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Paper 10
Entered: February 17, 2017

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.*

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

INTRODUCTION

Apotex, Inc. and Apotex Corp[1]. (collectively "Petitioner"), filed a Petition requesting an *inter partes* review of claims 1–24 of U.S. Patent No. 8,952,138 B2 ("the '138 patent"). Paper 2 ("Pet."). Amgen Inc. and Amgen Manufacturing Corp. (collectively "Patent Owner") filed a Preliminary Response. Paper 9 ("Prelim. Resp."). We have jurisdiction under 35 U.S.C. § 314 and 37 C.F.R. § 42.4(a).

For the reasons that follow, we *grant* the Petition.

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.[2] Pet. 2. Petitioner further cites to other matters including nonprovisional patent applications as related.[3] Pet. 2.

B. The '138 Patent (Ex. 1001)

The '138 patent is entitled "Refolding Proteins Using a Chemically Controlled Redox State." Ex. 1001, 1. The '138 patent states that the expression of recombinant proteins in the prior art prokaryotic systems is

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

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

problematic in that the expressed proteins are limited solubility precipitates called inclusion bodies, which are improperly folded proteins. *Id.* at 1:18–33.

According to the specification of the '138 patent, various 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.

Prior to the present invention, more complex molecules, such as antibodies, peptibodies and other large proteins, were said to be generally not amenable to detergent refold conditions and were typically refolded in so-called chaotropic refold solutions. 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. 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.* at 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, 17:46–59.

D. Prior Art Relied Upon

Petitioner relies upon 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
Brady	US 2006/0228329 A1	Oct. 12, 2006	Ex. 1005
Hakim[4]	"Inclonals" *mAbs*, 1:3, 281-287	June 2009	Ex. 1006

Petitioner also relies on the Declaration of Anne S. Robinson.

Ex. 1002.

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

E. Asserted Grounds of Unpatentability

Petitioner challenges claims 1–24 of the ’138 patent based on the following 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
1–7, 10, 13–17 and 23	§ 102(b)	Schlegl
1–7, 10, 12–17, 19, 22, and 23	§ 102(b)	Brady

II. ANALYSIS – OBVIOUSNESS GROUNDS

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 on combining known elements in the fashion claimed must articulate sufficient reasoning with rational underpinnings to combine teachings. *See KSR Int’l Co. v. Teleflex, Inc.*, 550 U.S. 398, 418 (2007).

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. 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, that is 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 a discipline and several years of industrial experience producing proteins in non-mammalian expression systems. Prelim. Resp. 18.

These two definitions are mostly consistent, but we tend more towards 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 of the area of protein refolding. We thus determine that 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. 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) (all holding that the

prior art of record may be probative of the level of ordinary skill in the art of the claimed invention).

A. 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).

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 nonnaturally 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 definition of "protein." Prelim. Resp. 12–13.

Buffer thiol-pair ratio "TPR"

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

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

Ex. 1001, 6:20-27.

Thiol-Pair buffer strength "BS"

The term "Thiol-Pair buffer strength" is interpreted to mean

2[oxidant] + [reductant].

Ex. 1001, 6:29-38.

refold mixture

The broadest reasonable interpretation for "refold mixture" is "a mixture formed from contacting [1] the protein with [2] the refold buffer." Ex. 1001, 17:50–57.

Patent Owner proposes to import from the specification the additional limitations concerning protein concentration, including that the refold mixture has a "'high protein concentration' … at or above about 1 g/L protein." Prelim. Resp. 13. We find no basis to impose that requirement. Claim 1 itself defines the term and what the refold mixture contains. We will not read additional limitations into the term.

complex protein

Patent Owner observes that the specification defines complex protein. Prelim. Resp. 16. In particular, the specification states:

> 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. We agree with Patent Owner that the specification has set forth this definition.

We need not interpret expressly any additional terms at this time.

C. Obviousness Grounds Based on Schlegl

Petitioner asserts two obviousness grounds of unpatentability that rely on Schlegl, combined with two other discrete references. A short summary of these references 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. Based on its publication date, Schlegl is prior art.

Schlegl describes methods for protein refolding, including the refolding and production of recombinant proteins. EX1003 at Abstract, ¶ [0004]. Schlegl utilizes a dilution method of protein refolding that results in a protein concentration up to 10 mg/ml. *Id*. at ¶¶ [0004]–[0008], [0016].

