UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN INSTITUTIONAL INC.,
Petitioner

v.

FRESENIUS KABI USA, LLC,
Patent Owner.

U.S. Patent No. 9,006,289 to Jiang *et al.*
Issue Date: April 14, 2015
Title: Levothyroxine Formulations

Inter Partes Review No.: IPR2017-00645

Petition for *Inter Partes* Review of U.S. Patent No. 9,006,289 Under 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.1-.80, 42.100-.123

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Petitioner's Exhibit List

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1001	U.S. Patent No. 9,006,289 to Jiang et al., "Levothyroxine Formulations"
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1003	U.S. Patent No. 9,168,239 to Jiang et al., "Levothyroxine Formulations"
1004	Declaration of James E. Kipp, Ph.D.
1005	Curricula Vitae of James E. Kipp, Ph.D.
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1007	APP Levothyroxine Sodium for Injection Prescribing Information
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1009	Collier *et al.*, "Influence of Formulation and Processing Factors on Stability of Levothyroxine Sodium Pentahydrate," APPS PharmSiTech 11(2), 2010, 818-825
1010	Baheti *et al.*, *Excipients Used in Lyophilization of Small Molecules*, J. Excipients and Food Chem. 1 (1), 41-54 (2010)
1011	U.S. Patent App. Pub. No. 2012/0190748 to Haren Treasurer, "Greater Utility with Thyroid hormone"
1012	Markman Opinion in *Fresenius Kabi USA, LLC v. Fera Pharmaceuticals, LLC, et al.*, No. 15-cv-3654-KM-MAH, ECF No. 327 (D.N.J. Sep. 20, 2016)
1013	Declaration of Arunya Usayapant dated December 23, 2014 filed in U.S. Patent App. No. 13/597,884
1014	Declaration of Jiang *et al.*, dated August 7, 2013 filed in U.S. Patent App. No. 13/597,884
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1038	Sznitowska *et al.*, *The Physical Characteristics of Lyophilized Tablets Containing a Model Drug in Different Chemical Forms and Concentrations*, Drug Research, Vol. 62 No. 1 pp. 25-29 (2005)

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1047	Appeal Brief of Defendants-Appellants filed in *Fresenius Kabi USA, LLC v. Fera Pharmaceuticals, LLC, et al.*, No. 2017-1099, ECF No. 24 (Fed. Cir. Dec. 27, 2016)
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1052	U.S. Patent No. 6,284,277 to Bouloumie et al., "Stable Freeze-Dried Pharmaceutical Formulation"
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I. INTRODUCTION

Mylan Institutional Inc. ("Petitioner") petitions for *Inter Partes* Review ("IPR"), and seeks cancellation of Claims 1–21 ("challenged claims") of U.S. Patent No. 9,006,289 ("the '289 patent") (EX1001), which is assigned to Fresenius Kabi USA, LLC ("Patent Owner").

II. OVERVIEW

Patent Owner admits that lyophilized compositions with levothyroxine, mannitol and a buffer were well-known before the filing date of the '289 patent. Nevertheless, the '289 patent purports to cover these same prior art lyophilized compositions—merely with lower amounts of mannitol.

The Board need look no further than the Background section to understand the well-known nature of the subject matter:

> Conventional formulations of levothyroxine sodium for injection are preservative-free lyophilized powders containing synthetic crystalline levothyroxine sodium and the excipients mannitol, tribasic sodium phosphate, and sodium hydroxide. These conventional formulations typically contain 10 milligrams (mg) of mannitol, 700 μg of tribasic sodium phosphate, and either 200 μg or 500 μg of levothyroxine sodium.

EX1001, 2:3–14. Petitioner agrees.

Faced with Patent Owner's recognition of these prior compositions, Patent Owner is left to assert that reducing the amount of mannitol unexpectedly improved

the stability of levothyroxine. EX1001, 3:41–46. This too fails. The prior art is replete with teachings that mannitol leads to instability of lyophilized levothyroxine compositions. *See, e.g.,* EX1007, 15; EX1006, 4, 9. Thus, a person of ordinary skill in the art ("POSA") would have been motivated to increase stability of such compositions by simply decreasing the amount of mannitol.

Petitioner is mindful that certain of the relied upon references herein were before the Examiner during the prosecution of the '289 patent. Nevertheless, that does not change the obviousness of the alleged invention and should not deter the Board from instituting this IPR, particularly in light of the new prior art, evidence, and arguments presented herein. As explained herein, and by Petitioner's expert Dr. Kipp (EX1004), decreasing mannitol from 10 milligrams to 2 to 4 milligrams (or 3 milligrams) would have been obvious as well as the other remaining limitations.

For these reasons, this Petition ultimately boils down to whether lowering mannitol in prior art compositions, when mannitol was known to increase instability, was novel. It was not.

III. STANDING (37 C.F.R. § 42.104(a); PROCEDURAL STATEMENTS)

Petitioner certifies that: (1) the '289 patent is available for IPR; and (2) Petitioner is not barred or estopped from requesting IPR of any claim of the '289 patent on the grounds identified herein. This Petition is filed in accordance with 37 C.F.R. § 42.106(a). Filed herewith are a Power of Attorney and an Exhibit List

pursuant to § 42.10(b) and § 42.63(e). The required fee is paid through an online credit card, and the Office is authorized to charge any fee deficiencies and credit overpayments to Deposit Acct. No. 160605 (Customer ID No. 00826).

IV. MANDATORY NOTICES (37 C.F.R. § 42.8(a)(1))

A. Each Real Party-In-Interest (37 C.F.R. § 42.8(b)(1))

Mylan Institutional Inc., Mylan Inc., and Mylan N.V.

B. Notice of Related Matters (37 C.F.R. § 42.8(b)(2))

1. Judicial Matters

The '289 patent is currently the subject of the following litigations: *Fresenius Kabi USA, LLC v. Fera Pharmaceuticals, LLC*, Docket No. 17-01099 (Fed. Cir. Oct 24, 2016); *Fresenius Kabi USA, LLC v. Innopharma Licensing, LLC et al.*, No. 2:15-cv-03655-KM-MAH (D.N.J.); *Fresenius Kabi USA, LLC v. Fera Pharmaceuticals, LLC*, No. 2:15-cv-03654-KM-MAH (D.N.J.); *Fresenius Kabi USA, LLC v. Par Sterile Products, LLC et al*., No. 2:15-cv-03852-KM-MAH (D.N.J.); *Fresenius Kabi USA, LLC v. Dr. Reddy's Laboratories, Inc. et al*., No. 1:16-cv-00169-GMS (D. Del.); *Fresenius Kabi USA, LLC v. Dr. Reddy's Laboratories, Inc. et al*., No. 2:16-cv-01542-KM-MAH (D.N.J.); *Fresenius Kabi USA, LLC v. Maia Pharmaceuticals, Inc*., No. 1:16-cv-00237-GMS (D. Del.); *Fresenius Kabi USA, LLC v. Dr. Reddy's Laboratories, Inc. et al*., No. 2:16-cv-03316-KM-MAH (D.N.J.); and *Fresenius Kabi USA, LLC v. Maia Pharmaceuticals, Inc.*, No. 2:16-cv-03315-KM-MAH

(D.N.J.).

2. Administrative Matters

At least the following related '289 patent family members exist: U.S. Patent No. 9,168,238 ("the '238 patent") (EX1002); U.S. Patent No. 9,168,239 ("the '239 patent") (EX1003); and U.S. App. No. 14/866,521.

C. Designation of Lead and Back-Up Counsel and Service (37 C.F.R. §§ 42.8(b)(3), 42.8(b)(4), 42.10(a), and 42.10(b)):

Lead Counsel	Back-Up Counsel
Jitendra Malik, Ph.D. Reg. No. 55,823 ALSTON & BIRD LLP 4721 Emperor Boulevard, Suite 400 Durham, North Carolina 27703-8580 919.862.2200 jitty.malik@alston.com	H. James Abe Reg. No. 61,182 ALSTON & BIRD LLP 333 South Hope Street, 16th Floor Los Angeles, CA 90071 213.576.1000 james.abe@alston.com Lance Soderstrom Reg. No. 65,405 ALSTON & BIRD LLP 90 Park Avenue, 15th Floor New York, New York 10016-1387 212.210.9400 lance.soderstrom@alston.com Alissa Pacchioli Reg. No. 74,252 ALSTON & BIRD LLP 4721 Emperor Boulevard, Suite 400 Durham, North Carolina 27703-8580 919.862.2200 alissa.pacchioli@alston.com

Petitioner consents to email service.

V. STATEMENT OF THE PRECISE RELIEF REQUESTED AND THE REASONS THEREFORE (37 C.F.R. § 42.22(a))

Petitioner requests IPR and cancellation of Claims 1–21 of the '289 patent. Petitioner's full statement of the reasons for the relief requested is set forth in detail below.

VI. THE '289 PATENT

The '289 patent has two independent claims (Claims 1 and 14). Independent Claim 1 is directed to a lyophilized solid composition comprising three components: (1) about 100 or about 200 micrograms of levothyroxine sodium; (2) a phosphate buffer; and (3) from 2 to 4 milligrams of mannitol. EX1001, 12:12–18. Claim 14 is the same as Claim 1 except that it requires about 500 micrograms of levothyroxine sodium. EX1001, 13:1–5. A complete analysis of the claims, as well as application of the relevant prior art, is presented below.

A. Claim Construction

In the corresponding district court litigation, the District of New Jersey provided the following constructions:

Term	**Construction**
Buffer	A system that resists changes in pH when acid or base is added.
Dibasic sodium phosphate	Anhydrous Na_2HPO_4 and the hydrate forms associated with Na_2HPO_4.
Converted to liothyronine	Turned into liothyronine.

Fresenius Kabi USA, LLC v. Fera Pharmaceuticals, LLC, et al., No. 15-cv-3654-KM-MAH, ECF No. 327 (D.N.J. Sep. 20, 2016) ("Markman Opinion") (EX1012) at 18–19. While Petitioner maintains that these claim terms should be given their broadest reasonable interpretation ("BRI") in this proceeding, the BRI should at least encompass the district court's constructions. 37 C.F.R. § 42.100(b).

The district court determined that "phosphate buffer" (*see, e.g.*, Claims 1 and 14 of the '289 patent) did not require further construction in light of the construction of "buffer" (EX1012, 18). Petitioner submits that "phosphate buffer" should be given its BRI, however, to explain the obviousness analysis below which involves prior art teachings of different phosphate buffers, Petitioner submits that the term "phosphate buffer" is not limited to a specific phosphate buffer and thus includes, *e.g.*, tribasic phosphate, dibasic phosphate, and monobasic phosphate buffers. The claims, specification, and prosecution history all support this construction.

First, under the ordinary and customary meaning, as would have been understood by a POSA at the time, the term "phosphate" buffer was not limited to any particular type thereof (*e.g.*, dibasic, tribasic, etc.), or even to any particular salt

form (*e.g.*, sodium, potassium, etc.) or hydrate (*e.g.,* anhydrous, heptahydrate, etc.). EX1004, footnote 21; EX1036, 1153 (defining sodium phosphate as "sodium metaphosphate; sodium phosphate, dibasic; sodium phosphate, monobasic; sodium phosphate (P-32); *sodium phosphate, tribasic*; sodium polyphosphate; sodium pyrophosphate; sodium pyrophosphate, acid; sodium tripolyphosphate"); EX1039, 1035 (listing potassium phosphate dibasic, monobasic, and tribasic).

