UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

APOTEX INC. and APOTEX CORP.
Petitioners

v.

AMGEN INC. and AMGEN MANUFACTURING LIMITED
Patent Owner

Inter Partes Review No.: IPR2016-01542
U.S. Patent No. 8,952,138

REPLY TO PATENT OWNER RESPONSE

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UPDATED EXHIBIT LIST

Exhibit	*Description*
1001	Shultz et al., U.S. Patent No. 8,952,138, "Refolding Proteins Using a Chemically Controlled Redox State," issued February 10, 2015.
1002	Declaration of Dr. Anne S. Robinson.
1003	Schlegl, U.S. Patent Publication No. 2007/0238860, "Method for Refolding a Protein," published October 11, 2007 ("*Schlegl*").
1004	Hevehan and Clark, "Oxidative Renaturation of Lysozyme at High Concentrations," Biotechnology and Bioengineering, 1996, 54(3): 221-230 ("*Hevehan*").
1005	Brady et al., U.S. Patent Publication No. 2006/0228329, "Homogenous Preparations of IL-31," published October 12, 2006 ("*Brady*").
1006	Hakim and Benhar, "Inclonals," mAbs, published online May 1, 2009, 1:3, 281-287 ("*Hakim*").
1007	Whitford, "Proteins: Structure and Function," September 1, 2005, excerpted.
1008	http://chemistry.umeche.maine.edu/CHY431/Ribo-fold.jpg
1009	*Reserved*
1010	Cohen et al., U.S. Patent No. 4,237,224, "Process for Producing Biologically Functional Molecular Chimeras," issued December 2, 1980.
1011	Cohen et al., U.S. Patent No. 4,468,464, "Biologically Functional Molecular Chimeras," issued August 28, 1984.
1012	Cohen et al., U.S. Patent No. 4,740,470, "Biologically Functional Molecular Chimeras," issued April 26, 1988.
1013	Johnson, "Human insulin from recombinant DNA technology". Science (1983) 219 (4585): 632–637.

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1014	Vallejo et al., "Strategies for the recovery of active proteins through refolding of bacterial inclusion body proteins," Microbial Cell Factories (2004) 3, 1-12.
1015	Neubauer et al., "Protein inclusion bodies in recombinant bacteria. Inclusions in Prokaryotes." Microbiology Monographs Edited by: Shively JM. Springer; (2006) 237-292.
1016	Ventura and Villaverde, "Protein quality in bacterial inclusion bodies" TRENDS in Biotechnology Vol.24, No.4 April 2006.
1017	https://www.profacgen.com/inclusion-body-purification-protein-refolding.htm
1018	Georgiou and Valax, "Isolating Inclusion Bodies from Bacteria", Chapter 3 in Methods in Enzymology, VOL. 309, p. 48-58 (1999) Academic Press.
1019	Palmer and Wingfield, "Preparation and Extraction of Insoluble (Inclusion-Body) Proteins from *Escherichia coli*" Curr Protoc Protein Sci. (2004) November; CHAPTER: Unit–6.3. doi:10.1002/0471140864.ps0603s38
1020	Clark, "Protein Refolding for Industrial Processes," Current Opinion in Biotechnology, (2001) 12:202-207.
1021	Clark, "Refolding of Recombinant Proteins" Current Opinion in Biotechnology, (1998) 9:157-163.
1022	Shortle et al., "Clustering of Low-Energy Conformations Near the Native Structures of Small Proteins," Proc Natl Acad Sci (1998) 95, 11158-62.
1023	Panda, "Bioprocessing of Therapeutic Proteins from the Inclusion Bodies of Escherichia coli" Adv Biochem Engin/Biotechnol (2003) 85: 43–93.
1024	Vincentelli, "High-throughput automated refolding screening of inclusion bodies," Protein Science (2004) 13:2782–2792.

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1025	Willis et al., "Investigation of protein refolding using a fractional factorial screen: A study of reagent effects and interactions." Protein Science (2005) 14(7), 1818–1826.
1026	Jungbauer and Kaar, "Current status of technical protein refolding," Journal of Biotechnology 128 (2007) 587–596.
1027	Ferrer-Miralles et al., "Microbial factories for recombinant pharmaceuticals" Microbial Cell Factories (2009) 8:17
1028	Graumann and Premsaller, "Manufacturing of recombinant therapeutic proteins in microbial systems," Biotech J. (2006) 1:164-186.
1029	Xie and Wetlaufer, "Control of aggregation in protein refolding: The temperature-leap tactic," Protein Science (1996) 5:517-523.
1030	Puri, "Refolding of recombinant porcine growth hormone in a reducing environment limits in vitro aggregate formation," FEBS (1991) vol. 292, no. 1.2, 187-190.
1031	Ejima, "High yield refolding and purification process for recombinant human interleukin-6 expressed in *Escherichia coli*," Biotechnology and Bioengineering (1999) vol. 62, no. 3, 301-310.
1032	Patra et al., "Optimization of inclusion body solubilization and renaturation of recombinant human growth hormone from *Escherichia coli*," Protein Expression and Purification (2000) 18, 182-192.
1033	Builder et al., U.S. Patent No. 5,663,304, "Refolding of misfolded insulin-like growth factor-1," issued September 2, 1997.
1034	Notice of Allowance, U.S. Patent Application No. 12/820,087 (now Patent No. 8,952,138), mailed October 23, 2014.
1035	Information Disclosure Statement, U.S. Patent Application No. 12/820,087 (now Patent No. 8,952,138), filed September 23, 2010.
1036	Information Disclosure Statement, U.S. Patent Application No. 12/820,087 (now Patent No. 8,952,138), filed September 20, 2012.