Schlegl teaches a continuous process, which 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.* at ¶¶ [0033]–[0061]. Schlegl teaches starting with a high concentration of unfolded protein before mixing. *Id*. at ¶ [0040].

Schlegl further describes a refolding buffer with a redox system having a defined thiol-pair ratio and redox buffer strength. *Id.* at ¶¶ [0036], [0041], [0075]. The refolding buffer also contains a denaturant, an aggregation suppressor, and/or a protein stabilizer. *Id.* at ¶¶ [0036], [0041], [0074]-[0075].

(2) Hevehan (Ex. 1004)

Hevehan and Clark, "Oxidative Renaturation of Lysozyme at High Concentrations," *Biotechnology and Bioengineering*, 1996, 54(3): 221-230 ("Hevehan") was published in 1996. Hevehan is prior art to the '138 Patent.

Hevehan describes refolding proteins 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, Hevehan observes 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%. Finally, Hevehan teaches that the refold mixture is incubated. *Id.* at 3.

(3) Hakim (Ex. 1006)

Hakim and Benhar, "Inclonals," *mAbs*, 2009, 1:3, 281-287 ("Hakim") was said to be published online on May 1, 2009. Hakim is prior art to the '138 Patent.

Hakim describes the production of fusion proteins. *Id.* at 4. Specifically, 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.*

(5) Analysis

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

Overview – Motivation to Combine

Petitioner initially asserts that one of ordinary skill in the art would be motivated to combine Schlegl and Hevehan related to protein refolding and would have had a reasonable expectation of success. 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, 2; Ex. 1002, ¶ 112.

Initially, we address the testimony of Anne S. Robinson, Ph. D. ("Dr. Robinson") (Ex. 1002). Dr. Robinson appears 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. This testimony is credible at this stage of the proceeding.

Petitioner is of the view that a person of ordinary skill in the art would have known that the refolding methods of Hevehan and Schlagl 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, asserts that Schlegl and Hevehan are fundamentally different and incompatible approaches to protein refolding. Prelim. Resp. 33. Schlegl's method is said to be a "mechanical approach" to achieve protein refolding at dilute protein concentrations. *Id., citing* Ex. 2001, ¶¶ 93, 111.

We turn aside briefly to discuss the declaration testimony of Richard C. Willson, Ph. D. ("Dr. Willson") Exhibit 2001. Dr. Willson appears 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 assertions. We note, however, that our rules provide that "a genuine issue of material fact created by such testimonial evidence will be viewed in the light most favorable to the petitioner solely for purposes of deciding whether to institute an *inter partes* review." 37 C.F.R. § 42.108(c). Accordingly, we resolve any disputed factual issues in the parties' declarations in Petitioners' favor at this stage.

According to the Patent Owner, Hevehan's method is a different approach – *i.e.,* 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.* at ¶ 112. By contrast, 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.*

On the present record, we determine that Petitioner have the better position as to whether one of ordinary skill in the art at the time the

invention was made would have combined the references. Schlegl's dilution approach itself suggests customizing the refolding buffer to be used for a particular protein. *Id.* at [0036], as well as the addition of refolding additives such as redox systems. *Id.* at [0041]. Hevehan optimizes those redox systems. Ex. 1004, 2.

We next turn to an analysis of the claimed subject matter against 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:*

Petitioners assert that Schlegl describes refolding of recombinant proteins expressed using nonmammalian expression systems such as bacterial and yeast expression systems. Pet 43., citing Ex. 1003, ¶ [0004]. 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. *Id.*, citing Ex. 1003, ¶ [0075].

> *(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;*

Petitioner asserts that the Example in Schlegl discloses contacting bovine α-lactalbumin 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, ¶ [0075]. 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, ¶ 124.

Importantly, Petitioners assert that this redox component has a thiol-pair ratio of 2 and a redox buffer strength of 6 mM. Pet. 45, citing Ex. 1003, ¶¶ [0036], [0075]. Dr. Robinson testifies to this fact. Ex. 1002, ¶ 124.

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, 6. Petitioners urge 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. 1004, 5.; Ex. 1002, ¶ 124.

Patent Owner strenuously urges that this conclusion has no evidentiary foundation. More specifically, relying on Dr. Willson, they urge that Apotex submits no evidence from Schlegl's disclosure reflecting a calculation of TPR and RBS based on a volume of a redox component. Prelim. Resp. 29, citing Ex. 2001, ¶¶ 101-102.