The doctrine of claim differentiation also supports Petitioner's construction. Several dependent claims of the '289 patent recite that "the phosphate buffer is dibasic sodium phosphate;" therefore, the claim term "phosphate buffer" recited by the independent claim includes more than just dibasic sodium phosphate. *See, e.g.*, EX1001, Claims 4, 9, 16; *Karlin Technology, Inc. v. Surgical Dynamics, Inc*., 177 F.3d 968, 971–72 (Fed. Cir. 1999) ("[D]ifferent words or phrases used in separate claims are presumed to indicate that the claims have different meanings and scope.").

Second, the specification of the '289 patent does not explicitly exclude any particular phosphate buffer—such as tribasic sodium phosphate—from the term "phosphate buffer." Although the '289 patent states that tribasic sodium phosphate is not included in the preferred embodiment, the Federal Circuit has held that "[t]he general rule, of course, is that the claims of a patent are not limited to the preferred embodiment, unless by their own language." *Karlin Technology, Inc.*, 177 F.3d at 973; EX1001, 4:42–48.

Third, during prosecution of the '289 patent, one of the named inventors filed a declaration ("Usayapant Decl.") (EX1013) in which the prior art composition containing tribasic sodium phosphate was described as having "a phosphate buffer." EX1013, ¶ 14. Accordingly, the term "phosphate buffer" should not be limited to specific phosphate buffers.

All remaining claim terms should be given their BRI, *i.e.*, their ordinary and customary meaning as would have been understood by a POSA at the time, in the context of the entire patent disclosure.[1] 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016); *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007).

[1] The '289 patent also explicitly defines certain terms: "mass ratio," "lyophilizing," and "spans the range." EX1001, 2:62–3:16. To the extent necessary, Petitioner applies the definitions provided in the patent specification.

VII. PERSON OF ORDINARY SKILL IN THE ART & STATE OF THE ART

The earliest possible priority date of the '289 patent is August 30, 2011.[2] As of that time, a POSA in the relevant field would have had education and/or experience in the field of drug delivery systems, with knowledge of the scientific literature concerning the same, including some understanding of lyophilized pharmaceutical compositions and injectable preparations. The education and experience levels may vary between POSAs, with some having a bachelor's degree in the chemical or pharmaceutical arts plus five years of relevant work experience, or with others holding more advanced degrees—*e.g.*, Ph.D. or Pharm.D.—while having fewer years of experience. EX1004, ¶45.

VIII. IDENTIFICATION OF CHALLENGE (37 C.F.R. § 42.104(b))

Petitioner respectfully requests IPR of Claims 1–21 of the '289 patent on each specific ground of unpatentability outlined below. Per 37 C.F.R. § 42.6(d), copies of the references are filed herewith. In support of the proposed grounds, this Petition includes the declaration of a technical expert, James E. Kipp, Ph.D. (EX1004),

[2] The'289 patent claims priority to U.S. Provisional Application No. 61/529,084 ("the '084 provisional") (EX1027), which was filed on August 30, 2011. EX1001, 1:5–8.

explaining what the art would have conveyed to a POSA as of the priority date of the '289 patent.

Ground	References	Basis	Claims Challenged
1	Abbott Label, Brower, Baheti, and Collier	35 U.S.C. § 103	1–21
2	APP Label, Brower, Baheti, and Collier	35 U.S.C. § 103	1–21
3	Abbott Label, APP Label, Brower, Baheti, and Collier	35 U.S.C. § 103	1–21

Prior art references in addition to the primary references listed above provide further background in the art, motivation to combine the teachings of these references, and/or support for why a POSA would have had a reasonable expectation of success to arrive at the purported invention recited in the challenged claims.

As the Board knows, the fact that a reference was disclosed to the Examiner is not a bar to institute an IPR. For example, the Board instituted IPR in *Sharp Corp. v. Surpass Tech Innovation LLC*, IPR2015-00021, Paper 10 (P.T.A.B. Mar. 18, 2015) even though the Petitioner relied on previous considered references, because the petitioner presented different arguments that "shed[] a different light on the [repeated] reference." *Id.* at 14; *Chi Mei Innolux Corp. v. Semiconductor Energy Lab. Co., Ltd.*, IPR2013-00028, Paper 14 at 10 (P.T.A.B. Mar. 21, 2014) (instituting IPR where the petitioner submitted an expert declaration even though the same arguments and prior art were allegedly considered). The Board also instituted IPR

in *Owens Corning v. Fast Felt Corp*., IPR2015-00650, Paper 9 (P.T.A.B. Aug. 13, 2015) even though the Examiner considered Petitioner's primary reference, because secondary references were added by the Petitioner. *Id.* at 25–26; *Praxair Distrib., Inc. v. Ino Therapeautics, LLC*, IPR2015-00893, Paper 14 at 7–9 (P.T.A.B. Sept. 22, 2015) (instituting IPR even though the two main references were considered, because the same combination of references was not before the examiner, including the declaration of petitioner's expert). Here, several prior art references were not disclosed to the Examiner (*e.g.,* Brower EX1018) and new evidence is submitted to shed a different light on the prior art (*e.g*., Kipp Decl. EX1004). Additionally, undisclosed data hindered the Examiner's ability to assess the Patent Owner's allegations. *See infra* p. 66.

IX. INVALIDITY ANALYSIS

The inquiry for obviousness was established by the Supreme Court in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17 (1966). The *Graham* factors require an examination of: (1) the scope and content of the prior art; (2) differences between the prior art and the claims at issue; (3) the level of ordinary skill in the pertinent art; and (4) secondary considerations of non-obviousness. *Id*.

A. The Scope and Content of the Prior Art

1. Instability of Levothyroxine Sodium Compositions

Levothyroxine is a thyroid hormone that has been commercially available as

a tablet and as a lyophilized composition for injection long before the '289 patent. *See, e.g.,* Prescribing Information for Synthroid® by Abbott ("Abbott Label") (EX1006)[3] at 1; Synthroid, Announcements: Postgraduate Medicine, 1969 Vol. 46, No. 4, p. 18 ("Travenol Label") (EX1051)[4]; EX1004, ¶¶49-51. The instability of levothyroxine and its salt derivatives was also well-known long before the '289 patent. EX1004, ¶¶52-63.

For example, Brower *et al*., *Determination of Sodium Levothyroxine in Bulk, Tablet, and Injection Formulations by High-Performance Liquid Chromatography*, J. Pharm. Sci. 73:1315–1317 (1984) ("Brower") (EX1018)[5] provided stability data of 100, 200, and 500 microgram lyophilized levothyroxine sodium compositions.

[3] The Abbott Label is dated April 2001 and is prior art under 35 U.S.C. § 102(b). The Abbott Label is not listed on the cover page of the '289 patent and, therefore, was not considered by the Examiner.

[4] The Travenol Label is prior art under 35 U.S.C. § 102(b). The Travenol Label is not cited on the cover page of the '289 patent and, therefore, was not considered by the Examiner.

[5] Brower is prior art under 35 U.S.C. § 102(b). Brower is not cited on the cover page of the '289 patent and, therefore, was not considered by the Examiner.

EX1018, 1315–16. Brower reported degradation levels of lyophilized levothyroxine compositions that were comparable to (or worse than) the degradation levels of levothyroxine tablets. EX1018, 1316–17; EX1004, ¶¶52–56. Brower stated that "[l]ow assay values were a problem experienced by most manufacturers" and that "the problems of low assays of marketed sodium levothyroxine are, in all probability, attributable to sodium levothyroxine instability." EX1018, 1317.

Likewise, U.S. Patent App. Pub. No. 2012/0190748 ("Treasurer") (EX1011)[6] disclosed lyophilized compositions for injection and teaches that "[b]oth T4 [(levothyroxine)] and T3 [(liothyronine)] are unstable molecules due to the likelihood of their iodine atoms to be removed by hydrolysis." EX1011, [0023], [0072], [0097], FIG. 2, 5. Thus, Brower and Treasurer show that lyophilized levothyroxine sodium compositions had degradation issues. EX1004, ¶59.

Furthermore, Shah *et al*., *Stability Indicating Validated HPLC Method for Quantification of Levothyroxine with Eight Degradation Peaks in the Presence of Excipients*, International Journal of Pharmaceutics 360 (2008) 77–82 ("Shah")

[6] Treasurer was filed on August 3, 2010 and is prior art under at least 35 U.S.C. § 102(e). Treasurer is not cited on the cover page of the '289 patent and, therefore, was not considered by the Examiner.

(EX1016)[7] also disclosed stability problems associated with levothyroxine:

> Previous studies have shown that *different dosage forms of levothyroxine are susceptible to degradation* under the influence of various environmental stress factors such as humidity and temperature. . . . There were numerous recalls of levothyroxine due to stability issues (FDA, 2006). Further, lacks of potency and stability assurances has brought in concerns from physicians regarding their therapeutic substitutions and are believed not to deliver right doses to the patients (Thyroid, 2004).

EX1016, 78 (emphasis added); EX1004, ¶60.

Won also described degradation of levothyroxine. Chong Min Won, *Kinetics of Degradation of Levothyroxine in Aqueous Solution and in Solid State*, Pharm. Res. Vol. 9 No., 131–137 (1992) ("Won") (EX1017)[8] at Abstract. Won stated that "[t]he purpose of this study was to obtain kinetic data on the degradation of T_4 [(levothyroxine)] in solution and in solid state and to investigate possible mechanisms of the degradation processes." EX1017, 131. Won found that

[7] Shah is prior art under 35 U.S.C. § 102(b). Shah is not cited on the cover page of the '289 patent and, therefore, was not considered by the Examiner.

[8] Won is prior art under 35 U.S.C. § 102(b). Won is listed on the cover page of the '289 patent, but was not referenced in any rejection by the Examiner.

degradation of levothyroxine occurs in both aqueous solution and in solid-state. EX1017, 131; EX1004, ¶58.

Glass *et al*., *Stability Considerations in Liquid Dosage Forms Extemporaneously Prepared from Commercially Available Products*, J. Pharmacy Pharm. Scis. 9 (3): 398–426 (2006) ("Glass") (EX1019)[9] made observations connected to the instability of a lyophilized powder of levothyroxine sodium:

> There have been some issues raised recently about the stability of thyroxine (solid state) to light, heat and humidity . . . .
>
> In an earlier article by Boulton et al. (106), comment was made of the availability of levothyroxine sodium as a lyophilized powder for injection which, although it could be administered orally, was not cost effective. . . . Significant degradation was observed in all the formulations studied by this group, with those formulations including the preservative proving to be more unstable than those without the preservative . . . .

EX1019, 415; EX1004, ¶61.

Collier *et al*., *Influence of Formulation and Processing Factors on Stability of Levothyroxine Sodium Pentahydrate*, APPS PharmSiTech 11(2), 2010, 818–825

[9] Glass is prior art under 35 U.S.C. § 102(b). Glass is not cited on the cover page of the '289 patent and, therefore, was not considered by the Examiner.

("Collier") (EX1009)[10] reported that "[l]evothyroxine has been a subject of advisory committee meetings at the FDA due to its potency and stability issues." Collier noted that light, air, and humidity had been reported as causing instability, and then discussed the role that excipients played in the degradation of levothyroxine sodium. EX1009, 818. Collier further recognized the influence of solid state hydration on instability of levothyroxine. EX1009, 818; EX1004, ¶52.