Exhibit	*Description*
1037	Markman Order, Amgen v. Apotex, Case no. 0:15-cv-61631-JIC, Document 119, entered April 7, 2016.
1038	Amgen Opening Markman Brief, Amgen v. Apotex, Case no. 0:15-cv-61631-JIC, Document 77, filed December 11, 2015.
1039	Information Disclosure Statement, U.S. Patent Application No. 12/820,087 (now Patent No. 8,952,138), filed October 20, 2010.
1040	Acknowledgement of consideration of references, U.S. Patent Application No. 12/820,087 (now Patent No. 8,952,138), January 9, 2012.
1041	Clark et al., "Oxidative renaturation of hen egg-white lysozyme. Folding vs Aggregation," Biotechnol. Prog. (1998) 14, 47-54.
1042	Mannall et al., "Factors Affecting Protein Refolding Yields in a Fed-Batch and Batch-Refolding System," Biotechnology and Bioengineering, (2007) vol. 97, no. 6, 1523-1534.
1043	Fischer et al., "Isolation, Renaturation, and Formation of Disulfide Bonds of Eukaryotic Proteins Expressed in *Escherichia coli* as Inclusion Bodies," Biotechnology and Bioengineering (1993) vol. 41, pp 3-13.
1044	Misawa and Kumagai, "Refolding of Therapeutic Proteins Produced in Escherichia coli as Inclusion Bodies" Biopoly (1999) 51: 297–307.
1045	Protein Data Bank, Hen Egg White Lysozyme, http://www.rcsb.org/pdb/explore/explore.do?structureId=193L; http://www.rcsb.org/pdb/explore/remediatedSequence.do?structureId=193L.
1046	Gegg et al., U.S. Patent No. 7,442,778, "Modified Fc Molecules," issued October 28, 2008.
1047	Enbrel™ (etanercept) label, November 1998.
1048	Bolado, "Amgen Opens Trial in Fight Over Neulasta Generic," Law360, July 11, 2016 (http://www.law360.com/articles/814748/amgen-opens-trial-in-fight-over-neulasta-generic).

Exhibit	*Description*
1049	Dr. Anne S. Robinson CV
1050	http://pubs.rsc.org/services/images/RSCpubs.ePlatform.Service.FreeContent.ImageService.svc/ImageService/Articleimage/2014/TB/c4tb00168k/c4tb00168k-f2_hi-res.gif
1051	Petitioners' Notice of Deposition of Dr. Willson, marked during deposition.
1052	Handwritten Drawing/Calculations by Dr. Willson, marked during deposition.
1053	Schlegl, U.S. Patent No. 7,651,848, "Method for Refolding a Protein," issued January 26, 2010.
1054	Deposition transcript of Dr. Roger Hart, August 3, 2017.
1055	Deposition transcript of Dr. Richard C. Willson, August 9, 2017.
1056	Second Declaration of Dr. Anne Robinson.
1057	Pan et al., "Engineering batch and pulse refolding with transition of aggregation kinetics: An investigation using green fluorescent protein (GFP)," Chemical Engineering Science, 131 (2015) 91-100.
1058	Excerpt of Transcript of Bench Trial held on 7/11/2016, *Amgen Inc. et al. v. Apotex Inc. et al.*, Case no. 0:15-cv- 61631-JIC, Dkt. 250.
1059	Majidzadeh et al, "Human Tissue Plasminogen Activator Expression in *Escherichia coli* using Cytoplasmic and Periplasmic Cumulative Power," Avicenna Journal of Medical Biotechnology, (2010) 2:131-136.
1060	Excerpt of Prosecution History of U.S. Application No. 11/695,950 to Schlegl, Declaration of Dr. Berkemeyer.
1061	Kuwajima, K., "The molten globule state of α-lactalbumin," FASEB J, (1996)10:102-109.

Exhibit	*Description*
1062	Web of Science database results of August 21, 2017 re Hevehan and Clark, "Oxidative Renaturation of Lysozyme at High Concentrations," Biotechnology and Bioengineering, 1996, 54(3): 221-230.
1063	Web of Science database results of August 21, 2017 re Buswell et al., "A New Kinetic Scheme for Lysozyme Refolding and Aggregation," Biotechnology and Bioengineering, 83(5), pp. 567-577 (September 5, 2003)
1064	Thatcher, D., "Recovery of therapeutic proteins from inclusion bodies: problems and process strategies," Biochemical Society Transactions (1990)18(2)234-235.
1065	Roberts, "Non-Native Protein Aggregation Kinetics" Biotechnology & Bioengineering, (2007) 98(5)927-938.

I. Introduction

It has long been known that refolding of proteins requires, among other things, balancing appropriate concentrations of reductant and oxidant in the solution containing the proteins to be refolded. EX1002, ¶50; EX1044, 5; EX2001, ¶56; EX1056, ¶9. The entirety of the alleged invention in the '138 patent is the creation of two arbitrary—and remarkably simple—formulae describing how one might do this balancing and selecting concentrations of reductant and oxidant for refolding. *E.g.*, EX1001, 4:12-15, 4:4-8, 4:39-45; *also* Patent Owner Response ("POR"), 10-13; EX2001, ¶58; EX2020, ¶20 ; EX1056, ¶8. Formulae standing alone are not patentable, of course. But, in any event, the art of record unequivocally discloses concentrations of reductant and oxidant that fall within the ranges claimed by these formulae. Pet., 45, EX1002, ¶124, EX1003, [0075]; EX1004, 5; EX1056, ¶60; Institution Decision (Paper 10)("Inst."), 15-16. This alone rebuts Patent Owner's central argument.

