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Paper No. 9
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FRESENIUS KABI USA, LLC,
Petitioner,

v.

CEPHALON, INC.,
Patent Owner.

Case IPR2016-00111
Patent 8,895,756 B2

Before JACQUELINE WRIGHT BONILLA, ZHENYU YANG, and TINA E. HULSE, *Administrative Patent Judges*.

HULSE, *Administrative Patent Judge*.

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

I. INTRODUCTION

Fresenius Kabi USA, LLC ("Petitioner") filed a Petition requesting an *inter partes* review of claims 1–4 of U.S. Patent No. 8,895,756 B2 (Ex. 1001, "the '756 patent"). Paper 2 ("Pet."). Cephalon, Inc. ("Patent Owner") filed a Preliminary Response to the Petition. Paper 7 ("Prelim. Resp.").

We have jurisdiction under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). Upon considering the Petition and Preliminary Response, we determine that Petitioner has established a reasonable likelihood that it would prevail in showing the unpatentability of claims 1–4. Accordingly, we institute an *inter partes* review of those claims.

A. Related Proceedings

The parties identify several copending district court proceedings as relating to the '756 patent. Pet. 5; Paper 5, 1–2. Petitioner is not a party to any of the proceedings. Pet. 5.

Petitioner also filed a Petition for *inter partes* review of related U.S. Patent No. 8,791,270 B2. *Fresenius Kabi USA, LLC v. Cephalon, Inc.*, IPR2016-00098, Paper 2 (PTAB Oct. 28, 2015). A decision instituting *inter partes* review has issued concurrently with this Decision. *Id.*, Paper 10.

B. The '756 Patent

The '756 patent relates to pharmaceutical formulations of lyophilized bendamustine. Ex. 1001, 1:18–21. Bendamustine is a nitrogen mustard, and nitrogen mustards are difficult to formulate as pharmaceuticals because of

their high reactivity in aqueous solutions. *Id.* at 1:35–36. Nitrogen mustards are therefore often supplied in a lyophilized form that requires reconstitution, usually in water, before administration. *Id.* at 1:36–38. Because nitrogen mustards are subject to degradation by hydrolysis once in aqueous solution, the reconstituted product should be administered to the patient as soon as possible after reconstitution. *Id.* at 1:39–42.

Bendamustine was first synthesized in 1964 in Germany and has been available in Germany under the names Cytostasan® or Ribomustin® since 1971. *Id.* at 1:60–64. Bendamustine has been widely used in Germany to treat chronic lymphocytic leukemia, Hodgkin's disease, non-Hodgkin's lymophoma, multiple myeloma, and breast cancer. *Id.* at 1:64–67.

Ribomustin® contains bendamustine hydrochloride and mannitol in a sterile lyophilized form. *Id.* at 2:3–5. Reconstitution of bendamustine lyophilized powder is difficult, taking at least fifteen to thirty minutes. *Id.* at 2:29–32. Besides being burdensome and time-consuming for the health care professional, the lengthy exposure of bendamustine to water during the reconstitution process increases the potential for loss of potency and impurity formation due to the hydrolysis of the product by water. *Id.* at 2:32–37. According to the Specification, "a need exists for lyophilized formulations of bendamustine that are easier to reconstitute and which have a better impurity profile than the current lyophilate (lyophilized powder) formulations of bendamustine." *Id.* at 2:38–41.

C. Illustrative Claim

Petitioner challenges claims 1–4 of the '756 patent, of which claims 1 and 4 are independent claims and are reproduced below:

> 1. A vial containing a reconstituted solution of bendamustine hydrochloride and mannitol in sterile water for

injection, wherein the ratio by weight of bendamustine hydrochloride to mannitol in the vial is 15:25.5, and wherein the bendamustine hydrochloride is present in the vial at a concentration of 100 mg per 20 mL.

4. A 20 mL vial containing 100 mg of bendamustine hydrochloride and 170 mg of mannitol reconstituted in sterile water for injection.

D. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of claims 1–4 of the '756 patent on the following grounds:

Reference	**Basis**	**Claim(s) challenged**
Ribomustin® Product Monograph[1] in view of Alexander[2] or Sauerbier[3]	§ 103	1–4
Ribomustin® Product Monograph in view of Alexander or Sauerbier and further in view of Teagarden[4]	§ 103	1–4
Ribomustin® Product Monograph in view of Alexander or Sauerbier and Teagarden, and further in view of DeLuca[5]	§ 103	1–4

[1] Ribomustin® Product Monograph, updated Jan. 2002 (Ex. 1005).
[2] Alexander et al., US 4,537,883, issued Aug. 27, 1985 (Ex. 1006).
[3] Sauerbier et al., US 5,204,335, issued Apr. 20, 1993 (Ex. 1007).
[4] Teagarden et al., *Practice Aspects of Lyophilization Using Non-Aqueous Co-Solvent Systems*, 15 EUR. J. PHARM. SCI. 115–33 (2002) (Ex. 1008).
[5] DeLuca, *Formulation of Small Volume Parenterals, in Pharmaceutical Dosage Forms: Parenteral Medications*, Vol. 1, Chapter 5 (Kenneth E. Avis et al. eds., 1992) (Ex. 1011).

Reference	Basis	Claim(s) challenged
Maas[6] and Ribomustin® Product Monograph in view of Alexander or Sauerbier, Teagarden, and DeLuca	§ 103	1–4

Pet. 9, 14–58.

II. ANALYSIS

A. Person of Ordinary Skill in the Art

Petitioner asserts that a person of ordinary skill in the art would have a Ph.D. in pharmaceutics, pharmaceutical sciences, or a related field, with at least three years of practice experience in the pharmaceutical formulation, including the formulation of lyophilized products. Pet. 13 (citing Ex. 1012 ¶ 22). Patent Owner does not offer a definition of the level of ordinary skill at this time. Prelim. Resp. 12. At this stage of the proceeding, we adopt the level of ordinary skill set forth by Petitioner and note that the prior art itself also demonstrates the level of skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (holding the absence of specific findings on "level of skill in the art does not give rise to reversible error 'where the prior art itself reflects an appropriate level and a need for testimony is not shown'") (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985)).

B. Claim Construction

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light

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[6] Maas et al., *Stabilität von Bendamustinhydrochlorid in Infusionslösungen [Stability of Bendamustine Hydrochloride in Infusions]*, 49 PHARMAZIE 775–77 (1994) (Ex. 1009).

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