Trials@uspto.gov
571-272-7822

Paper 13
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FRESENIUS KABI USA, LLC and
FRESENIUS KABI SWISSBIOSIM GmbH,
Petitioners,

v.

AMGEN, INC. and AMGEN MANUFACTURING, LIMITED,
Patent Owner.

Case IPR2019-00971
Patent 9,856,287 B2

Before ZHENYU YANG, J. JOHN LEE, and
CHRISTOPHER G. PAULRAJ, *Administrative Patent Judges*.

LEE, *Administrative Patent Judge*.

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

INTRODUCTION

Fresenius Kabi USA, LLC and Fresenius Kabi SwissBioSim GmbH (collectively, "Fresenius") filed a Petition (Paper 3, "Pet.") requesting an *inter partes* review of claims 1, 4–6, 8–10, 12, 14–16, 19–21, 23–26, 29, and 30 ("the challenged claims") of U.S. Patent No. 9,856,287 B2 (Ex. 1001, "the '287 Patent"). Amgen Inc. and Amgen Manufacturing, Limited (collectively, "Amgen")[1] timely filed a Preliminary Response (Paper 8, "Prelim. Resp."). Fresenius filed an authorized Reply to the Preliminary Response (Paper 11, "Reply"), and Amgen filed an authorized Sur-Reply (Paper 12, "Sur-Reply").

Upon consideration of the Petition and the Preliminary Response, and in light of Board precedent, we conclude that the Petition should be denied under the discretion provided to the Director in 35 U.S.C. § 314(a).

A. Related Cases

The parties identify the following matters as related to the '287 Patent and, thus, the present case:

Amgen Inc. v. Adello Biologics LLC, No. 2:18-cv-03347 (D.N.J.)

Amgen Inc. v. Apotex Inc., No. 19-cv-61828 (S.D. Fla.)

Adello Biologics LLC v. Amgen Inc., Case PGR2019-00001 (PTAB)

Pet. 4; Paper 6, 1. The parties also note that U.S. Patent No. 8,952,138 and U.S. Patent Application Nos. 14/793,590, 14/611,037, and 15/889,559 are related or may be affected by the present case.

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[1] Amgen notes that Amgen Inc. is the owner of the '287 Patent whereas Amgen Manufacturing, Limited is an exclusive licensee. Prelim. Resp. 1 n.2.

B. Background of 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.

C. Challenged Claims

Fresenius challenges claims 1, 4–6, 8–10, 12, 14–16, 19–21, 23–26, 29, and 30. Claims 1, 10, 16, and 26 are the independent claims. Claim 1 is illustrative and is reproduced below:

> 1. A method or refolding proteins expressed in a non-mammalian 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.

D. Asserted Grounds of Unpatentability and Asserted Prior Art

Fresenius challenges the patentability of claims 1, 4–6, 8–10, 12, 14–16, 19–21, 23–26, 29, and 30 of the '287 Patent on the following grounds (Pet. 23):

Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
1, 4, 8–10, 12, 14–16, 19, 23–26, 29, 30	102(a)(1)	Vallejo[2]
16, 19–21, 23–26, 29, 30	102(a)(1)	Ruddon[3]

[2] Eur. Patent App. No. EP 1449848 A1, published Aug. 25, 2004 (Ex. 1031, "Vallejo").

[3] PCT Int'l App. Pub. No. WO 95/32216, published Nov. 30, 1995 (Ex. 1025, "Ruddon").

Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
1, 4–6, 8–10, 12, 14–16, 19–21, 23–26, 29, 30	103	Ruddon, Clark 1998,[4] Schafer[5]/Gilbert 1995[6]
8, 9, 14, 15, 23–25, 30	103	Ruddon, Clark 1998, Vallejo, Schafer/Gilbert 1995

In addition, Fresenius relies on the Declaration of Paul A. Dalby, Ph.D. (Ex. 1002) in support of the asserted grounds of unpatentability.

ANALYSIS

Discretionary Denial of Petition Under § 314(a)

Amgen argues that institution of an *inter partes* review should be denied under 35 U.S.C. § 314(a) and the Board's precedents in *General Plastic Industrial Co. v. Canon Kabushiki Kaisha*, Case IPR2016-01357,

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[4] Eliana De Bernardez Clark et al., *Oxidative Renaturation of Hen Egg-White Lysozome*, BIOTECH. PROGRESS, Jan./Feb. 1998, at 47–54 (Ex. 1007, "Clark 1998").

[5] Freya Q. Schafer & Garry R. Buettner, *Redox Environment of the Cell as Viewed Through the Redox State of the Glutathione Disulfide/Glutathione Couple*, 30 FREE RADICAL BIOL. & MED. 1191–1212 (Ex. 1027, "Schafer").

[6] Hiram F. Gilbert, *Thiol/Disulfide Exchange Equilibria and Disulfide Bond Stability, in* 251 METHODS IN ENZYMOLOGY 8 (Lester Packer ed., 1995) (Ex. 1014, "Gilbert 1995"). The Petition initially indicates its reliance on Gilbert 1995 (called "Gilbert" in the Petition). *See* Pet. 48 n.9. As Amgen points out (Prelim. Resp. 53–54), however, the Petition also cites repeatedly to "Gilbert 1990," a different reference albeit by the same author. *See, e.g.*, Pet. 53. Although we do not reach the merits of Fresenius' challenges, we note that 37 C.F.R. § 42.104(b)(5) requires a petition for *inter partes* review to provide a clear statement of, *inter alia*, "[t]he exhibit number of the supporting evidence relied upon to support the challenge and the relevance of the evidence to the challenge raised."

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