Patent Owner and its expert, Dr. Willson, ignore these disclosures of the prior art and allege that the claims of the '138 patent are still patentable because of four things: (1) the formulae for thiol-pair ratio and redox buffer strength are not explicitly disclosed in the prior art; (2) a purported lack of motivation to combine the references, (3) the fact that the methodology disclosed in the '138 patent was intended to be used with high-concentration protein solutions, and (4) the manner

in which the formulae were developed. For the reasons discussed below, none of these reasons is persuasive.

II. Claim Construction

In its Institution Decision, the Board construed "complex protein" to mean "[t]he 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" Inst., 10 (emphases in original). The Board directly copied this definition from a single portion of the specification of the '138 patent. Ex1001, 12:58-61. Petitioners respectfully disagree with the Board's construction, because the specification actually contains a broader recitation of "complex protein" at col 4, lines 23-27 that need only satisfy a single characteristic:

> 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)....

(Emphases added). This definition is the broadest reasonable interpretation of the term in light of the entirety of the specification, rather than a single embodiment in it. EX1056, ¶¶5-7.

III. Argument

A. Patent Owner's Arguments Regarding the Formulae Misstates the Law

Patent Owner argues that Schlegl and Hevehan cannot render any of the claims of the '138 patent obvious because neither reference discloses the formulae for thiol-pair ratio and redox buffer strength. POR, 22-23; EX1055, 67:18-68:6. Patent Owner's position is wholly unsupported and misstates the law.

Claim 1 recites, among other things, a "final thiol-pair ratio having a range of 0.001 to 100 and a redox buffer strength of 2 mM or greater." The question for the Board is whether Schlegl and Hevehan disclose these limitations. While the drafters of the '138 patent defined the terms "thiol-pair ratio" ("TPR") and "redox buffer strength" ("RBS") mathematically, rather than in words, it makes no difference. The analysis for the Board is simply to determine whether the prior art teaches a TPR and RBS within the range of the claim. EX1056, ¶¶10-13.

It is well-established that where ranges in a claim "'overlap or lie inside ranges disclosed by the prior art' a *prima facie* case of obviousness exists." *In re Wertheim,* 541 F.2d 257 (CCPA 1976); *In re Woodruff,* 919 F.2d 1575 (Fed. Cir. 1990); *In re Geisler*, 116 F.3d 1465, 1469-71, (Fed. Cir. 1997); MPEP 2144.05. Furthermore, "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." *In re Aller*, 220 F.2d. 454, 456 (CCPA 1955); *In re Peterson,*

315 F.3d 1325, 1330, ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); and MPEP 2144.05(II)(A). And finally, there is a motivation for a person of skill in the art to optimize result-effective variables. MPEP 2144.05(II)(B); *In re Antonie*, 559 F.2d. 618 (CCPA 1977) ("a particular parameter must first be recognized as a result-effective variable, *i.e.*, a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation").

In order to rebut the *prima facie* case of obviousness, Patent Owner would have had to demonstrate a criticality of the claimed range relative to the range disclosed in the prior art. *In re Woodruff,* 919 F.2d 1575, (Fed. Cir. 1990); MPEP 2144.05(III)(A). Fatally, Patent Owner has not even attempted to do so.

B. There Is Ample Motivation To Combine the Teachings of Schlegl and Hevehan

Patent Owner and Dr. Willson take the nonsensical position that a person of skill in the art, looking to refold a protein, would look only at *either* a chemical approach or a mechanical approach to refolding, and would not consider them in combination. EX2020, ¶37 (quoting EX2001, 111). In taking this position, Patent Owner ignores entire—important—sections of the prior art and, more

fundamentally, the basic and well-known requirements of protein refolding. EX1056, ¶¶14-15.

Contrary to Patent Owner's position, the approaches of Schlegl and Hevehan actually complement one another. Schlegl teaches the application of dilution techniques to protein refolding, which optimize the flow rate of the refolding process. EX1056, ¶¶22, 44. As noted by the Board, the method of local dilution used by Schlegl is an example of how the protein may be contacted with the refold buffer, consistent with step (a) of claim 1 of the '138 patent. Inst., 20; *also* EX1056, ¶¶19-21 (discussing Hevehan's own application of the optimization of refolding conditions to standard dilution methods, at EX1004, 2-3). But simply diluting concentrations of protein will not result in successful refolding to the bioactive form. A chemical reaction must occur. EX1056, ¶16. To this end, Schlegl discloses the use of redox components in a refold buffer. EX1056, ¶17. In fact, in addition to using redox components in the refold buffer, Schlegl provides an example that is directed to oxidative refolding, *i.e.*, the formation of disulfide bonds during refolding by oxidizing the cysteine amino acids. EX1056, ¶¶17, 23; EX1003, [0074]-[0075], [0079]-[0080]. In the example, Schlegl teaches "removing 100 µl samples at specific time intervals and quenching the formation of disulfide bonds." *Id*; see also EX1056, ¶24 (discussing that claim 9 of Schlegl, directed to incubation until the protein is "completely present in its biologically

active form" cannot be practiced without redox chemistry). Thus, Schlegl teaches the use of redox chemistry in protein refolding, and in fact suggests customizing the refold buffer. EX1056, ¶17; EX1003, [0036]. Hevehan teaches the optimization of refolding conditions, including explaining the importance of the redox parameters in refolding protein at high concentrations. EX1056, ¶¶14, 18.