Consistent with the well-known instability of levothyroxine, the Abbott Label and the prescribing information for Levothyroxine Sodium for Injection by APP Pharmaceuticals, LLC ("APP Label") (EX1007)[11] contained storage instruction warnings against exposing those lyophilized levothyroxine sodium compositions to multiple factors that impact stability. *See* EX1007, 15 (stating that the composition

[10] Collier is prior art under at least 35 U.S.C. § 102(b). Collier was considered during prosecution of the '289 patent.

[11] The APP Label is dated June 2011 and is prior art under 35 U.S.C. § 102(a). The APP Label was disclosed during prosecution of the '289 patent, but was not referenced in any rejection. The formulation disclosed in the APP Label differs from the Abbott Label in that the phosphate buffer recited on the Abbott Label is tribasic sodium phosphate anhydrous while the APP Label is dibasic sodium phosphate heptahydrate. EX1007 at 10.

is to be protected from light and stored dry at 20° to 25°C); EX1006, 4, 9 (stating that the composition is to be stored at 25°C and away from heat and moisture); EX1004, ¶63.

Accordingly, it would have been clear to a POSA that levothyroxine compositions—regardless of dosage forms—were inherently unstable. EX1004, ¶¶57–63.

2. Mannitol was the Most Commonly Used Bulking Agent and was Used in Lyophilized Levothyroxine Sodium Compositions

The use of mannitol as a bulking agent in lyophilized compositions was well-known. EX1004, ¶¶64-68. For example, Baheti *et al.*, *Excipients Used in Lyophilization of Small Molecules*, J. Excipients and Food Chem. 1 (1), 41–54 (2010) ("Baheti") (EX1010)[12] taught that mannitol was the single most commonly used bulking agent for lyophilized compositions and, in doing so, specifically identified lyophilized compositions of levothyroxine sodium. EX1010, 43; EX1004, ¶¶66–67. Baheti also noted that mannitol provided better stability compared to lactose. EX1010, 46. Baheti also explained that the inclusion of a bulking agent was necessary in lyophilized compositions, stating they are "used for low dose (high

[12] Baheti is prior art under 35 U.S.C. § 102(b). Baheti was considered during prosecution of the '289 patent.

potency) drugs that *per se* do not have the necessary bulk to support their own structure." EX1010, 43; EX1004, ¶¶64–65.

Moreover, as the '289 patent explains, prior art lyophilized levothyroxine sodium compositions were well known to contain the same amount (*i.e.*, 10 milligrams) of mannitol as a bulking agent for different dosages. EX1001, 2:3–15; EX1027, [0024]; Bedford Laboratories, Levothyroxine Sodium for Injection Rx Only ("Bedford Label") (EX1053),[13] 1; EX1004, ¶68. Consistent with the statements of the '289 patent, the Abbott Label teaches two dosages of lyophilized levothyroxine sodium compositions that both contain "10 mg mannitol, USP." EX1006, 2 ("Inactive Ingredients (SYNTHROID Injection)").

3. Mannitol's Impact on the Stability of Lyophilized Levothyroxine Sodium Compositions was Known

Mannitol was known to have a detrimental impact on lyophilized levothyroxine sodium compositions. Baheti taught that crystallization of the bulking agent (*e.g.*, mannitol) due to the lyophilization process caused faster degradation of the active pharmaceutical ingredient because more water would be available to facilitate hydrolysis. EX1010, 46; Michael J. Akers, *Sterile Drug Products,*

[13] The Bedford Label is prior art under 35 U.S.C. § 102(b). The Bedford Label was considered during prosecution of the '289 patent.

Formulation, Packaging, Manufacturing, and Quality, Informa Healthcare (2010) 138-139, 154-168 ("Akers") (EX1042)[14] at 155, 158–59; EX1004, ¶¶70, 72. Baheti further disclosed that the amount of crystallization was affected by the ratio of the bulking agent (*e.g.*, mannitol) to the active ingredient (*e.g.*, levothyroxine sodium). EX1010, 49 ("The nature of lyophilized cake also depends on the ratio of drug and bulking agent, showing an increased crystallization with an increase in amount of bulking agent. . . . The degree of crystallization increased with an increase in the mole fraction of the excipient."); EX1004, ¶71.

Put another way, Baheti taught that reducing the amount of mannitol used in lyophilized compositions would improve the stability of moisture-sensitive compounds, which would include levothyroxine sodium. *See also* Kim *et al.*, *The Physical State of Mannitol after Freeze-Drying: Effects of Mannitol Concentration, Freezing Rate, and a Noncrystallizing Cosolute*, 87 J. Pharm. Sci. 931-935 (1998) ("Kim") (EX1048),[15] 931 (discussing the adverse effects of mannitol on drug

[14] Akers was published on August 20, 2010 and is prior art under 35 U.S.C. § 102(b). Akers was not considered during prosecution of the '289 patent.

[15] Kim is prior art under 35 U.S.C. § 102(b). Kim was considered during prosecution of the '289 patent.

stability); Yu *et al*., *Existence of a Mannitol Hydrate during Freeze-Drying and Practical Implications*, 88 J. Pharm. Sci. 196-198 (1999) ("Yu") (EX1049),[16] 198 (teaching the formation of mannitol hydrate and threat to product stability); EX1004, ¶¶73–74. Indeed, the importance of the ratio of mannitol to active ingredient was well-known. *See* U.S. Patent No. 6,284,277 ("Bouloumie") (EX1052)[17] at 4:21-28 (teaching that the ratio of mannitol to the active ingredient can have a stabilizing effect); Torrado *et al*., Characterization of Physical State of Mannitol after Freeze-Drying: Effect of Acetylsalicylic Acid as a Second Crystalline Cosolute, Chem. Pharm. Bull. 50(5) 567-570 (2002) ("Torrado") (EX1050)[18] at 567; EX1004, ¶¶75, 76. Therefore, a POSA would have known that less mannitol was better. EX1004, ¶76.

Additionally, Collier recognized that excipients could cause instability of pharmaceutical compositions and focused specifically on levothyroxine sodium.

[16] Yu is prior art under 35 U.S.C. § 102(b). Yu was not considered during prosecution of the '289 patent.

[17] Bouloumie is prior art under 35 U.S.C. § 102(b). Bouloumie was not considered during prosecution of the '289 patent.

[18] Torrado is prior art under 35 U.S.C. § 102(b). Torrado was not considered during prosecution of the '289 patent

EX1009, 819 ("Lack of compatibility between levothyroxine and its excipients can lead to stability problems . . . ."). Collier tested levothyroxine sodium against various excipients, including mannitol, in the presence of 5% moisture. EX1009, 820 (Table 1). The mannitol sample exhibited a 50.0% degradation of the levothyroxine sodium. EX1009, 822. Accordingly, a POSA would have known that mannitol would impact the stability of a lyophilized levothyroxine sodium composition. EX1004, ¶¶77–78.

Thus, a POSA would have known of the instability of lyophilized levothyroxine sodium compositions, and that this instability was attributable to mannitol. Specifically, a POSA would have known that the amount of mannitol used impacted the amount of moisture present in the composition. Despite these drawbacks, mannitol—which was the most widely used bulking agent in the prior art (as well as the only one used in lyophilized levothyroxine compositions)—could not completely be removed because the presence of some bulking agent was necessary. EX1004, ¶¶79–80, footnote 7.

B. Ground 1: Claims 1–21 Would Have Been Obvious over the Abbott Label, Brower, Baheti, and Collier

1. Claims 1 and 14

The Abbott Label taught each limitation of Claims 1 and 14 of the '289 patent as shown in the chart below except that the Abbott Label does not disclose the "2 to

4" milligrams of mannitol limitation. Instead, it described 10 milligrams of mannitol. As explained below, it would have been obvious to a POSA to reduce the amount of mannitol to "2 to 4" milligrams. EX1004, ¶¶81–82.

Claim	**Prior Art**
1. A composition, comprising:	Abbott Label teaches a pharmaceutical composition. EX1006, 9.
about 100 or about 200 micrograms of levothyroxine sodium;	Abbott Label teaches 200 micrograms of levothyroxine sodium. EX1006, 9.
a phosphate buffer; and	Abbott Label teaches tribasic sodium phosphate. EX1006, 2.[19]
from 2 to 4 milligrams of mannitol,	Abbott Label teaches 10 milligrams mannitol. EX1006, 2.
where the composition is a lyophilized solid.	Abbott Label teaches a lyophilized powder. EX1006, 9.
14. A composition, comprising:	Abbott Label teaches a pharmaceutical composition. EX1006, 9.
about 500 micrograms of levothyroxine sodium;	Abbott Label teaches 500 micrograms of levothyroxine sodium. EX1006, 9.
a phosphate buffer; and	Abbott Label teaches tribasic sodium phosphate. EX1006, 2.
from 2 to 4 milligrams of mannitol,	Abbott Label teaches 10 milligrams mannitol. EX1006, 2.
where the composition is a lyophilized solid.	Abbott Label teaches a lyophilized powder. EX1006, 9.

[19] *See supra* pp. 6–8 (discussing the construction of "phosphate buffer" to include, *e.g.*, tribasic phosphate, dibasic phosphate, and monobasic phosphate buffers). To the extent the Board finds that the claim term "phosphate buffer" does not include "tribasic sodium phosphate," replacing it with dibasic sodium phosphate would have been obvious. *See infra* Part IX.B.3.

a. A POSA Would Have Been Motivated to Reduce the Amount of Mannitol Below the 10 Milligrams Used in the Abbott Label

Any POSA would have been (and is) motivated to improve the stability of pharmaceutical compositions. *See, e.g.,* EX1016, 77 ("Stability is considered one of the most important requirements of pharmaceutical product quality."); EX1004, ¶92. Moreover, a POSA would have used the least amount of excipients necessary to prepare a stable composition. EX1004, ¶92; *see also* Carpenter *et al*., *Rational Design of Stable Lyophilized Protein Formulations: Some Practical Advice*, Pharm. Research, Vol. 14, No. 8, 1997 ("Carpenter") (EX1025)[20] at 972 ("[F]or any lyophilized formulation, the minimum number of components necessary for . . . stability and cake structure should be used.").

As explained below, it would have been obvious to reduce the amount of mannitol below 10 milligrams to improve stability of the prior art lyophilized levothyroxine sodium composition described in the Abbott Label.

[20] Carpenter is prior art under 35 U.S.C. § 102(b). Carpenter is not cited on the cover page of the '289 patent, and thus was not considered by the examiner.

(i) Instability of Lyophilized Levothyroxine Sodium Compositions was Known

As discussed above, the instability of lyophilized levothyroxine sodium compositions (including lyophilized compositions containing 10 milligrams of mannitol) was well known prior to August 30, 2011. *See supra* Part IX.A.1. Specifically, Brower provides data that shows conventional lyophilized levothyroxine sodium compositions had degradation problems. EX1018, 1316–17; EX1004, ¶¶53-56. As such, a POSA would have been motivated to improve the stability of a lyophilized levothyroxine sodium composition. EX1004, ¶¶93–94.

