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Paper 8
Date: July 12, 2021

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

LUPIN, LTD. and LUPIN PHARMACEUTICALS, INC.,
Petitioner,

v.

AMGEN, INC.,
Patent Owner.

IPR2021-00326
Patent 9,856,287 B2

Before ZHENYU YANG, CHRISTOPHER G. PAULRAJ, and JOHN E. SCHNEIDER, *Administrative Patent Judges.*

SCHNEIDER, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

Lupin, Ltd. and Lupin Pharamaceuticals, Inc. (collectively "Petitioner") filed a Petition (Paper 1, "Pet.") requesting an *inter partes* review of claims 1–30 of U.S. Patent No. 9,856,287 B2 ("the '287 patent," Ex. 1001). Amgen, Inc. and Amgen Manufacturing, Limited (collectively "Patent Owner") filed a Preliminary Response. Paper 7 ("Prelim. Resp.").

We have authority to determine whether to institute an *inter partes* review. 35 U.S.C. § 314. Upon consideration of the Petition and the Preliminary Response, and in light of Board precedent, we conclude Petitioner has not demonstrated a reasonable likelihood of showing that at least one claim is unpatenable

A. Real Parties-in-Interest

Petitioner identifies Lupin, Ltd., Lupin Pharmaceuticals, Inc., Lupin, Inc., and Nanomi BV as the real parties-in-interest for Petitioner. Pet. 2 Patent Owner identifies Amgen, Inc. and Amgen Manufacturing, Limited as the real parties-in-interest for Patent Owner. Paper 4, 1.

B. Related Matters

Petitioner states that there is no pending district court action involving the '287 patent and that the '287 patent was the subject of litigation in three district court actions:

- *Amgen Inc. et al. v. Tanvex BioPharma USA, Inc. et al.*, 19-cv-01374, S.D. Cal. (the "*Tanvex* litigation"), which was dismissed December 19, 2019.

- *Amgen Inc. et al. v. Adello Biologics, LLC et al*., 18-cv-3347, D.N.J., (the "*Adello* litigation"), which was dismissed November 25, 2019.

- *Amgen Inc. et al. v. Accord BioPharma USA, Inc. et al.,* 18-cv-61828, S.D. Fl., which was dismissed November 15, 2019.

Petitioner also states that there are no currently pending Patent Trial and Appeal Board ("PTAB") proceedings that address the validity of the '287 patent and that the '287 patent was the subject of three prior PTAB proceedings:

- PGR2019-00001, *Adello Biologics, LLC et al. v. Amgen Inc. et al.* (the "*Adello* PGR") was terminated on December 6, 2019. PGR2019-00001, Paper 28 (PTAB Dec. 6, 2019).

- IPR2019-00971, *Fresenius Kabi USA, LLC et al. v. Amgen, Inc. et al.* (the "2019 *Fresenius* IPR"), was denied institution under § 314(a) as duplicative of the then-pending *Adello* PGR, without evaluation on the merits. *See* 2019 *Fresenius* IPR, Paper 13 (PTAB Oct. 16, 2019).

- IPR2020-00314, *Fresenius Kabi USA, LLC et al. v. Amgen, Inc. et al.* (the "2020 *Fresenius* IPR") was terminated on June 19, 2020. *Fresenius* IPR, Paper 17 (PTAB. Jun. 19, 2020).

C. The '287 Patent

The '287 patent relates to a method of refolding proteins expressed in non-mammalian cells. Ex. 1001, 2:62–3:4. Such refolding is necessary in some non-mammalian expression systems, such as bacteria, because of the "inability of a bacterial host cell to fold recombinant proteins properly at high levels of expression." *Id*. at 1:25–32. As a result, the improperly-folded proteins are insoluble and precipitate out of solution to form inclusion bodies. *Id.* According to the '287 patent, prior art refolding techniques did not demonstrate refolding of larger, more complex protein molecules at high concentrations, i.e., 2.0g/L or higher, at a scale suitable for industrial applications. *Id.* at 2:8–32.

D. Illustrative Claims

Petitioner challenges claims 1–30. Claims 1, 10, 16, and 26 are the independent claims. Claim 1 is illustrative and is reproduced below:

> 1. A method refolding proteins expressed in a nonmammalian expression system, the method comprising: contacting the proteins with a preparation that supports the renaturation of at least one of the proteins to a biologically active form, to form a refold mixture, the preparation comprising:
>
> at least one ingredient selected from the group consisting of a denaturant, an aggregation suppressor and a protein stabilizer;
>
> an amount of oxidant; and
>
> an amount of reductant;
>
> wherein the amounts of the oxidant and the reductant are related through a thiol-pair ratio and a thiol-pair buffer strength, wherein the thiol-pair ratio is in the range of 0.001-100; and wherein the thiol-pair buffer strength maintains the solubility of the preparation; and incubating the refold mixture so that at least about 25% of the proteins are properly refolded.

Ex. 1001, 18:21–41.

E. Evidence

Petitioner relies on the following evidence:

Vallejo, et al., EP 1449848 A1, published August 25, 2004. (Ex. 1003 "Vallejo").

Schlegl, US 2007/0238860 A1, published October 11, 2007 (Ex. 1004 "Schlegl").

Hevehan, D. and Clark, E., "*Oxidative Renaturation of Lysozyme at High Concentrations*," 54:3 BIOTECHNOLOGY AND BIOENGINEERING. 221–230 (May 1997) (Ex. 1005 "Hevehan").

Schafer et al., *"Redox Environment of the Cell as Viewed Through the Redox State of the Glutathione Disulfide/Glutathione Couple,"* 30 Free Radical Biol. Med. 1191–1212 (2001) (Ex. 1007 "Schafer").

Ruddon et al., WO 95/32216, published November 30, 1995. (Ex. 1006 "Ruddon").

Petitioner also relies on the Declaration of George Georgiou, Ph.D. (Ex. 1002 "Georgiou Decl.").

F. Prior Art and Asserted Grounds

Petitioner asserts that claims 1–30 would have been unpatentable on the following grounds:

Claim(s) Challenged	35 U.S.C. §[1]	Reference(s)/Basis
1–4, 7–19, 22–30	102(b)	Vallejo
1–4, 7–19, 22–30	102(b)	Schlegl
1–30	103(a)	Vallejo, Hevehan
1–6, 8–21, 23–30	103(a)	Schlegl, Hevehan
8–9, 14–15, 23–25, 30	103(a)	Vallejo, Schafer, Ruddon
8–9, 14–15, 23–25, 30	103(a)	Schlegl, Schafer, Ruddon

II. ANALYSIS

A. Legal Standards

1. Burden of Proof

At this stage of the proceeding, the burden rests on the petitioner to establish a reasonable likelihood that it will prevail in showing that at least one of the challenged claims is unpatentable. 35 U.S.C. § 314(a) (2018).

[1] The Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112–29, 125 Stat. 284, 287–88 (2011), amended 35 U.S.C. §§ 102 and 103. Because the '287 patent was filed before March 16, 2013 (the effective date of the relevant amendments), the pre-AIA versions of §§ 102 and 103 apply.

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