Patent Owner further argues that Schlegl dilutes to a low concentration of protein, which is incompatible with the high concentrations of Hevehan. While being a direct acknowledgment that Hevehan teaches refolding protein at high concentrations, this position ignores the high concentration refolding of Schlegl. Section III(C), below.

1. Refolding of Model Proteins Is Applicable to Refolding Proteins Made in a Non-Mammalian Expression System

Patent Owner argues that the model proteins used in Schlegl and Hevehan are not applicable to the proteins generated in non-mammalian expression systems because possible host-cell contamination will affect refolded protein yields. This argument fails for at least four reasons:

First, while yields may potentially be reduced because of contaminants, that does not change the optimal refolding buffer conditions needed to refold a protein. As Dr. Robinson explains, yields are distinct from refolding buffer conditions—the very point of novelty argued by Patent Owner. EX1056, ¶¶47-48.

Second, proteins isolated from inclusion bodies are very pure, as Dr. Willson has acknowledged. EX1058, 212:18-213:10 ("the inventors of the '138 patent thought that inclusion bodies were *almost all protein*, especially after they had been washed" (emphasis added)). Patent Owner's own exhibits demonstrate that inclusion bodies contained up to 95% pure protein. POR, 29; EX2034, 2. Further, "inclusion bodies often contain almost exclusively the overexpressed protein," where the "[m]ajor contaminants... are outer membrane proteins" that can be separated from the proteins "by extensive washing with detergents." EX2031, 2. Additionally, as Dr. Robinson explains, inclusion bodies from non-mammalian expression systems typically do not have to be purified prior to refolding. EX1056, ¶49-52.

Third, Schlegl's methods *were* applied to proteins expressed in non-mammalian expression systems. Petition, 29; EX1003, Abstract and [0004]. During the prosecution of the application that became the Schlegl publication, when faced with an enablement rejection, Applicant submitted a declaration of Dr. Berkemeyer who demonstrated that the methods claimed in the Schlegl publication are applicable to any number of proteins, and he provided examples of two proteins that were expressed in *E. coli*, a non-mammalian expression system being, refolded using those methods. EX1060, 2. Therefore, not only did Schlegl teach that its methods could be applied to proteins expressed in a non-mammalian

expression system, but he also demonstrated that through two example proteins. EX1056, ¶53.

Fourth, the '138 patent is silent regarding the purity of the starting materials used in the claimed methods. EX1056, ¶54. As discussed above, the presence of contaminants in a protein solution does not affect the optimal redox amounts that would be necessary to successfully refold the protein.

2. Hevehan Is a Widely Respected Teaching for Optimizing Redox Conditions

Patent Owner also argues that Hevehan does not disclose the use of a reductant, and thereby, the TPR and RBS in Hevehan are zero. Patent Owner's argument is based on a chop-quote from Hevehan: "[a]ddition of GSSG's reducing partner, GSH, to the renaturation system was not necessary due to the DTT carried over from the denatured [protein] solution." Patent Owner conveniently ignores the very next sentence, which clearly discloses an oxidant/reductant pair: "[i]n 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." EX1004, 3; EX1056, ¶29.

In fact, Hevehan is full of references to oxidant/reductant pairs and how their optimization affects protein refolding. Hevehan states, "[t]he right mixture of low molecular weight thiol components in oxidized and reduced forms needs to be added to the renaturation buffer to allow disulfide bond formation and shuffling."

EX1004, 5; EX1056, ¶¶30, 39. Further, Hevehan states, "[a] matrix approach was used in this study to determine the optimal concentrations of DTT and GSSG which would give the highest yields." EX1004, 5. As explained by Dr. Robinson, Hevehan translates these parameters to GSH/GSSG ratios after explaining the fast conversion of GSSG by DTT to the thiol pair. EX1004, 5; EX1056, ¶30.

Indeed, the TPR in Hevehan cannot be zero. Hevehan states that protein yields are "strongly dependent" on thiol concentrations in the renaturation buffer. EX1004, 5. This conclusion would not be possible if Hevehan were teaching a TPR of zero. In fact, Hevehan discloses that the optimum thiol-pair ratio is between 0.57 and 2.3 (DTT/GSSG). EX1004, Fig. 4; EX1002, ¶68; EX1056, ¶¶31-33.

Hevehan's optimization of the refold conditions was not based on the selection of "random concentrations" of reductant and oxidant as alleged by Patent Owner. POR, 26. Instead, Hevehan based its selection of concentrations on previous studies that indicated the optimum thiol concentrations in the renaturation buffer. EX1056, ¶37. For example, Hevehan explains that "[t]o achieve refolding of native lysozyme, a method similar to that described by Saxena and Wetlaufer (1970) was employed." EX1056, ¶37; EX1004, 2-3. Patent Owner's chop-quoting of Dr. Robinson's testimony to imply that she testified that the method of Hevehan used the exact concentrations of oxidant and reductant as in the Saxena and

Wetlaufer article does not change the fact that Hevehan itself explains that it used a "method similar to that described by Saxena and Wetlaufer." Hevehan does not use that exact method, and Dr. Robinson did not testify that it did. EX1056, ¶38 Furthermore, Hevehan explains that a number of previous studies had indicated the optimal thiol concentrations in the renaturation buffer for low-protein concentrations, and that it used a matrix approach to determine the optimum concentrations of oxidant and reductant for higher protein concentrations. EX1056, ¶38; EX1004, 5. This matrix approach to determine the optimal amount of oxidant and reductant is exactly what Patent Owner describes in the '138 patent as a "rational design" for determining the optimal conditions to refold a protein. EX1056, ¶¶38-39.