(ii) Degradation of Levothyroxine Sodium by Mannitol was Known as was Reducing the Amount of Mannitol to Improve the Composition

A POSA would have also known that relatively high amounts of mannitol contributed to the instability of moisture sensitive drugs such as levothyroxine sodium.[21] *See supra* Part IX.A.3. Indeed, Baheti specifically noted that

[21] For example, a POSA would have known that levothyroxine "is sensitive to moisture" (EX1009, 822; EX1016, 78), and that mannitol can cause degradation of moisture-sensitive drugs. EX1010, 49 (explaining that crystallized mannitol releases water during shipping and storage, causing degradation of moisture-sensitive drugs); *see also id.* at 46 ("The non-hygroscopic nature of crystalline mannitol, led to an increase in the amount of water available with the drug.").

crystallization of mannitol caused faster degradation because more water would be available. EX1010, 46. Baheti also taught that the ratio of the bulking agent to the active ingredient was relevant, observing "an increased crystallization with an increase in amount of bulking agent." EX1010, 49; EX1004, ¶¶95-96.

Further, Collier measured the stability of levothyroxine sodium against various excipients, including mannitol, and reported that levothyroxine sodium had 50.0% degradation after 28 days of accelerated aging at 60°C in the presence of mannitol and 5% moisture. EX1009, 820, 822. Collier also demonstrated that other excipients—such as colloidal silicon dioxide, magnesium stearate, acacia, lactose monohydrate, croscarmellose sodium, corn starch, sodium starch glycolate—caused less degradation than mannitol, while six other excipients—microcrystalline cellulose, confectioner's sugar, crospovidone, povidone, sodium laurate sulfate—caused comparable or higher degradation. EX1009, 822–23. Accordingly, a POSA would have understood that mannitol affects the stability of levothyroxine sodium and that mannitol does not protect levothyroxine sodium from moisture degradation. EX1004, ¶98.

As Dr. Kipp explains, in view of Baheti and Collier, a POSA would have first reduced the amount of mannitol below 10 milligrams to improve the stability, rather than replace mannitol with a different bulking agent. EX1004, ¶¶96–102, 127. The Abbott Label includes mannitol and does not include any other bulking agent (*e.g.,*

lactose monohydrate), thus the first natural step would be to reduce the amount of mannitol to address the known degradation caused by mannitol crystallization. EX1006, 2; *see also* EX1007, 9–10 & EX1010, 45 (mannitol in levothyroxine sodium compositions); EX1021, 716 (same); EX1018, 1316 (same); EX1004, ¶¶101-102.

Moreover, as Patent Owner's Declarant explained to the Examiner, "[o]ther than mannitol and lactose monohydrate, none of the excipients tested in Collier are FDA-approved for use in a composition intended for intravenous administration," thereby necessarily focusing a POSA on mannitol and lactose monohydrate. EX1015, ¶ 18; EX1004, ¶127. "Where a skilled artisan merely pursues known options from a finite number of identified, predictable solutions, obviousness under § 103 arises." *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009).

Furthermore, as Dr. Kipp explains, a POSA would have also focused on mannitol, and not lactose monohydrate, for a number of other reasons. Mannitol was the most widely used bulking agent in lyophilized compositions—*e.g.*, used four times as much as lactose monohydrate—and it also was the single, most-used bulking agent for injectable applications, in particular. EX1004, ¶102; EX1010, 43; EX1010, 44-45 (table showing mannitol was the most used excipient for intermuscular and intravenous applications). Mannitol was also recognized as safe by the FDA and recognized as a good cryoprotectant. EX1004, ¶¶102, 127; Rowe

et al., "Mannitol," Handbook of Pharmaceutical Excipients, 5th Ed. (2006) pp. 449-453, 452 ("Handbook") (EX1008)[22]; EX1042, 156; *see supra* footnote 29 (discussing that levothyroxine sodium contains an amino acid (*i.e*., building blocks of proteins) and free amino groups). Therefore, a POSA's efforts to improve the stability of a levothyroxine sodium composition would have focused on—at least at the outset—reducing the amount of mannitol from the 10 milligrams recited on the Abbott Label. EX1004, ¶¶99–102, 127; *see also infra* pp. 32–34 (discussing levothyroxine degradation caused by lactose).

b. A POSA Would Have Had a Reasonable Expectation of Success

Given that reducing the amount of mannitol would have been such a simple modification, a POSA would have had a reasonable expectation of success in obtaining a lyophilized levothyroxine sodium composition having improved stability. EX1004, ¶¶100, 114. First, a POSA would have conducted routine experimentation starting with an amount less than 10 milligrams and ultimately arriving at the recited "2 to 4" milligrams; it would have been obvious to determine

[22] The Handbook is prior art under 35 U.S.C. § 102(b). The Handbook is listed on the cover of the '289 patent, but the Examiner did not rely on the Handbook in any rejections.

the optimal amount through routine experimentation. EX1004, ¶¶79, 96, 100, 137; *In re Aller*, 220 F.2d 454, 456–57 (C.C.P.A. 1955).

Second, a POSA would have had a reasonable expectation of success because an amount of mannitol below 10 milligrams was within the typical range of mannitol in lyophilized compositions as shown by the Handbook, a reference commonly consulted by POSAs. EX1004, ¶¶67, 104. The Handbook discloses that "[i]n lyophilized preparations, mannitol (20–90% w/w) has been included as a carrier to produce a stiff, homogeneous cake that improves the appearance of the lyophilized plug in a vial." EX1008, 449. As Dr. Kipp explains, if the range disclosed in the Handbook (20–90% w/w) is applied to the lyophilized levothyroxine sodium compositions according to the Abbott Label, then the corresponding range of mannitol would be as shown in the table below:[23]

[23] As discussed below in connection with Claim 2, a 100 microgram (0.1 milligram) levothyroxine sodium lyophilized composition would have been obvious. *See infra* Part IX.B.2.a. The amount of mannitol that would be used according to the Handbook for a 100 microgram levothyroxine sodium lyophilized composition can be determined through apportionment of the 200 microgram composition. EX1004, ¶¶111–112. In other words, by comparing the

Levothyroxine Sodium (milligrams)	**Mannitol (% w/w)**	**Mannitol (milligrams)**
0.1 (100 micrograms)	20	0.1125
0.1	90	4.05
0.2 (200 micrograms)	20	0.225
0.2	90	8.1
0.5 (500 micrograms)	20	0.5625
0.5	90	20.25

EX1004, ¶¶105–113. As shown in the table, the claimed range of "2 to 4" milligrams of mannitol falls within the typical range of mannitol calculated according to the Handbook's disclosure.[24] EX1004, ¶114. Accordingly, a POSA would have had a reasonable expectation of success.

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compositions of the 200 and 500 microgram levothyroxine sodium lyophilized compositions, one can determine that the amount of mannitol according to the Handbook is proportional to the amount of levothyroxine sodium.

[24] Moreover, overlapping ranges establish a *prima facie* case of obviousness. *In re Peterson*, 315 F.3d 1325, 1329–30 (Fed. Cir. 2005); *Biomarin Pharms. Inc. v. Genzyme Therapeutics Products Ltd*., IPR2013-00534, Paper 81 (Final Written Decision) at 15 (P.T.A.B. Feb. 23, 2015) ("All that remained to be achieved over the prior art was the determination that a specific dose within a previously suggested dose range . . . would have been safe and effective . . . ."). Furthermore, a POSA would have been motivated to have a single amount of mannitol for all

c. Patent Owner's Arguments during Prosecution Do Not Support Patentability

During prosecution, Patent Owner advanced various arguments to support patentability. For the reasons explained below, those arguments should not be given any weight and should not deter the Board from instituting this IPR.

In reference to Baheti (*see supra* Parts IX.A.3, IX.B.1.a(ii)), Patent Owner argued that Baheti's teachings in relation to Herman *et al*., *The Effect of Bulking Agent on the Solid-State Stability of Freeze-Dried Methylprednisolone Sodium Succinate*, Pharm. Res., 11:1467-1473 (1994) ("Herman") (EX1054)[25] are limited to methylprednisolone sodium succinate and thus a POSA would not apply them to levothyroxine sodium.[26] Patent Owner's narrow reading of Baheti is contradicted even by the title of Baheti, "Excipients Used in Lyophilization of Small Molecules,"

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levothyroxine dosages, as was the case for the Abbott Label. EX1006, 2; EX1004, ¶114; EX1002, 2:8–10; EX1027, [0024].

[25] Herman is prior art under 35 U.S.C. § 102(b). Herman was considered during prosecution of the '289 patent.

[26] EX1035 at 9 (Patent Owner suggesting that the teachings of Baheti support that crystallization of bulking agent might adversely impact the stability of methylprednisolone sodium succinate).

and by Baheti's statement that "[t]his review deals with the excipients used in various lyophilized formulations of small molecules." EX1010, 41. Baheti even mentions lyophilized levothyroxine sodium compositions that contain mannitol. EX1010, 45. Thus, by Baheti's own explicit disclosure, the teachings of Baheti relating to lyophilization and bulking agents (mannitol) would have been relevant in improving the stability of a lyophilized levothyroxine sodium composition. EX1004, ¶117. Even Baheti's general teaching that mannitol and moisture causes degradation by hydrolysis (EX1010, 46) would have been relevant to lyophilized levothyroxine sodium compositions, because levothyroxine was also known to degrade by hydrolysis in the presence of mannitol and moisture (EX1011, [0023]; EX1009, 820, 822). EX1004, ¶118. Moreover, other prior art have also applied the teachings of Herman broadly and not limited to methylprednisolone sodium succinate. *See, e.g.,* EX1050 at 567, 570 (discussing the generalized relationship between Herman's findings and moisture release upon crystallization in reference to the drug acetylsalicylic acid); EX1004, ¶¶119–20.

With respect to Collier (*see supra* Parts IX.A.3, IX.B.1.a(ii)), Patent Owner argued that Collier showed that lactose monohydrate caused less degradation than mannitol. According to Patent Owner, a POSA would have replaced mannitol with

lactose monohydrate.[27] However, the Federal Circuit has explained that "just because better alternatives exist in the prior art does not mean that an inferior combination is inapt for obviousness purposes." *In re Mouttet,* 686 F.3d 1322, 1334 (Fed. Cir. 2012); *Gnosis S.P.A. v. S. Ala. Med. Sci. Found.,* IPR2013-00116, Paper 68 (Final Written Decision) at 15 (P.T.A.B. June 20, 2014) ("Mere inferiority of a modification does not make that modification unobvious."). Furthermore, as Patent Owner's Declarant admitted, there were only two options from the excipients tested in Collier: lactose monohydrate and mannitol. EX1015, ¶ 18. Given that there were only two options, at the very least, both would have been obvious or obvious to try. *In re Kubin*, 561 F.3d at 1359.

Dr. Kipp already provided the numerous reasons why a POSA would have first reduced the amount of mannitol below 10 milligrams to improve the stability, rather than replace mannitol with a different bulking agent. *Supra* Part IX.B.1.a(ii); EX1004, ¶¶66-67, 101-102, 126–27. Moreover, lactose was known to cause degradation of levothyroxine. For example, Baheti noted that mannitol provided

[27] *See* EX1035 at 11 ("Applicants respectfully request that the Office explain why [a POSA] would not have chosen to replace the mannitol in the solid levothyroxine composition . . . [with] lactose monohydrate . . . .").

better stability compared to lactose. EX1010, 46; EX1004, ¶128. Likewise, U.S. Patent No. 6,399,101 ("Frontanes") (EX1043)[28] taught the susceptibility of levothyroxine sodium to moisture, especially in the presence of certain carbohydrates, including lactose, sucrose, dextrose, and starch. EX1043, 1:34-40. Specifically, Frontanes taught that lactose caused degradation of levothyroxine by a "Maillard" condensation reaction and that "a levothyroxine formulation which does not utilize lactose" was needed. EX1043, 46-60; EX1004, ¶128.

