a human Fc at the N terminus and a myostatin-neutralizing bioactive peptide at the C terminus.

Ex. 2026, 2.

This description is contained in a 2014 journal article written by researchers who are not the listed inventors of the instant claimed invention. Dr. Hart also testifies that "the AMG 745 identified in the presentations is a protein (Claim 1) and is also a recombinant protein (Claim 7), a 'complex protein' (Claim 10), a multimeric protein (Claim 11), and an Fc-protein conjugate (Claim 12)." Ex. 2021 ¶ 35. He points us to Ex. 2024 at page 5 and Ex. 2022 at page 24. Neither of those exhibits appear to explain what AMG 745 actually is, and the origin and likely continuity of the nomenclature from 2008-2014. We have not been pointed to, nor found, persuasive testimony on this point. We have carefully reviewed the 2008 presentation (Ex. 2024) and are unable to discern sufficient description of AMG 745. Ex. 2022 is somewhat better, giving a model (Ex. 2022, 16) that resembles an antibody, but again no persuasive example of precisely what AMG 745 is.

We are cognizant of Dr. Hart's later testimony (Ex. 2021), and have carefully considered it in its entirety, including paragraphs 33 *et seq.* which

attempt to fill in the gaps of the documentary evidence. However, his testimony is somewhat conclusory. See, *e.g*. paragraphs 35 and 36.

We therefore are unpersuaded that the description in a later publication is sufficient to establish what AMG 745 was in 2008-2009.

In any event, we remain of the viewpoint that Dr. Robinson's testimony (e.g. Ex. 1002 ¶ 151; Ex. 2019, 61–62) is credible. Therefore, even if we do not consider Ex. 1006, we find one of ordinary skill would recognize that the methods of Schlegl could be applied to these types of protein molecules. Schlegl's own description that the methods can be applied to "any protein, protein fragment or peptide that requires refolding upon recombinant expression in order to obtain such protein in its biologically active form" Ex. 1003 ¶ 31 is very direct on this point and consequently very persuasive, despite Patent Owner's characterization of it as overbroad.

We therefore determine that Petitioner has demonstrated that claim 12 is unpatentable as obvious over Schlegl, Hevehan, and Hakim

IV. THE MOTIONS

Paper 17, a joint motion for protective order, requests entry of a protective order slightly modified relative to the Board's protective order. We have reviewed the motion and modified protective order, and find that the modifications are reasonable. Accordingly, the joint motion is GRANTED.

Paper 16 is Patent Owner's Motion to seal exhibits 2021, 2022, and 2024. Patent Owner asserts these are confidential business documents. We have reviewed the documents and, based upon Patent Owner's

representation, agree that their disclosure is not necessary. Accordingly, Patent Owner's Motion to Seal is GRANTED.

Paper 27 is Petitioner's Motion to seal portions of Ex. 1054, which is Dr. Hart's deposition transcript, and portions of the Reply (Paper 26) which rely upon the transcript. We have reviewed the transcript, and based upon Patent Owner's representation, agree that portions asserted to contain confidential information are not necessary to be disclosed. Accordingly, Petitioner's Motion to Seal is GRANTED.

Paper 31 is Patent Owner's Motion to Submit Supplemental Information. As the decision today does not rely upon the supplemental information, the motion is dismissed as moot. Paper 33, a motion to seal the supplemental information that would be submitted if Paper 31 were granted, is also DISMISSED as moot. The papers will remain in the file in confidential status until such time as the Board grants a request for expungement from Patent Owner, following the expiration of any appeal period.

Additionally, we have considered Patent Owner's Motion to seal portions of Exhibit 2059, 2061 (Paper 40), Amgen's Motion for Observations (Papers 41/42) and Amgen's Motion to Exclude (Papers 43/44). We have reviewed these documents, and based on Patent Owner's representation, we agree that the asserted confidential information is not necessary to be disclosed. Accordingly, Patent Owner's Motion to Seal is GRANTED.

Paper 50 is Patent Owner's Motion to Seal its Opposition to Petitioner's Motion to Exclude (Paper 51/52). We have reviewed these

documents and, based on Patent Owner's representation, we agree that the portions redacted in the public version (Paper 52) need not be disclosed. Accordingly, Patent Owner's Motion to Seal is GRANTED.

Paper 44 is Patent Owner's Motion to Exclude several items: (1) portions of Dr. Hart's deposition testimony concerning metadata. (Exhibit 1054) as irrelevant and prejudicial; (2) a construction of "non-aerobic conditions" after Petitioner's Reply as inadmissible; (3) arguments relating to human tissue-type plasminogen activator as new, irrelevant, and misleading; (4) Apotex's arguments and evidence regarding Hevehan's mention of HTTPA as new; (5) Apotex's reliance on Hevehan's mention of L-Arginine in relation to HTTPA as irrelevant, misleading, and confusing; and (6) Apotex's arguments as to the undesirability of oxygen during protein refolds in relation to Claim 18 as new. As we did not rely upon any of the foregoing in rendering this decision, this motion is DISMISSED as moot.

V. CONCLUSION

For the foregoing reasons, we determine that Petitioner has demonstrated that challenged claims 1–17 and 19–24 are unpatentable Petitioner, however, has not demonstrated that challenged claim 18 is unpatentable.

V. ORDER

Accordingly, it is ORDERED that:

Claims 1-11, 13-17 and 19-24 under 35 U.S.C. § 103(a) are unpatentable over Schlegl and Hevehan

Claim 12 under 35 U.S.C. § 103(a) is unpatentable over Schlegl, Hevehan, and Hakim.

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