Patent Owner contends that Hevehan has been discredited as being overly simplistic. In support, Patent Owner cites an article by Buswell (EX2042). Patent Owner, however, has misapplied Buswell, which merely 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. EX1056, ¶¶34-35; EX1057, 91. Further, Buswell's model has itself been discredited. EX1056, ¶35; EX1057, 95.

Hevehan, in fact, has become a widely cited paper for its teaching of optimizing redox components; it has been cited 184 times, including in 2017. In

comparison, Buswell has only been cited 34 times. EX1056, ¶36. Even Patent Owner's expert, Dr. Willson, acknowledges that hen egg white lysozyme, the protein studied in Hevehan, is a well-known protein for purposes of protein refolding. EX2020, ¶70; EX1056, ¶36.

Thus, despite Patent Owner's many attempts to mischaracterize and ignore the teachings of Schlegl and Hevehan that do not support its argument, the refolding methods of Schlegl and Hevehan are entirely compatible with one another, and a person of skill in the art would have immediately recognized this compatibility.

C. The Art of Record Discloses High-Protein-Concentration Solutions

Patent Owner also argues that Schlegl is directed only to extreme dilutions resulting in low concentrations of protein. Yet this argument conflates the "unfolded protein' with "total protein," as the dilute concentrations of Schlegl are of diluted *unfolded* protein, not *total* protein. EX1056, ¶¶41-44.

Schlegl is primarily directed to optimizing the flow rate of the protein solution feed for "ideal" mixing conditions with the refolding buffer. EX1056, ¶44; EX1003, ¶¶[0023]-[0024], [0032], [0037]. Schlegl optimizes this 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. EX1056, ¶44; EX1003, ¶¶[0033], [0037]-[0038], [0041]-[0042], [0045], [0056], [0061]. Before

mixing, however, Schlegl starts with a "high concentration of unfolded protein." EX1056, ¶44; EX1003, ¶¶[0040], [0075] (the concentration of bovine α-lactalbumin[1] in solubilized inclusion bodies (the protein-containing volume) is 16.5 mg/ml (*i.e.*, 16.5 g/L) before dilution), [0035] (after dilution with the refolding buffer, the protein concentration can be as high as 10 mg/ml (10 g/L)), claim 6 (concentration after mixing "between ca. 1 ng/ml and ca. 10 mg/ml"), claim 7 (concentration after mixing "between ca. 100 ng/ml and ca. 5 mg/ml").[2] Accordingly, protein concentrations of greater than 2 g/L of total protein following

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[1] As Dr. Robinson explains, the role of calcium in refolding at low-salt concentrations in no way diminishes the key role of redox components. EX1056, ¶¶25-27, 46.

[2] Claims 6 and 7 of Schlegl issued without amendment as claims 6 and 7 of U.S. Patent No. 7,651,848. EX1053. While Patent Owner argues that Schlegl is directed to extreme dilutions down to low concentrations of protein that would render it incompatible with Hevehan, the Schlegl patentees considered refolding proteins up to concentrations of 10 mg/ml to be important enough to merit a claim. That this claim issued indicates that Schlegl is an enabling disclosure for refolded proteins at up to 10 mg/ml.

contact of the protein with the refold buffer are fully disclosed by Schlegl. EX1056, ¶45.

Patent Owner attempts to disregard Schlegl's disclosure of refolding proteins up to a concentration of 10 mg/ml as a drafting error. *E.g.*, EX1055, 43:9-13 (Dr. Willson testifying that the high-protein concentrations could not result from a 300-fold dilution). In so doing, Patent Owner ignores the extensive disclosures in Schlegl of dilution rates as low as 1:10, 1:5, and even 1:1. EX1003, ¶¶[0026], [0033], [0035], claims 1, 4, 5. In the end, however, Dr. Willson admitted that the dilution ranges disclosed in Schlegl allow final protein concentrations in excess of 2 g/L. EX1055, 44:3-45:12.

D. The Manner in Which the Alleged Invention Was Developed Is Irrelevant to the Patentability of the Claims

Finally, Section 103(a) of the Patent Act was written to "provide the Patent Examiners and the Courts with a yardstick that in considering the patentability of any article from January 1, 1953 on, it would be immaterial whether the invention 'resulted from long toil and experimentation or from a flash of genius.'" *Gagnier Fibre Products Co. v. Fourslides, Inc.*, 112 F.Supp. 926, 929 (E.D. Mich. 1953). Thus, Patent Owner's arguments regarding the alleged significance of how the '138 patent was developed should be disregarded. POR, 8-9 (quoting EX2021, 17-24).

IV. Claims 1-24 Are Unpatentable

A. Claims 1-11 and 13-24 Are Obvious over Schlegl and Hevehan

Patent Owner argues the patentability of claims 1, 5, 9-11, and 18, and relies on these arguments for the remainder of the challenged claims. Therefore, Petitioner responds in kind.