Similarly, Carpenter teaches that reducing sugars (including lactose) should be avoided as stabilizers for lyophilized compositions. EX1025, 972. Carpenter explains that reducing sugars "have the propensity to degrade proteins[29] via the Maillard reaction between carbonyls of the sugar and free amino groups of the protein." EX1025, 972. Thus, a POSA would have known that using lactose as a

[28] Frontanes is prior art under 35 U.S.C. § 102(b). Frontanes is not cited on the cover page of the '289 patent and thus was not considered by the Examiner.

[29] Levothyroxine sodium contains an amino acid (*i.e.*, building blocks of proteins) and free amino groups. EX1043 at 1:50-55 ("[T]he amino group of the L-tyrosine portion of the levothyroxine molecule reacts with the glycosidic hydroxyl group of the glucose unit of the lactose excipient, undergoing the Maillard reaction.").

bulking agent in a lyophilized composition would cause degradation of levothyroxine sodium through the Maillard reaction. EX1004, ¶129.

Patent Owner also suggested to the Examiner that there was no motivation to modify prior art compositions because Patent Owner's Declarant was unaware of any reported instability issues with them. EX1026, 7 ("Dr. Usayapant was unaware of teaching in the art regarding instability of [prior art] lyophilized pharmaceutical products . . . ."); EX1013, ¶ 7. Such allegations are inconsistent with the numerous prior art references that disclosed instability in lyophilized levothyroxine sodium compositions—including Treasurer (EX1011), Brower (EX1018), Collier (EX1009), Abbott Label (EX1006), and APP Label (EX1007)—and that mannitol/moisture was the cause. *See supra* Parts IX.A.1, IX.A.3, IX.B.1.a(i), IX.B.1.a(ii).[30] Besides, the Board has previously found similar arguments to be "unpersuasive, because it does not follow that a [POSA] would have avoided alternatives simply because a standard is known to be suitable and to work well."

[30] Tellingly, the other two named inventors, including the first named inventor, did not join in the Usayapant Declaration and no such allegation was made in the Jiang Declaration or the Chyall Declaration. *See also* EX1047, 8 (discussing the veracity of the Usayapant Declaration).

Gnosis, IPR2013-00116, Paper 68 at 11–12 (PTAB rejecting similar "gold standard" arguments).

Patent Owner also contended that a POSA would not have applied some of the foregoing teachings because they were allegedly directed to different dosage forms (*e.g.*, tablets). *See, e.g.,* EX1037, 10 (asserting that "any document or study that discusses levothyroxine stability in water or a compressed tablet would not be referenced or helpful"). This argument is inconsistent with teachings of the prior art and, moreover, was already rejected by the Board in another case. *See supra* Parts IX.A.1, IX.A.3; EX1010, 41, 45; EX1009, 819; *In re Kwan*, 837 F.2d 1097 (Fed. Cir. 1987) (non-precedential) (affirming an obviousness determination of a claim directed to a lyophilized composition, stating that "the Board did not err in combining the teachings of solid and solution state stabilization in reaching its determination").

Moreover, as Dr. Kipp explains, the prior art references themselves do not limit their teachings to a specific aspect. For example, while Collier may have mentioned levothyroxine tablets, a POSA would understand that the teachings of Collier are also applicable to other solid dosage forms (*i.e.*, lyophilized compositions). EX1004, ¶¶122–24; EX1009, 819 (stating that "[t]he formulation of a stable and effective *dosage form* requires careful selection of excipients used").

Brower measured the amount of lyophilized levothyroxine sodium compositions and levothyroxine sodium tablets, and found the amount of levothyroxine sodium to be 92.3% (lyophilized levothyroxine sodium) and 98.0% (levothyroxine sodium tablets), respectively. EX1018, 1316–17; EX1004, ¶¶53–57. With this observation, Brower concluded that "[l]ow assay values were a problem experienced by most manufacturers" and that "the problems of low assays of marketed sodium levothyroxine are, in all probability, attributable to sodium levothyroxine instability." EX1018, 1317. Thus, Brower shows that lyophilized compositions and tablets of levothyroxine sodium were being studied together.

Baheti is also relevant to lyophilized levothyroxine compositions, because its teachings regarding mannitol's degradation of moisture-sensitive drugs "logically would have commended itself to [a POSA's] attention in considering [the] problem" of levothyroxine instability. *In re Icon Health and Fitness, Inc.*, 496 F.3d 1374, 1379–80 (Fed. Cir. 2007). Furthermore, such prior art *as a whole* clearly establishes that levothyroxine's instability was known in a variety of dosage forms, as was mannitol's adverse impact on its stability. *Ethicon Endo-Surgery, Inc. v. Covidien*, IPR2015-01274, Paper 25 (Final Written Decision) at 14 (P.T.A.B. Nov. 30, 2016) ("[W]e must read each prior art, not in isolation, but for what it fairly teaches in combination with other references as a whole.").

A POSA also would have known that lyophilized levothyroxine compositions and levothyroxine tablets are closely related. For example, the Abbott Label provides information for both the tablet and lyophilized compositions *in a single document*, with information regarding clinical pharmacology, pharmacokinetics, and precautions being the same for both dosage forms. EX1006, 2, 3, 8; *see also* Byrn *et al.*, *Chemical Reactivity in Solid-State Pharmaceuticals: Formulation Implications*, Advanced Drug Delivery Reviews 48 (2001) 115–136 ("Byrn") (EX1033)[31] at 127–132 (discussing solid-state reactions in relation to lyophilized compositions and tablets); EX1008 (Handbook) at 449 (discussing mannitol as an excipient for both tablets and lyophilized compositions); Sznitowska *et al.*, *The Physical Characteristics of Lyophilized Tablets Containing a Model Drug in Different Chemical Forms and Concentrations*, Drug Research, Vol. 62 No. 1 pp. 25–29 (2005) ("Sznitowska") (EX1038)[32] (describing lyophilized tablets) at 25; EX1004, ¶¶130–31.

[31] Byrn is prior art under 35 U.S.C. § 102(b). Byrn was not considered during prosecution of the '289 patent.

[32] Sznitowska is prior art under 35 U.S.C. § 102(b). Sznitowska was not considered during prosecution of the '289 patent.

2. Claims 2, 3, and 15: Amount of Levothyroxine Sodium and/or Mannitol

Claim 2 depends from Claim 1 and recites "the amount of levothyroxine sodium is about 100 micrograms and the amount of mannitol is about 3 milligrams." Claim 3 depends from Claim 1 and recites "the amount of levothyroxine sodium is about 200 micrograms and the amount of mannitol is about 3 milligrams." Claim 15 depends from Claim 14 and further requires the amount of mannitol to be "about 3 milligrams." As set forth below, Claims 2, 3, and 15 would have been obvious.

a. Amount of Levothyroxine Sodium

(i) Claim 2

The "about 100 micrograms of levothyroxine sodium" limitation of Claim 2 is obvious based on the composition disclosed in the Abbott Label—the Abbott Label explicitly disclosed a dose of about 100 micrograms. *See* EX1006, 7 ("The initial dose is followed by daily intravenous doses of 75 to 100 [micrograms] . . . ."); *Biomarin*, IPR2013-00534, Paper 81 at 15 ("All that remained to be achieved over the prior art was the determination that a specific dose within a previously suggested dose range . . . would have been safe and effective . . . ."); EX1004, ¶¶90, 133. Furthermore, given the similarity of the disclosed dosage, it would have been a matter of routine skill to optimize the amount of the active agent. *See Titanium Metals Corp. v. Banner*, 778 F.2d 775, 783 (Fed. Cir. 1985); *In re Aller*, 220 F.2d at 456–57; *see also* EX1027, [0029] ("[A] change in the levothyroxine sodium level

by a factor of 2 has not historically resulted in a substantial change in stability."). Accordingly, the levothyroxine sodium limitation of Claim 2 would have been obvious in view of the Abbott Label and the Handbook.

(ii) Claim 3

The Abbott Label also discloses a composition with 200 micrograms of levothyroxine sodium thereby meeting that same limitation of Claim 3 of the '289 patent. EX1006, 9. Accordingly, the levothyroxine sodium limitation of Claim 3 of the '289 patent would have been obvious in view of the Abbott Label. EX1004, ¶¶134-135.

b. Amount of Mannitol

The "about 3 milligrams" mannitol limitation in Claims 2, 3, and 15 of the '289 patent would have been obvious because a POSA would have been motivated to reduce the amount of mannitol below the 10 milligrams recited on the Abbott Label. *See supra* Part IX.B.1.a. It would have been obvious to determine the optimal amount through routine experimentation given reducing the amount of mannitol would have been such a simple modification. EX1004, ¶137. A POSA would have had a reasonable expectation that an amount below 10 milligrams, including 3 milligrams, would be successful because it is within the typical range as taught by the Handbook. Overlapping ranges establish a prima facie case of obviousness. *In Re Peterson*, 315, F.3d at 1329-30. Accordingly, the mannitol limitation of Claims

2, 3, and 15 of the '289 patent would have been obvious.

3. Claims 4, 9, and 16: Phosphate Buffer is 400 to 600 Micrograms of Dibasic Sodium Phosphate

Claims 4, 9, and 16 depend from Claims 2, 3, and 15, respectively, and recite that "the phosphate buffer is dibasic sodium phosphate in an amount from 400 to 600 micrograms." The Abbott Label discloses the use of 0.7 milligrams (700 micrograms) of *tribasic* sodium phosphate anhydrous for the 200 micrograms composition. EX1006, 2.

It would have been obvious to switch from tribasic sodium phosphate to dibasic sodium phosphate because a POSA would have known that those two, well-known buffers are interchangeable. EX1004, ¶140; EX1045, 694 ("Related Substances"). And "known interchangeability," absent persuasive objective evidence to the contrary, is enough to support obviousness. *In re Mayne*, 104 F.3d 1339, 1340 (Fed. Cir. 1997) ("Because the applicants merely substituted one element known in the art for a known equivalent, this court affirms [the conclusion of obviousness]."); *Lupin Ltd. et al. v. Senju Pharmaceutical Co., Ltd.*, IPR2015-01099, Paper 69 (Final Written Decision) at 14 (P.T.A.B. Sep. 12, 2016) (finding the non-ionic surfactants polysorbate 80 and tyloxapol to be interchangeable). Moreover, an express suggestion to substitute one known phosphate buffer for another in the Abbott Label composition is not needed to render the substitution obvious. *In re*

Fout, 675 F.2d 297, 301 (C.C.P.A. 1982); *In re Siebentritt*, 372 F.2d 566, 568 (C.C.P.A. 1967); *Lupin Ltd*, IPR2015-01099, Paper 69 at 14 (explaining that known interchangeability "is enough to support the proposed substitution, even in the absence of an express suggestion to do so.").

The claim term "dibasic sodium phosphate" includes the anhydrous form and hydrate forms. *See supra* pp. 6–8 VI.A; EX1012, 18–19. The claimed range of buffer (*i.e.*, "400 to 600 micrograms") would have been obvious to a POSA because it is proportional to the amount of tribasic sodium phosphate anhydrous in the Abbott Label. Specifically, 0.7 milligrams (700 micrograms) of tribasic sodium phosphate anhydrous in the 200 microgram composition corresponds to 0.6 milligrams (600 micrograms) dibasic sodium phosphate anhydrous. EX1006, 2; EX1004, ¶141.[33] *In re Peterson*, 315 F.3d at 1329–30; *Titanium Metals*, 778 F.2d at 783 (affirming obviousness where the ranges were adjacent).