We turn first to the testimony of Dr. Robinson. Paragraph 124 of her testimony states that:

> a person of skill in the art would understand that the addition of cysteine and cysteine [sic – cystine] here serve as the redox system or redox component for bovine α- lactalbumin. That redox component has a thiol-pair ratio of 2 and a redox buffer strength of 6 mM. EX1003 at ¶ [0036] ("Denatured and reduced aliquots at 16.5 mg/ml

> are rapidly diluted (batch-dilution) 32 fold into renaturation buffer consisting of 100 mM Tris-HCl, 5 mM CaCl2, 2 mM cystine and 2 mM cysteine . . . .").

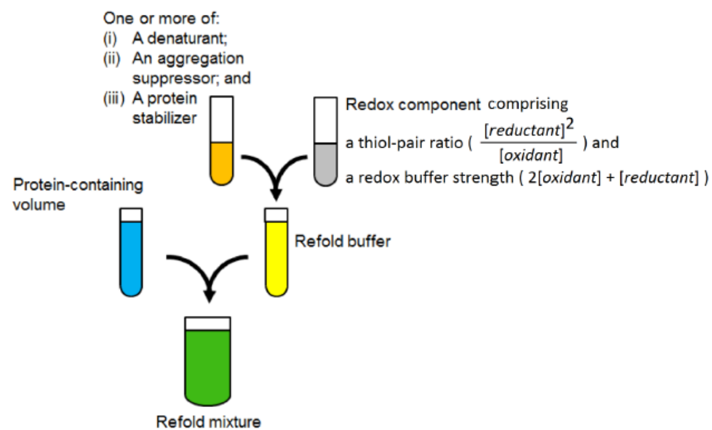
Ex. 1002, ¶ 124.

Dr. Robinson explains her calculations earlier in her declaration. Ex. 1002, ¶ 60, n. 3, 4. She also observes that the ratios of the thiol pair will be the same in the redox component and the buffer. *Id.* at n. 3.

RBS=2[cystine(2mM)]+[cysteine(2mM)]=6mM. *Id.* at n. 3.

$$TPR = \frac{[cysteine]^{2}}{[cystine]} = \frac{[2mM]^{2}}{[2mM]} = 2mM.$$ *Id.* at n. 4.

Patent Owner asserts that the calculations are flawed in that Schlegl teaches concentrations of redox chemicals in the refold buffer ("renaturation buffer") with no mention of their concentrations in a redox component. Prelim. Resp. 30. Patent Owner has provided an illuminating diagrammatic representation of the claim to illustrate the point, reproduced below.



Prelim. Resp. 12.

The main thrust of Patent Owner's argument is that as TPR and RBS are based upon the redox component, Petitioner has mistakenly conflated the refold buffer with the redox component. Prelim. Resp. 29–30.

We disagree with Patent Owner's narrow interpretation of claim 1. Nowhere in claim 1 must there be a separate solution of "redox component" having a discrete volume and the "one or more of" components (i), (ii), and (iii) having a discrete volume. Rather, the broadest reasonable reading of the redox "component" is as a component portion of the refold buffer overall.

Looking, for example, at one of the specification's exemplary embodiments, a protein is contacted with a "refold buffer comprising a denaturant, an aggregation suppressor, a protein stabilizer and a redox component, wherein the redox component has a final thiol-pair ratio (as defined herein) having a range of 0.001 to 100 . . . and a Thiol-pair buffer strength (as defined herein) equal to or greater than 2 mM…" Ex. 1001, 10:22–30. We do not discern, and are not pointed to any discussion about,

the necessity of creating separate volumes of components in the specification or examples of the '138 patent itself, let alone as a distinct claim element. The refold buffer itself comprises a redox *component* to the buffer, as recited in claim 1.

As for Hevehan, Patent Owner states that Hevehan does not teach or suggest concentrations of reductant or oxidant in a redox component. Prelim. Resp. 35, citing Ex. 2001, ¶ 114. The argument made against Hevehan is similar to that made against Schlegl – that Dr. Robinson mistakenly conflated redox component and refold mixture. *Id.*

Patent Owner notes that Hevehan reports that, in the final refold mixture, "DTT[(a reductant] and GSSG [an oxidant] concentrations were varied between 1 and 6 mM and 4 and 13 mM, respectively." Prelim. Resp. 35-36, citing Ex. 1004, 5; Ex. 2001, ¶116.