1. Claim 1 Is Obvious

Schlegl and Hevehan each discloses the refolding of a protein expressed using a non-mammalian expression system and present at a concentration of 2.0 g/L or greater. Pet., 43; EX1002, ¶¶120-123; EX1003, [0004], [0075]; EX1004, 5-6; Inst., 15; EX1056, ¶¶55-57. Schlegl teaches the "one or more" components of the refold buffer, as well the incubation of the refold mixture and isolation of the protein from the refold mixture. Pet., 47-48; EX1002, ¶¶127-131, EX1003, [0016], [0036], [0060], [0065]. Schlegl and Hevehan each discloses contacting the protein with a refold buffer 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 a denaturant, an aggregations suppressor and a protein stabilizer, to form a refold mixture. Pet., 44-45, EX1002, ¶124, EX1003, [0075], EX1004, 5; Inst., 15-21.

On TPR and RBS, Patent Owner disagrees with the volume for which the formulae should be calculated, but the Board concluded that the TPR and RBS should be calculated in the refold buffer, and Patent Owner's arguments otherwise are contrary to the Institution Decision in this case. Inst., 18.

Regardless of whether the TPR and RBS are calculated in the refold buffer or the refold mixture, Schlegl teaches TPR and RBS values that fall within the claimed range. EX1056, ¶¶58-61. In the event the claims are construed such that the TPR and RBS are calculated in the refold buffer, as in the Institution Decision at 18, TPR is 2 and the RBS is 6. EX1056, ¶60. In the event that TPR and RBS are calculated in the refold mixture, the TPR is 1.94 and the RBS is 5.8, values within 3% of the values calculated in the refold buffer. *Id*. In fact, Dr. Willson acknowledged that increasing the dilution of a protein solution by adding greater volumes of refold buffer does not significantly alter the TPR and RBS values. EX1055, 16:3-36:3.

2. Claim 5 Is Obvious

Schlegl also discloses that the protein is deposited as inclusion bodies and Hevehan teaches recovery of protein from inclusion bodies, as recited in claim 5. Pet., 52-53; EX1002, ¶142; EX1003, [0006]; EX1004, Abstract; EX1056, ¶62.

3. Claims 9-11 and 18 Are Obvious

a. Claims 9 and 11

Claims 9 and 11 limit the "protein" in claim 1 to "an antibody" and a "multimeric protein," respectively. Schlegl teaches that its methods apply to "any protein, protein fragment or peptide that requires refolding upon recombinant expression in order to obtain such protein in its biologically active form". EX1003, [0031]; EX1002, ¶144. As discussed above, and in the Petition, a person of skill in

the art would consider Schlegl's methods to be widely applicable. Pet., 54; EX1002, ¶145; EX1056, ¶63. And, a person of skill in the art would expect that by using Schlegl's dilution method in combination with the optimized redox conditions obtained through the trial-and-error-matrix approach taught by Hevehan, proper refolding of an antibody or a multimeric protein could be obtained. EX1056, ¶63.

b. Claim 10

As discussed above in Section II, Petitioner believes that the proper definition for complex proteins is set forth at col 4, lines 23-27 of the '138 patent. However, even under the construction for "complex protein" set forth in the Institution Decision, claim 10 is still obvious over the prior art. EX1056, ¶64. As discussed above, the '138 patentees state that prior to their disclosure, protein refolding at high concentrations was demonstrated with proteins that were "significantly smaller in molecular weight, less complex molecules containing only one or two disulfide bonds." EX1001, 2:1-5.

Schlegl teaches the refolding of bovine α-lactalbumin, a protein containing 123 amino acid residues and four disulfide bonds. EX1003, ¶[0073]. Hevehan teaches the refolding of hen egg white lysozyme, a protein that has 129 amino acids, a MW of 14389.68, and four disulfide bonds. EX1004, 2; EX1045. Both of these proteins have more than two disulfide bonds and with regard to size, are not

significantly smaller than the arbitrary definition of "complex" found in the '138 patent. EX1056, ¶65. Further, Hevehan discloses "complex proteins" in the introduction. EX1004, 2; EX1056, ¶66; EX1059, 1.

Given the teaching of the art and the '138 patent, a person of ordinary skill in the art would immediately recognize that the methods of Schlegl and Hevehan could be applied to the complex protein of claim 10. EX1056, ¶66.

c. Claim 18

One of ordinary skill knew at the time of the invention that aerobic conditions could impact the redox chemistry of the refolding reaction. Pet., 55; EX1002, ¶148; EX1056, ¶67. Hevehan describes solutions of reduced DTT that were prepared immediately prior to each experiment to minimize air oxidation. Pet., 55, EX1004, 2, 3; EX1028 (fermentation); EX1020. Thus, a person of ordinary skill would have been motivated to eliminate oxygen from the refolding reaction. EX1056, ¶67; EX1021, 2; EX1014, 7.

4. Claims 2-4, 6-8, 13-17, and 19-24 Are Obvious

Patent Owner does not separately argue the patentability any of claims 2-4, 6-8, 13-17, and 19-24. With respect to Petitioners' position that these claims are unpatentable, Petitioners respectfully refer the Board to the discussion above concerning claim 1, the Petition, and EX1002, ¶132-141, 143-149; EX1056, ¶68.