Finally, it would have been obvious for a POSA to use the same range of dibasic sodium phosphate anhydrous in the 100 microgram (Claim 4), 200

[33] Tribasic sodium phosphate anhydrous has a molecular weight of 163.94 g/mol, thus 0.7 mg (700 micrograms) corresponds to 0.00427 mmol. EX1004, ¶141. Dibasic sodium phosphate anhydrous has a molecular weight of 141.96 g/mol; thus, 0.00427 mmol corresponds to 0.6 mg (600 micrograms). EX1004, ¶141.

microgram (Claim 9) and 500 microgram (Claim 16) compositions. First, as the '289 patent explains conventional formulations contained the same amount of phosphate buffer *regardless of the amount of levothyroxine sodium*. EX1001, 2:8-10.

	Conventional	
	A	B
Levothyroxine sodium, USP	200 μg	500 μg
Mannitol, USP	10 mg	10 mg
Tribasic sodium phosphate	700 μg	700 μg

EX1027, [0024]; *see also* EX1053, 1 (teaching 200 and 500 microgram levothyroxine sodium lyophilized compositions both with 700 micrograms tribasic sodium phosphate). Second, as Dr. Kipp explains, a POSA would have expected that the same amount of buffer could be used for the lyophilized compositions of the Abbott Label regardless of the dosage. EX1004, ¶142.

Moreover, the '289 patent does not assign a particular importance to the specific amount of the phosphate buffer. *See* EX1001, 4:48–54. Optimizing the amount of dibasic phosphate buffer would have required nothing more than routine experimentation. *In re Aller*, 220 F.2d at 456–57; *Biomarin*, IPR2013-00534, Paper 81 at 15. EX1004, ¶140. Accordingly, Claims 4, 9, and 16 would have been obvious.

4. Claims 5, 10, and 17: Composition Formed by Combining Components and Lyophilizing a Liquid Mixture

Claims 5, 10, and 17 depend from Claims 4, 9, and 16, respectively, and recite that "the composition is formed by forming a liquid mixture by combining the levothyroxine sodium, the mannitol, dibasic sodium phosphate, and a solvent comprising water; and lyophilizing the liquid mixture."

"The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698 (Fed. Cir. 1985) (citations omitted). Moreover, as set forth in the '289 patent and explained by Dr. Kipp, the claimed process is nothing more than a standard process for preparing lyophilized compositions. EX1004, ¶145–46; EX1001, 10:65–11:16 (the '289 patent admitting that a "typical lyophilization process" involves forming "liquid mixtures" followed by lyophilization); *Constant,* 848 F.2d at 1570 (an applicant's admissions regarding prior art are binding). Accordingly, Claims 5, 10, and 17 of the '289 patent are invalid because the resulting composition would be obvious for the same reasons as Claims 4, 9, and 16.

5. Claims 6–8, 11–13, and 18–21: Amount of Levothyroxine Sodium Converted to Liothyronine

a. Claims 6, 8, 12, 18, and 19

Claims 6, 8, and 12 depend from Claims 1, 4, and 9, respectively, and require that "when the composition is stored at 25°C, at most 0.20% of the levothyroxine sodium is converted to liothyronine over a period of 12 months." Claims 18 and 19 depend from Claims 14 and 16, respectively, and require "at most 0.15% of the levothyroxine sodium is converted to liothyronine" under the same test conditions.

The '084 provisional application (EX1027), to which the '289 patent claims priority and incorporates by reference (EX1001, 1:5–8), states that the prior art compositions (Conventional A and B) comprising 10 milligrams of mannitol, 700 micrograms of tribasic sodium phosphate, and either 200 or 500 micrograms of levothyroxine sodium, respectively, "did not exhibit an increase over time" of the degradant (*i.e.*, liothyronine). EX1027, [0024], [0028]. The '084 provisional application also observed that the prior art compositions exhibited superior stability compared to modified compositions (Modified C, D, and E), which contained 10 milligrams of mannitol, 500 micrograms of dibasic sodium phosphate, and either 100, 200, or 500 micrograms of levothyroxine sodium, respectively. EX1027,

[0028]–[0031].[34] The '084 provisional application shows that the parameters recited in Claims 6, 8, 12, 18, and 19 were present even in the *less stable* modified formulations, as shown in the table below summarizing the amount of liothyronine (T3) measured in modified compositions C, D, and E after storage at 25°C:

		% T3					
Formulation:		C		D		E	
Time (mo.)	Temp.	Inverted	Upright	Inverted	Upright	Inverted	Upright
0	--	0.17	0.17	0.18	0.18	0.17	0.17
2	25 °C	0.20	0.20	0.18	0.19	0.18	0.17
3		0.24	0.22	0.20	0.19	0.18	0.17
6		0.28	0.25	0.24	0.21	0.19	0.20
9		0.20	0.24	0.20	0.24	0.18	0.19
12		0.35	0.29	0.25	0.21	0.20	0.19
18		0.25	0.35	0.25	0.24	0.18	0.21
1	40 °C	0.34	0.34	0.26	0.21	0.19	0.20
2		0.22	0.30	0.28	0.23	0.19	0.21
3		0.44	0.57	0.33	0.32	0.19	0.20

[34] The information regarding prior art compositions disclosed in the '084 provisional application was omitted from the specification of the '289 patent. The Examiner did not refer to the teachings of the '084 provisional in any office action and did not examine it. *See Star Scientific Inc. v. R.J. Reynolds Tobacco Co.,* 537 F.3d 1357, 1367 n.7 (Fed. Cir. 2008) (noting that "provisional applications are not examined").

EX1027, [0025]; *see also* EX1001, Table 3, FIG. 3.

As Dr. Kipp explains, the data in the '084 provisional application show that the amount of liothyronine formed during the time period of 0 to 12 months at 25°C for the 200 micrograms levothyroxine/10 milligrams mannitol modified composition D was less than 0.20% and thus meets the requirement of Claims 6 and 12. EX1004, ¶151.

As Dr. Kipp further explains, the data in the '084 provisional application also show that the amount of liothyronine that was formed during the time period of 0 to 12 months at 25°C for the 500 micrograms levothyroxine/10 milligrams mannitol modified composition E was less than 0.15% and thus meets the requirement of Claims 18 and 19. EX1004, ¶152.

The amount of liothyronine that was formed during the time period of 0 to 12 months at 25°C for the 100 micrograms levothyroxine/10 milligrams mannitol modified composition C was less than 0.20% and thus meets the requirement of Claim 8. EX1004, ¶150.

Thus, the modified compositions comprising 10 milligrams of mannitol met the limitations recited in Claims 6, 8, 12, 18, and 19. The prior art compositions, which the '084 provisional application admits had better stability, would thus also meet the limitations. EX1027, [0028]–[0031]; EX1004, ¶¶153–54. *Constant,* 848 F.2d at 1570 (an applicant's admissions regarding prior art are binding). Moreover,

a POSA would also have expected that, if the amount of mannitol were reduced, the resulting amount of liothyronine (converted from the degradation of levothyroxine) would have met the claimed limitations of Claims 6, 8, 12, 18, and 19 of the '289 patent because reducing the amount of mannitol from 10 milligrams would have resulted in a more stable composition. EX1004, ¶155. Accordingly, Claims 6, 8, 12, 18, and 19 of the '289 patent would have been obvious.

b. Claims 7, 11, 13, 20, and 21

Claims 7, 11, and 13 also depend from Claims 1, 4, and 9, respectively, and require that "when the composition is stored at 40°C, at most 0.20% of the levothyroxine sodium is converted to liothyronine over a period of 3 months." Claims 20 and 21 depend from Claims 16 and 14, respectively, and require "at most 0.15% of the levothyroxine sodium is converted to liothyronine" under the same test conditions. As set forth below, Claims 6–8, 11–13, and 18–21 would have been obvious.

The '084 provisional application shows that the parameters recited in Claims 7, 11, 13, 20, and 21 were present even in the less stable modified formulations, as shown in the table reproduced above summarizing the amount of liothyronine (T3) measured in modified compositions C, D, and E after storage at 40°C. EX1027, [0025]; *see also* EX1001, Table 3, FIG. 3.

As Dr. Kipp explains, the data in the '084 provisional application show that the amount of liothyronine formed during the time period of 0 to 3 months at 40°C for the 200 micrograms levothyroxine/10 milligrams mannitol modified composition D was less than 0.20% and thus meets the requirement of Claims 7 and 13. EX1004, ¶159.

As Dr. Kipp further explains, the data in the '084 provisional application show that the amount of liothyronine that was formed during the time period of 0 to 3 months at 40°C for the 500 micrograms levothyroxine/10 milligrams mannitol modified composition E was less than 0.15% and thus meets the requirement of Claims 20 and 21. EX1004, ¶160.

The amount of liothyronine that was formed during the time period of 0 to 3 months at 40°C for the 100 micrograms levothyroxine/10 milligrams mannitol modified composition C was adjacent to the range recited in Claim 11. EX1004, ¶158. *Titanium Metals*, 778 F.2d at 783 (affirming obviousness where the ranges were adjacent).

Thus, the modified compositions comprising 10 milligrams of mannitol met the limitations of Claims 7, 13, 20, and 21, and was adjacent to Claim 11. The prior art compositions, which the '084 provisional application states had better stability, would thus meet the limitations of Claims 7, 11, 13, 20, and 21. EX1027, [0028]–[0031]; EX1004, ¶161. Moreover, a POSA would have also expected that, if the

amount of mannitol were reduced, the resulting amount of liothyronine (converted from the degradation of levothyroxine) would have met the claimed limitations of Claims 7, 11, 13, 20, and 21 of the '289 patent because reducing the amount of mannitol from 10 milligrams would have resulted in a more stable composition. EX1004, ¶162. As such, Claims 7, 11, 13, 20, and 21 of the '289 patent would have been obvious.[35]

C. Ground 2: Claims 1–21 Would Have Been Obvious over the APP Label, Brower, Baheti, and Collier

1. Claims 1 and 14

The following table sets out the manner in which the APP Label taught each limitation of Claims 1 and 14 of the '289 patent, except the "2 to 4" milligrams of mannitol limitation. But, as stated above, it would have been obvious to a POSA to use "2 to 4" milligrams of mannitol. EX1004, ¶¶299–300.

[35] In any event, the limitations of Claims 6–8, 11–13, and 18–21 do not confer patentability because the rate of conversion from levothyroxine to liothyronine is a latent property of the resulting composition (even if the property is not specifically stated by the prior art). *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012) (stating that an obvious composition does not become patentable merely by claiming a latent property).

Claim	Prior Art
1. A composition, comprising:	APP Label teaches a pharmaceutical composition. EX1007, 9.
about 100 or about 200 micrograms of levothyroxine sodium;	APP Label teaches 100 micrograms and 200 micrograms of levothyroxine sodium. EX1007, 10.
a phosphate buffer; and	APP Label teaches dibasic sodium phosphate. EX1007, 9.[36]
from 2 to 4 milligrams of mannitol,	APP Label teaches mannitol. EX1007, 9.
where the composition is a lyophilized solid.	APP Label teaches a lyophilized powder. EX1007, 9.
14. A composition, comprising:	APP Label teaches a pharmaceutical composition. EX1007, 9.
about 500 micrograms of levothyroxine sodium;	APP Label teaches 500 micrograms of levothyroxine sodium. EX1007, 10.
a phosphate buffer; and	APP Label teaches dibasic sodium phosphate. EX1007, 9.
from 2 to 4 milligrams of mannitol,	APP Label teaches mannitol. EX1007, 9.
where the composition is a lyophilized solid.	APP Label teaches a lyophilized powder. EX1007, 9.

a. A POSA Would Have Been Motivated to Reduce the Amount of Mannitol Below the 10 Milligram Amount Used in Conventional Compositions

As with Ground 1, a POSA would have been (and is) motivated to improve the stability of pharmaceutical compositions and use the least amount of excipients necessary to prepare a stable composition. *See supra* Part IX.B.1.a.