Accordingly, Patent Owner urges that Dr. Robinson's Hevehan-related calculations are based only on concentrations in a refold mixture and not concentrations in a redox component as required by Claim 1. *Id.*at 36, citing Ex. 2001, ¶¶ 115, 117.

Dr. Willson testifies that Claim 1 makes clear that the refold mixture and redox component are two separate and distinct elements with different volumes. Given the different volumes, the concentrations of oxidant and reductant in the redox component and refold mixture are not the same. Thus, Patent Owner reasons that Dr. Robinson and Apotex never properly calculate the claimed TPR and RBS using the volume of a redox component in accordance with the agreed definition of TPR and RBS. Ex. 2001, ¶ 117.

We do agree with Patent Owner that claim 1 initially recites the protein to be present in a volume at a concentration of 2.0 g/L or greater, as recited in the preamble of claim 1. Step (a) of the claimed method then requires the *protein* to be contacted with the refold buffer comprising recited elements.

How that contact occurs is not relevant to the scope of the claimed subject matter. Indeed, the Schlegl method of local dilution is an example of how that might happen. Ex. 1003. *See especially* ¶¶ [0033-35]. Depending on flow rates, the local dilution can be as much as 1:50,000.

Petitioner states that this dilution means that (1) the thiol-pair ratio of a refold buffer in a dilution refolding method is the same as the thiol-pair ratio of a refold mixture after contact with a protein regardless of dilution (Pet. 45); and (2) the redox buffer strength of a refold buffer in a dilution refolding method is necessarily higher than the redox buffer strength of a refold mixture after contact with a protein. *Id.* at 46.

This position is supported by the testimony of Dr. Robinson. She testifies:

> This is because the refold buffer can only become more diluted after contact with the protein and, as a result, the redox buffer strength can only be reduced (weakened) by contact with the protein. Therefore, Schlegl teaches a person of skill in the art to use a redox buffer strength of greater than 6 mM in the refold mixture. *See* EX1003 (Schlegl) at ¶ [0075]. Similarly, *Hevehan* teaches a person of skill in the art to use a redox buffer strength of greater than 5 mM to 19 mM in the refold mixture. *See* EX1004 (*Hevehan*) at 5.

Ex. 1002, ¶ 126.

Patent Owner asserts that Dr. Robinson "miscalculates TPR and RBS with concentrations of reductant and oxidant based on the volume of the refold buffer or refold mixture— not the redox component. There is no justification for Apotex's approach." Prelim. Resp. 3. Patent Owner continues that Petitioner does "not demonstrate how the claimed TPR based on the volume of a redox component can be extrapolated from its calculation of TPR based on the volume of a refold buffer or a refold mixture." *Id.*

To the contrary, Dr. Robinson did explain her rationale for determining the concentrations and ratios. We find her testimony to be credible and persuasive at this stage in the proceeding. Dr. Willson testifies that calculating the TPR in a volume other than that of a redox component does not establish that the final TPR has a range of 0.001-100 of claim 1. Ex. 2001, ¶ 90. But, Dr. Willson relies on a concentration that falls outside the claim language. *Id.* at ¶ 89. We are not persuaded at this time by Dr. Willson's testimony, as Dr. Robinson's calculations to the contrary are based upon the actual described examples with an explanation as to why they can be adjusted for dilution. If necessary, this issue can be more fully developed during a trial on the merits.

As to the remaining "one or more of" components, Petitioner asserts that Schlegl discloses a refold buffer containing guadinium chloride, DTT and optionally a redox system (e.g., GSH/GSSG), EDTA, detergents, salts, and refolding additives like L-arginine. Pet. 47, citing Ex. 1003, ¶ [0036].

(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, ¶¶ [0016], [0060].

(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, ¶¶ [0039], [0065].

We find Petitioner's initial contentions to be persuasive. As a consequence, we are persuaded that Petitioner has demonstrated a reasonable likelihood of prevailing on its assertion that challenged 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, 17:59–18:2.

Petitioner asserts that Schlegl describes contacting the protein with a refold buffer with a thiol-pair ratio of 2. Pet. 49, citing Ex. 1003, ¶ [0075]. 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 final TPR in Schlegl and Hevehan appears to fall within the claimed range of claim 2, we are persuaded that Petitioner has demonstrated a reasonable likelihood of prevailing on its assertion 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, ¶ [0075]. 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 a reasonable likelihood of prevailing on its assertion 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 recites that the form is an inclusion body. *Id.* at 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, ¶ [0006]. 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 final inclusion bodies in Schlegl and Hevehan appear to 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 a reasonable likelihood of prevailing on its assertion 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, 18:10–12.