B. Claim 12 Is Obvious over Schlegl, Hevehan, and Hakim

Patent Owner attempts to save claim 12 by arguing that Hakim is not prior art to the '138 patent, but does so by relying on evidence of uncertain vintage and insufficient proof of an actual reduction to practice. Therefore, Patent Owner's documentary evidence fails to "show[] that the inventor disclosed to others his 'completed thought expressed in such clear terms as to enable those skilled in the art' to make the invention," as would be required to antedate Hakim. *Coleman v. Dines*, 754 F.2d 353, 359 (Fed. Cir. 1985); *see also Dawson v. Dawson*, 710 F.3d 1347, 1352 (Fed. Cir. 2013). Patent Owner attempts to fill these gaps through testimony of an inventor, Dr. Hart. But Dr. Hart's testimony relates to "assertions of inventive facts" and thus "require[s] corroboration by independent evidence." *Brown v. Barbacid*, 276 F.3d 1327, 1335 (Fed. Cir. 2002). Because Patent Owner did not corroborate Dr. Hart's gap-filling testimony with *additional* independent evidence, Patent Owner *cannot* antedate Hakim's May 1, 2009 publication date.

1. Patent Owner Has Not Corroborated the Date of Its Physical Evidence

Patent Owner's documentary evidence is fatally flawed in that it is alleged to support a February 26, 2009 conception-and-reduction-to-practice date, but *does not actually contain a date itself.*[3] *See generally* EX2022.

While it is true that Patent Owner need not corroborate the technical content of the document, *see* POR, 51, Patent Owner *is* required to corroborate the *date* of the document, and do so with sufficient non-inventor evidence. *Microsoft Corporation v. Surfcast Inc.*, Paper 93, IPR2013-00292,-3,-4, and -5, p.17 ("The principle that corroboration is not required … is directed to the technical content of

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[3] While Patent Owner and Dr. Hart also cite to an earlier presentation (dated, September 16, 2008) (EX2024), Patent Owner does not take the position in its Response that this earlier document evidences conception and reduction to practice sufficient to antedate Hakim. POR, 50 ("Amgen's inventors fully reduced to practice the invention of Claim 12 as of at least February 26, 2009..."). Regardless, Patent Owner's use of Exhibit 2024 is further flawed for the same reasons as in section (IV)(B)(2)(b), below, and [redacted]

the document, *not to the date or origin of the document*. The law requires sufficient proof for the date and identity of a physical exhibit offered to show conception." (citing *Price v. Symsek*, 988 F.2d 1187, 1194–95 (Fed. Cir. 1993)) (emphasis added)). Patent Owner has failed to do so.

Patent Owner attempts to support the alleged date of the [redacted] (EX2022) by testimony of Dr. Hart (EX2021) and by an exhibit that allegedly shows the document's metadata (EX2023). Both of these fall short of Patent Owner's burden. First, as a matter of law, Dr. Hart's testimony cannot be taken on its own to substantiate a date for Exhibit 2022 because it is on an "assertion[] of inventive facts." *Brown*, 276 F.3d at 1335. Second, the metadata (EX2023) cannot be authenticated or verified for accuracy and truthfulness as would be necessary to swear behind Hakim. Patent Owner failed to produce any declarant with personal knowledge of Exhibit 2023 to substantiate the document. *See* EX1054, 14:13-24; 103:18-114:1; 114:4-117:6 (Dr. Hart testifying that he (1) has no idea what metadata is; (2) is "not an expert in information systems"; and (3) is "largely uninformed" as to what the fields present in Exhibit 2023[4] actually mean); *also id.*, 105:13-21 Moreover, it is well known that time stamps "can be easily modified, even accidentally" and have been found

[4] And Exhibit 2025, note 3, above.

insufficient to prove a prior-invention date when, like here, the underlying document otherwise lacks any date. *Kenexa Brassring, Inc. v. Taleo Corp.*, 751 F. Supp. 2d 735, 760-61 (D. Del. 2010).

Patent Owner's lack of corroboration of the date of the physical evidence, and its attempt to shoehorn in evidence through an unqualified and interested witness is fatal to its attempt to swear behind the Hakim reference.

2. Patent Owner's Evidence Does Not Prove a Reduction to Practice of Claim 12

a. Refolding of AMG 745 Is Not Enough in Light of Hakim's Refolding of Multiple Fc-Protein Conjugates

Claim 12 is directed to a method of refolding a protein expressed in a non-mammalian expression system, wherein the protein "is an Fc-protein conjugate." The specification describes an "Fc-protein conjugate" as "a protein fused or linked to a Fc domain," where the term "Fc" means "a fragment of an antibody that comprises human or non-human (e.g., murine) C_{H2} and C_{H3} immunoglobulin domains, or which comprises two contiguous regions which are at least 90% identical to human or non-human C_{H2} and C_{H3} immunoglobulin domains." EX1001, 3:24-25 and 5:37-41. Because the term "Fc-protein conjugate" encompasses a genus of possible proteins, claim 12 is essentially directed to a subgenus of claim 1. EX1056, ¶69.

Hakim teaches the production of multiple fusion proteins that fall within the scope of the genus of an "Fc-protein conjugate." *Id*.; EX1056, ¶70. Therefore, the MPEP provides three ways that Patent Owner can swear behind Hakim. Patent Owner had three options, but failed to satisfy any one.

First, Patent Owner could have demonstrated refolding of all the species shown in Hakim, MPEP 715.03(I)(B) (citing *In re Stempel*, 241 F.2d. 755). But Patent Owner's evidence at best demonstrates that only a single Fc-protein conjugate, AMG 745, was refolded according to the method of claim 1, EX2021, ¶¶35-43, rather than the multiple species shown in Hakim.