[36] *See supra* pp. 6–8.

It would have been obvious to reduce the amount of mannitol below 10 milligrams, which as the '289 patent concedes was known in conventional compositions (*see supra* Part IX.A.2; EX1001, 2:7-8), to improve stability. *Pharmacosmos A/S v. Luitpold Pharms., Inc.* IPR2015-01490 Paper 54 (Final Written Decision) at 46 (P.T.A.B. Jan. 4, 2017) ("[Prior art] is silent as to core size. Thus, the ordinary artisan would have looked to formulations known in the art . . ."). The instability of levothyroxine sodium was known (*see supra* Part IX.A.1), just as it was known that relatively high amounts of mannitol were a source of that instability (*see supra* Part IX.A.3).[37] Knowing the detrimental impact of mannitol, a POSA would have been motivated to reduce the amount of mannitol and improve the properties of a lyophilized levothyroxine sodium composition. *See supra* Part IX.B.1.a(ii); EX1004, ¶¶92–102, 115–31, 236.

[37] Although the APP Label does not specify the amount of mannitol in its lyophilized composition, a POSA would have known that 10 milligrams of mannitol was used conventionally for lyophilized levothyroxine sodium compositions. EX1004, ¶65, footnote 25; *see, e.g.,* EX1001 at 2:7–10.

b. A POSA Would Have Had a Reasonable Expectation of Success

As above, given such a simple modification, a POSA would have had a reasonable expectation of success in obtaining a lyophilized levothyroxine sodium composition having improved stability. EX1004, ¶¶100, 247. First, a POSA would have conducted routine experimentation starting with an amount less than 10 milligrams and ultimately arriving at the recited "2 to 4" milligrams; it would have been obvious to determine the optimal amount through routine experimentation. EX1004, ¶¶79, 96; *In re Aller*, 220 F.2d 454 at 456–57.

Second, a POSA would have had a reasonable expectation of success because an amount of mannitol below 10 milligrams was within the typical range of mannitol in lyophilized compositions as shown by the Handbook (EX1008), a reference commonly consulted by POSAs. EX1004, ¶¶67, 238. The Handbook discloses that "[i]n lyophilized preparations, mannitol (20–90% w/w) has been included." EX1008, 449. As Dr. Kipp explains, if the range disclosed in the Handbook (20–90 % w/w) is applied to the 100, 200, and 500 microgram levothyroxine sodium

compositions described in the APP Label, then the corresponding ranges of mannitol for each composition are as follows:[38]

Levothyroxine Sodium (milligrams)	**Mannitol (% w/w)**	**Mannitol (milligrams)**
0.1 (100 micrograms)	20	0.175
0.1	90	6.3
0.2 (200 micrograms)	20	0.2
0.2	90	7.2
0.5 (500 micrograms)	20	0.275
0.5	90	9.9

EX1004, ¶¶237–46. As shown, the claimed range of "2 to 4" milligrams of mannitol falls within the typical range of mannitol calculated according to the Handbook's disclosure.[39] Accordingly, a POSA would have had a reasonable expectation of success.

[38] The APP Label does not recite the amount of phosphate buffer, however, as discussed below, it would have been obvious to use 600 micrograms of dibasic sodium phosphate. *See infra* Part IX.C.3.

[39] Overlapping ranges establish a *prima facie* case of obviousness. *In re Peterson*, 315 F.3d at 1329–30; *Biomarin*, IPR2013-00534, Paper 81 at 15. Furthermore, a POSA would have been motivated to have a single amount of mannitol for all compositions, as was the case for prior art compositions. EX1001, 2:8–10; EX1027, [0024]; EX1004, ¶114.

2. Claims 2, 3, and 15: Amount of Levothyroxine Sodium and/or Mannitol

As set forth below, Claims 2, 3, and 15 would have been obvious.[40]

a. Amount of Levothyroxine Sodium

The APP Label discloses a composition with 100 and 200 micrograms of levothyroxine sodium (EX1007, 15) as recited in Claims 2 and 3 of the '289 patent. Accordingly, the amount of levothyroxine sodium expressly recited in Claims 2 and 3 would have been obvious in view of the APP Label.

b. Amount of Mannitol

The "about 3 milligrams" mannitol limitation in Claims 2, 3, and 15 of the '289 patent would have been obvious because a POSA would have been motivated to reduce the amount of mannitol below 10 milligrams. *See supra* Part IX.B.1.a. It would have been obvious to determine the optimal amount through routine experimentation given reducing the amount of mannitol would have been such a simple modification. EX1004, ¶¶92–102, 115–131, 237, 247, 253. A POSA would have had a reasonable expectation that an amount below 10 milligrams, including 3 milligrams, would be successful as it is within the typical range as taught by the Handbook. *See supra* Part IX.B.1.b. Overlapping ranges establish a *prima facie* case of obviousness. *In re Peterson*, 315 F.3d at 1329–30. Accordingly, the

[40] *See supra* p. 38 for a recitation of the limitations.

mannitol limitation of Claims 2, 3, and 15 of the '289 patent would have been obvious.

3. Claims 4, 9, and 16: Phosphate Buffer is 400 to 600 Micrograms of Dibasic Sodium Phosphate

Claims 4, 9, and 16 depend from Claims 2, 3, and 15, respectively, and recite that "the phosphate buffer is dibasic sodium phosphate in an amount from 400 to 600 micrograms." The APP Label discloses dibasic sodium phosphate heptahydrate as the phosphate buffer. EX1007, 9; EX1012 (district court defining "dibasic sodium phosphate" as "anhydrous Na_2HPO_4 and *the hydrate forms* associated with Na_2HPO_4"). Therefore, a disclosure of sodium phosphate heptahydrate would meet the claim limitation.

The APP Label does not disclose the amount of dibasic sodium phosphate. However, a POSA would have found 400 to 600 micrograms of dibasic sodium phosphate—which includes the anhydrous form—to be an obvious range in view of the prior art.[41] For example, a POSA would have known that 700 micrograms of

[41] It would also have been obvious to switch from dibasic sodium phosphate heptahydrate to the anhydrous form because a POSA would have known that the two well-known buffers are interchangeable. EX1004, ¶140; *In re Mayne*, 104 F.3d at 1340.

tribasic sodium phosphate anhydrous was used for conventional lyophilized levothyroxine sodium composition (EX1003, 2:3–15; EX1027, [0024], EX1053, 1),[42] and that replacing this buffer with dibasic sodium phosphate anhydrous would have resulted in 600 micrograms of dibasic sodium phosphate anhydrous buffer. EX1004, ¶¶140, 141, 256; *see supra* Part IX.B.3; *Pharmacosmos A/S,* IPR2015-01490, Paper 54 at 46 ("[Prior art] is silent as to core size. Thus, the ordinary artisan would have looked to formulations known in the art. . . ."). As the disclosed range and the claimed range overlap, the claimed range would have been obvious. *In re Peterson*, 315 F.3d at 1329–30.

Moreover, the '289 patent does not assign a particular importance to the specific amount of the phosphate buffer. *See* EX1001, 4:48–54; *In re Aller,* 220 F.2d at 456 (requiring a showing of criticality, *i.e.*, a difference in kind and not merely degree). Optimizing the amount of dibasic phosphate buffer would have required nothing more than routine experimentation. *Id.* at 456–57. Accordingly, Claims 4, 9, and 16 would have been obvious.

[42] It would have been obvious for a POSA to use the same range of dibasic sodium phosphate anhydrous in the 100, 200 and 500 microgram compositions because a POSA would have known that the range would work successfully in those compositions. EX1004, ¶141–42; EX1003, 2:3–15; EX1027, [0024], EX1053, 1.

4. Claims 5, 10, and 17: Composition Formed by Combining Components and Lyophilizing a Liquid Mixture

Claims 5, 10, and 17 depend from Claims 4, 9, and 16, respectively, and recite that "the composition is formed by forming a liquid mixture by combining the levothyroxine sodium, the mannitol, dibasic sodium phosphate, and a solvent comprising water; and lyophilizing the liquid mixture." As set forth in the '289 patent and explained by Dr. Kipp, the claimed process is nothing more than a standard process for preparing lyophilized compositions. EX1004, ¶¶145, 146, 259; EX1001, 10:65–11:16. Accordingly, Claims 5, 10, and 17 are invalid because the resulting composition would be obvious for the same reasons as Claims 4, 9, and 16. *In re Thorpe*, 777 F.2d at 698; *see supra* Part IX.B.4.

5. Claims 6–8, 11–13, and 18–21: Amount of Levothyroxine Sodium Converted to Liothyronine

As set forth below, Claims 6–8, 11–13, and 18–21 would have been obvious.[43]

a. Claims 6, 8, 12, 18, and 19

As with Ground 1, the '084 provisional application shows that the recited parameters in Claims 6, 8, 12, 18, and 19 were present in prior art compositions comprising 10 milligrams of mannitol, which "did not exhibit an increase over time" of the degradant (*i.e.*, liothyronine). EX1027, [0024], [0028]; EX1004, ¶¶148–54,

[43] *See supra* p. 43 for a recitation of the limitations.

261; *supra* Part IX.B.5.a. Moreover, a POSA would have expected that, if the amount of mannitol were reduced, the amount of liothyronine converted from levothyroxine would also meet the limitations of Claims 6, 8, 12, 18, and 19. EX1004, ¶155. Accordingly, Claims 6, 8, 12, 18, and 19 would have been obvious. *See also supra* footnote 35 (explaining that Claims 6–8, 11–13, and 18–21 are directed to latent properties).

b. Claims 7, 11, 13, 20, and 21

As with Ground 1, the '084 provisional application shows that the recited parameters in Claims 7, 11, 13, 20, and 21 were present in the prior art compositions comprising 10 milligrams of mannitol, which "did not exhibit an increase over time" of the degradant (*i.e.*, liothyronine). EX1027, [0024], [0028]; EX1004, ¶¶157–61; *supra* Part IX.B.5.b. Moreover, a POSA would have expected that, if the amount of mannitol were reduced, the amount of liothyronine converted from levothyroxine would also meet the limitations of Claims 7, 11, 13, 20, and 21. EX1004, ¶162. Accordingly, Claims 7, 11, 13, 20, and 21 of the '289 patent would have been obvious. *See also supra* footnote 35 (explaining that Claims 6–8, 11–13, and 18–21 are directed to latent properties).

D. Ground 3: Claims 1–21 Would Have Been Obvious over the Abbott Label, APP Label, Brower, Baheti, and Collier

1. Claims 1 and 14

Claims 1 and 14 of the '289 patent would have been obvious based on the

combination of the Abbott Label, the APP Label, and the Handbook.[44] As with Grounds 1 and 2, both the Abbott Label and the APP Label teach all limitations of Claims 1 and 14 except the requirement for "2 to 4" milligrams of mannitol.

a. A POSA Would Have Been Motivated to Reduce the Amount of Mannitol

As with Grounds 1 and 2, a POSA would have been (and is) motivated to improve the stability of pharmaceutical compositions and use the least amount of excipients necessary to prepare a stable composition. *See supra* Part IX.B.1.a, IX.C.1.a.