Petitioner asserts that Schlegl describes a method of refolding a protein, in which the protein, prior to refolding, is dissolved as a protein solution. Pet. 53, citing Ex. 1003, ¶¶ [0016], [0063].

Patent Owner does not separately argue claim 6.

As the protein solution in Schlegl appears to fall within the soluble form of claim 6, we are persuaded that Petitioner has demonstrated a reasonable likelihood of prevailing on its assertion that 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, 18:12–13. Claim 8 depends from claim 1 and further recites that the protein is an endogenous protein. *Id.* at 18:14–15. Claim 9 depends from claim 1, and further recites that the protein is an antibody. *Id.* at 18:16–17. Claim 10 depends from claim 1, and further recites that the protein is a complex protein. *Id.* at 18:18–19. Claim 11 depends from claim 1, and recites that the protein is a multimeric protein. *Id.* at 18:20–21.

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, ¶ [0031]. 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, 281.

Patent Owner does not materially argue the limitations of claims 7 and 8. Prelim. Resp. 43–44. Patent Owner does make arguments for claims 9, 10, and 11. *Id.* at 44.

Patent Owner urges that none of the refolded proteins of Schlegl and Hevehan are complex proteins as recited in claim 10. Prelim. Resp. 44. While this is true, the grounds is based on obviousness, not anticipation. The Petition asserts that that one of ordinary skill in the art would immediately recognize that the methods of Schlegl could be applied to those types of molecules.

Patent Owner asserts a similar argument for claims 9 and 11 because none of the refolded proteins in Schlegl and Hevehan qualify as "antibod[ies]" (Claim 9) or "multimeric protein[s]" (Claim 11). Prelim. Resp. 46. We think that the description in Schlegl paragraph 31 that the protein is broadly defined includes such complex proteins. *See* Ex. 1003 ¶ 31 ("A 'protein' in the meaning of the present invention is any protein, protein fragment or peptide that requites refolding upon recombinant expression in order to obtain such protein in a biologically active form.").

Consequently, as the proteins described in Schlegl appear to fall within the types recited by these claims, or there is sufficient evidence at this stage that they likely would have been obvious to those of ordinary skill, we are persuaded that Petitioner has demonstrated a reasonable likelihood of prevailing on its assertion 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, ¶ [0004].

Patent Owner does not separately argue claim 13.

As the expression systems described in Schlegl appears to fall within the types recited by these claims, or there is sufficient evidence at this stage that they likely would have been obvious to those of ordinary skill, we are

persuaded that Petitioner has demonstrated a reasonable likelihood of prevailing on its assertion 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 ethyl urea. Ex. 1001, 18:27–29.

Petitioner asserts 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, ¶ [0064].

Patent Owner does not separately argue claim 14.

As the denaturant described in Schlegl appears to fall within the types recited by this claim, we are persuaded that Petitioner has demonstrated a reasonable likelihood of prevailing on its assertion that challenged claim 14 as 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, 18:30–34.

Petitioner asserts that Schlegl describes refolding buffers that 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. Pet. 50, citing Ex. 1003, ¶¶ [0036] and [0041].

Patent Owner does not separately argue claim 15.

As Schlegl appears to describe arginine, which falls within the stabilizers recited by this claim, we are persuaded that Petitioner has demonstrated a reasonable likelihood of prevailing on its assertion that challenged claim 15 as 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, 18:35–41.

Patent Owner does not separately argue claim 16.

As Schlegl appears to describe arginine, which falls within the aggregation suppresors recited by this claim, we are persuaded that Petitioner has demonstrated a reasonable likelihood of prevailing on its assertion that challenged claim 16 as 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 beta-mercaptoethanol. Ex. 1001, 18:42–44.

Petitioner asserts that 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, ¶ [0041].

Patent Owner does not separately argue claim 17.

As Schlegl appears to describe GSH, which is glutathione-reduced and GSSG, which is glutathione-oxidized arginine, which falls within the thiol pairs recited by this claim, we are persuaded that Petitioner has demonstrated a reasonable likelihood of prevailing on its assertion that challenged claim 17 as 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, 18:45–46.

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, 2; Ex. 1028 (fermentation); Ex. 1020. *See also* p.3 (also discussing fermentation).