Second, Patent Owner could have showed refolding of different species "if the species shown in the reference or activity would have been obvious in view of the species shown to have been made by the applicant," MPEP 715.03(I)(B) (citing *In re Clarke,* 356 F.2d 987, (CCPA 1966); *In re Plumb,* 470 F.2d 1403, (CCPA 1973); *In re Hostettler*, 356 F.2d 562, (CCPA 1966)). Patent Owner, however, has offered no evidence to demonstrate that the species shown in Hakim would have been obvious in view of the refolding of AMG 745.

Third, Patent Owner could have showed refolding of one or more species that would "provide[] an adequate basis for inferring that the invention has generic applicability," MPEP 715.03(I)(B) (citing *In re Plumb*; *In re Rainer,* 390 F.2d 771 (CCPA 1968); *In re Clarke*; *In re Shokal,* 242 F.2d 771 (CCPA 1957)). Yet again,

Patent Owner offers no evidence to demonstrate that a person of skill in the art would infer that the refolding of AMG 745 would have generic applicability to the entire genus of Fc-protein conjugates. Patent Owner, in fact, states the opposite, *i.e.*, that protein refolding was notoriously unpredictable and that evidence of the refolding of one protein should not be extrapolated to other proteins. POR, 31, 38-42, 46; EX2020, ¶¶43, 76, 81-84. Patent Owner thus has admitted that its alleged evidence of the refolding of a single Fc-protein conjugate, AMG 745, is not broadly applicable to the entire genus of Fc-protein conjugates.

b. One of Skill in the Art in February 2009 Would Not Understand AMG 745 To Be an Fc-Protein Conjugate

Even Patent Owner's evidence that AMG 745 is an "Fc-protein conjugate" according to claim 12 is deficient for three reasons.[5]

[5] Dr. Hart testified that he was unfamiliar with the phrase "Fc-protein conjugate," even though he uses that term throughout his Declaration. EX1054, 36:21-37:3. Patent Owner attempted to fix his testimony on re-direct testimony, but Dr. Hart was only able to define "Fc-protein conjugate" based on the definition provided in post-dated publications. Nowhere in his Declaration or his deposition did he apply the definition from the '138 patent to determine that AMG 745 fell within the scope of claim 12.

First, the '138 patent does not mention AMG 745, and therefore does not describe AMG 745 as an Fc-protein conjugate. EX1056, ¶69.

Second, Patent Owner offers no contemporaneous evidence as to what the protein labeled as "AMG 745" referred to in the PowerPoint presentations actually is. Patent Owner instead relies on two documents published by a different group of people five years after the alleged evidence of reduction to practice.

Third, Exhibits 2022 and 2024 do not state what AMG 745 actually is. [redacted] But the test here is not whether *Amgen* scientists skilled in the art would be able to know what AMG 745 is. The test is whether a person of skill in the art would. Neither party here suggested that the level of skill requires employment at Amgen, or login credentials to Amgen's "secure databases."

The facts here are similar to those in *Stamps.com Inc. v. Endicia, Inc.*, where the Federal Circuit rejected the patent owner's attempts to antedate a prior-art reference. There, like here, the patent owner relied on a document presented to other internal company personnel that made only "opaque and incomprehensible references" to the claimed subject matter from the perspective of one skilled in the

art. 437 F. App'x 897, 908 (Fed. Cir. 2011). This document was insufficient to allow one of skill in the art to recognize conception, let alone reduction to practice, sufficient to swear behind a prior-art reference. *Id.,* 908-09. The Board here should follow the lead of the Federal Circuit and similarly reject Patent Owner's faulty evidence.

C. Patent Owner Has Presented No Evidence of Secondary Considerations

Finally, Petitioner notes that Patent Owner does not raise secondary considerations as a defense in its Preliminary Response or in its Response. In fact, the only possible evidence in the record of secondary considerations consists of two off-hand statements in Dr. Willson's *second* declaration. EX2020, ¶33 (based on Dr. Hart's declaration, determining the formulae "led to unexpected results and satisfied a long-felt need for a more rational, less random, design of refold buffers"); *id.*, ¶34; *also* POR, 1, 11. In order to demonstrate unexpected results, a patent owner must provide actual evidence, and not just argument, conclusory statements, or speculation that the claimed method possesses unexpected properties. *In re Mayne,* 104 F.3d 1339, 1343-44 (Fed. Cir. 1997) (conclusory statements that claimed compound possesses unusually low immune response or unexpected biological activity that is unsupported by comparative data held insufficient to overcome *prima facie* case of obviousness). To demonstrate long-felt need, a patent owner must provide objective evidence that an art recognized

problem existed in the art for a long period of time without a solution. *In re Gershon,* 372 F.2d 535, 539 (CCPA 1967); *Newell Companies v. Kenney Mfg. Co.,* 864 F.2d 757, 768 (Fed. Cir. 1988). Dr. Willson's assertions do neither. Therefore, Patent Owner's arguments in this regard should be rejected. EX1056, ¶¶39-40, 71-75.

Respectfully submitted,

August 21, 2017

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), I hereby certify that this Reply complies with the type-volume limitation of 37 C.F.R. § 42.24(c)(1) because it contains 5,581 words as determined by the Microsoft® Office Word 2010 word-processing system used to prepare the brief, excluding the parts of the brief exempted by 37 C.F.R. § 42.24(c).

/Teresa Stanek Rea/
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CERTIFICATION OF SERVICE

The undersigned hereby certifies that the foregoing document entitled REPLY TO PATENT OWNER RESPONSE, and all accompanying exhibits were served electronically via email on August 21, 2017 to Patent Owner's counsel of record upon the following:

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