Patent Owner does not separately argue claim 18.

As Hevehan and other cited art appears to describe anaerobic conditions for unfolding, which falls within the method recited by this claim, we are persuaded that Petitioner has demonstrated a reasonable likelihood of

prevailing on its assertion 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, 18:47–48. Claim 20 depends from claim 19, and recites that the affinity separation matrix is a Protein A resin. Ex. 1001, 18:49–50. Claim 21 depends from claim 19, and further recites that the affinity resin is a mixed mode separation matrix. Ex. 1001, 18:51–53. Claim 22 depends from claim 1, and further recites that the isolating comprises contacting the mixture with an ion exchange separation matrix. Ex. 1001, 18:53–56. Claim 23 depends from claim 1, and recites that the isolating further comprises a filtration step. Ex. 1001, 18:56–57. Claim 24 depends from claim 23, and further recites that the filtration step comprises depth filtration. Ex. 1001, 18:58–59.

Petitioner asserts that, as 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, ¶ 149. Petitioners urge that these standard methods and their usage are the result of routine optimization, and thus are not patentably distinguishing claim elements. *Id.* Additionally, Petitioners observe 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, ¶ [0065].

Patent Owner does not separately argue claims 19–24.

As Schlegl appears to describe the customary known isolation methods, which appear to 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 a reasonable likelihood of prevailing on its assertion that challenged claims 19–24 as unpatentable as obvious over Schlegl and Hevehan.

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

Claim 12 depends from claim 1, and further recites that the protein is an Fc-protein conjugate. Ex. 1001, 18:22–23.

Petitioners assert 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, Petitioners conclude, 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. However, the position is that while Hakim describes refolding of its IgG-toxin fusion proteins that are expressed in non-mammalian E. coli expression systems, it does not teach or suggest the claimed 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. Prelim Resp. 40.

As we have found that Petitioner persuasively relies upon Schlegl and Hevehan to meet that element, and as Hakim describes a fusion protein, which appears to fall within claim 12, we are persuaded that Petitioner has demonstrated a reasonable likelihood of prevailing on its assertion that challenged claim 12 as unpatentable as obvious over Schlegl, Hevehan, and Hakim.

IV. ANALYSIS - ANTICIPATION GROUNDS

a. *Claims 1-7, 10, 13-17, and 23 Under 35 U.S.C. § 102(b) over Schlegl*

Petitioner, in two paragraphs on page 58 of the Petition, asserts that "[e]ach element of claims 1-7, 10, 13-17, and 23 of the '138 Patent comes from a general teaching in Schlegl or from the Example at pages 5-6. Thus, the elements of the claims of the '138 Patent do not come from different embodiments disclosed in *Schlegl*." Pet. 58. We are then referred to previous sections of the Petition.

This approach fails to comply with 37 C.F.R. §42.104. This ground is directed towards a separate statutory ground of unpatentability. As a

consequence, we decline to institute on this ground. We will not undertake to parse from the reasoning and rationale applied throughout the earlier sections of the Petition on obviousness to arrive at those that only apply to the different standard required for anticipation.

b. Claims 1-7, 10, 12-17, 19, 22,and 23 Under 35 U.S.C. § 102(b) over Brady

Petitioner asserts that claims 1-24 are unpatentable under 35 U.S.C. § 102(b) over Brady only if the phrase "a protein … present in a volume at a concentration of 2.0 g/L or greater" is interpreted to mean "a protein as it exists in a volume before contacting the volume with a refold buffer." Pet. 58-59.

As we do not so interpret the claim, and have otherwise instituted on all claims on a different ground, we need not reach this ground. Accordingly, we exercise our discretion not to institute on this ground.

IV. CONCLUSION

For the foregoing reasons, we determine that Petitioner has demonstrated a reasonable likelihood of prevailing on its assertion that challenged claims 1-24 are unpatentable over Schlegl, Heveham, and Hakim.

The Board has not made a final determination on the patentability of any challenged claims. The Board's final determination will be based on the record as fully developed during trial.

V. ORDER

Accordingly, it is:

ORDERED that pursuant to 35 U.S.C. § 314, an *inter partes* review is hereby instituted as to the challenged claims of the ’138 patent on the following grounds:

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

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

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(d) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial; the trial commencing on the entry date of this decision; and

FURTHER ORDERED that no other ground of unpatentability alleged in the Petition for any claim is authorized for this *inter partes* review.

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