It would have been obvious to reduce the amount of mannitol below 10 milligrams as taught by the Abbott Label (EX1006) to improve stability, because the instability of levothyroxine sodium was known (*see supra* Part IX.A.1), just as it was known that relatively high amounts of mannitol were a source of that instability (*see supra* Part IX.A.3). Knowing the detrimental impact of mannitol, a POSA

[44] The Abbott Label and the APP Label both cover lyophilized levothyroxine sodium compositions, with a bulking agent (mannitol), a buffer (sodium phosphate), and a pH adjuster (sodium hydroxide). Given the overlapping subject matter, a POSA would have been motivated to combine the teaching of the APP Label with the Abbott Label, and vice versa. EX1004, ¶305.

would have been motivated to reduce the amount of mannitol and improve the properties of a lyophilized levothyroxine sodium composition. *See supra* Part IX.B.1.a(ii); EX1004, ¶¶306–07. A POSA would also have known that the claimed range of mannitol is within the typical range of mannitol for lyophilized compositions and have a reasonable expectation of success. *See supra* Parts IX.B.1.b, IX.C.1.b.

2. Claims 2, 3, and 15: Amount of Levothyroxine Sodium and/or Mannitol

As set forth below, Claims 2, 3, and 15 would have been obvious.[45]

a. Amount of Levothyroxine Sodium

The APP Label discloses a composition with 100 and 200 micrograms of levothyroxine sodium (EX1007, 15) as recited in Claims 2 and 3. Accordingly, the amount of levothyroxine sodium recited in Claims 2 and 3 would have been obvious in view of the APP Label which taught the claimed dosage.

b. Amount of Mannitol

The "about 3 milligrams" mannitol limitation in Claims 2, 3, and 15 of the '289 patent would have been obvious because a POSA would have been motivated to reduce the amount of mannitol below 10 milligrams. *See supra* Part IX.B.1.a. It would have been obvious to determine the optimal amount through routine

[45] *See supra* p. 43 for a recitation of the limitations.

experimentation given reducing the amount of mannitol would have been such a simple modification. EX1004, ¶313. A POSA would have had a reasonable expectation that an amount below 10 milligrams, including 3 milligrams, would be successful as it is within the typical range as taught by the Handbook. *See supra* Part IX.B.1.b. Overlapping ranges establish a *prima facie* case of obviousness. *In re Peterson*, 315 F.3d at 1329–30. Accordingly, the mannitol limitation of Claims 2, 3, and 15 of the '289 patent would have been obvious.

3. Claims 4, 9, and 16: Phosphate Buffer is 400 to 600 Micrograms of Dibasic Sodium Phosphate

Claims 4, 9, and 16 depend from Claims 2, 3, and 15, respectively, and recite that "the phosphate buffer is dibasic sodium phosphate in an amount from 400 to 600 micrograms."

The APP Label discloses dibasic sodium phosphate heptahydrate as the phosphate buffer. EX1007, 9; *see supra* Part IX.B.3. While, the APP Label does not disclose the amount of dibasic sodium phosphate heptahydrate, the Abbott Label discloses using 700 micrograms of tribasic sodium phosphate anhydrous for the lyophilized composition containing 200 micrograms of levothyroxine sodium. EX1006, 2; *Pharmacosmos A/S,* IPR2015-01490, Paper 54 at 46. As calculated above, the equivalent amount of dibasic sodium phosphate anhydrous is 600 micrograms. *See supra* Part IX.B.3. It would have been obvious to use the same

molar amount of dibasic sodium phosphate anhydrous as taught by the Abbott Label. Further, it would have been obvious for a POSA to use the same range of dibasic sodium phosphate anhydrous in the 100, 200 and 500 micrograms compositions because a POSA would have known that the range would work successfully in those compositions. EX1004, ¶142. As the disclosed range and the claimed range overlap, the claimed range would have been obvious. *In re Peterson*, 315 F.3d at 1329–30.

Moreover, the '289 patent does not assign a particular importance to the specific amount of the phosphate buffer. *See* EX1001, 4:48–54. Nevertheless, optimizing the amount of dibasic phosphate buffer would have required nothing more than routine experimentation. *In re Aller*, 220 F.2d at 456–57. Accordingly, Claims 4, 9, and 16 would have been obvious.

4. Claims 5, 10, and 17: Composition Formed by Combining Components and Lyophilizing a Liquid Mixture

Claims 5, 10, and 17 depend from Claims 4, 9, and 16, respectively, and recite that "the composition is formed by forming a liquid mixture by combining the levothyroxine sodium, the mannitol, dibasic sodium phosphate, and a solvent comprising water; and lyophilizing the liquid mixture." As set forth in the '289 patent and explained by Dr. Kipp, the claimed process is a standard one for preparing lyophilized compositions. EX1004, ¶317; EX1001, 10:65–11:20. As such, Claims 5, 10, and 17 are invalid because the resulting composition would have been obvious

for the same reasons as Claims 4, 9, and 16 of the '289 patent. *In re Thorpe*, 777 F.2d at 698; *see supra* Part IX.B.4.

5. Claims 6–8, 11–13, and 18–21: Amount of Levothyroxine Sodium Converted to Liothyronine

As set forth below, Claims 6–8, 11–13, and 18–21 would have been obvious.[46]

a. Claims 6, 8, 12, 18, and 19

As above, the '084 provisional application shows that the recited parameters in Claims 6, 8, 12, 18, and 19 were disclosed in the prior art compositions comprising 10 milligrams of mannitol, which "did not exhibit an increase over time" of the degradant. EX1027, [0024], [0028]; *supra* Part IX.B.5.a. Moreover, a POSA would have expected that, if the amount of mannitol were reduced, the amount of liothyronine converted from levothyroxine would also meet the limitations of Claims 6, 8, 12, 18, and 19. Accordingly, Claims 6, 8, 12, 18, and 19 would have been obvious. *See also supra* footnote 35 (explaining that Claims 6–8, 11–13, and 18–21 are directed to latent properties).

b. Claims 7, 11, 13, 20, and 21

As set forth above, the '084 provisional application shows that the recited parameters in Claims 7, 11, 13, 20, and 21 were found in the prior art compositions comprising 10 milligrams of mannitol, which "did not exhibit an increase over time"

[46] *See supra* at 43 for a recitation of the limitations.

of the degradant. EX1027, [0024], [0028]; *supra* Part IX.B.5.b. Moreover, a POSA would have expected that, if the amount of mannitol were reduced, the amount of liothyronine converted from levothyroxine would also meet the claimed limitations of Claims 7, 11, 13, 20, and 21. As such, Claims 7, 11, 13, 20, and 21 would have been obvious. *See also supra* footnote 35 (explaining that Claims 6–8, 11–13, and 18–21 are directed to latent properties).

E. Objective Indicia of Non-Obviousness

Although objective indicia of non-obviousness must be taken into account, they do not necessarily control an obviousness determination. *Newell Cos., Inc. v. Kenney Mfg. Co*., 864 F.2d 757, 768 (Fed. Cir. 1988). A strong case of obviousness, as is present here, cannot be overcome by objective evidence of non-obviousness. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2008). Here, Petitioner addresses potential objective indicia arguments that Patent Owner may raise. To the extent that Patent Owner does assert any objective indicia in support of non-obviousness, detailed consideration of such evidence should not be undertaken until Petitioner has an opportunity to respond. *Amneal Pharmaceuticals, LLC v. Supernus Pharmaceuticals, Inc*., IPR2013-00368, Paper 8 (Institution Decision) at 12–13 (P.T.A.B. Dec. 17, 2013).

1. No Unexpected Results Over the Closest Prior Art

Allegations of unexpected results are insufficient to rebut a strong *prima facie* case of obviousness. Nonetheless, in light of the prior art, the alleged improved stability was to be expected.

It was well known that mannitol causes degradation of levothyroxine sodium compositions (*e.g.,* EX1009 (Collier)). As a result, a POSA would have expected that reducing the amount of mannitol below 10 milligrams would improve the stability of known lyophilized levothyroxine sodium compositions. EX1004, ¶364; *see supra* Parts IX.B.1.a, IX.B.1.b. Accordingly, the allegedly improved stability of the claimed composition would not have been an unexpected result. For example, Baheti noted that the release of water from mannitol causes degradation of moisture-sensitive drugs and, consequently, affect the stability of drug products. EX1010, 46. In light of the known moisture sensitivity of levothyroxine sodium, Baheti would have suggested to a POSA that reducing the amount of mannitol would also reduce the likelihood of any moisture that would cause degradation to levothyroxine sodium. EX1004, ¶364.

In any event, Patent Owner's allegations of unexpected results are not supported by the evidence presented during prosecution of the '289 patent. *See* EX1037, 10; EX1014, ¶ 6; EX1035, 12; EX1013, ¶¶ 9–13. As Dr. Kipp explains, the '289 patent and the declarations filed during prosecution of the '289 patent do

not provide any information regarding the test method or raw data. EX1004, ¶¶365–66; *see Altaire Pharms., Inc. v. Paragon Bioteck, Inc.,* PGR2015-00011, Paper 48 at 14, 17 (P.T.A.B. Nov. 14, 2016) (giving no weight to HPLC data that failed to explain how the test was performed and how the data was generated); 37 CFR § 42.65(b)(2) (requiring parties to explain "[h]ow the test was performed and the data was generated").

Furthermore, according to an appeal brief filed with the Federal Circuit ("Appeal Brief") (EX1047), Patent Owner withheld information regarding stability testing, including test data of prior art compositions that showed "prior art formulations were stable over 28 months, in terms of the amount of [liothyronine (T3)] over time" and stable "even when measure[d] by the 'loss of [levothyroxine (T4)]' metric." EX1047, 24–27, 31. The Board should afford no weight to any test data until such time the Patent Owner provides all necessary information it has in its possession to evaluate any alleged improvement—information it should have provided to the Examiner. 37 CFR § 42.65(b)(5) (requiring that for test data to be

given weight, the Patent Owner must provide "*any other information* necessary for the Board to evaluate the test and data") (emphasis added).[47]

Furthermore, the purported difference in stability variance, which is not adequately defined by the '289 patent or the Jiang Declaration (EX1014) to begin with, is a result of the small amount of liothyronine (T3) that is at issue, which makes the stability variance appear large because of the division of a number by a small number. EX1004, ¶370. Regardless, at most, the difference in stability variance is not a material improvement because it merely shows improved repeatability of the testing. EX1004, ¶370.

Furthermore, Patent Owner's allegation of a 7-fold increase in stability is based on the following results which were obtained from samples aged at 40°C for three months:

(1) 10 milligrams mannitol formulation provided an approximate degradation of 0.286% T3;

[47] Moreover, there is no adequate explanation as to why the amount of liothyronine (T3) is indicative of stability. EX1004, ¶365, footnote 16. The Usayapant Declaration contains data regarding the amount of levothyroxine, however, only provides the data in summary fashion and again does not provide any information regarding the method or the raw data. EX1013, ¶ 16.

(2) 3 milligrams mannitol formulation provided an approximate degradation of 0.131% T3.

EX1014, ¶ 6. The difference in the amount of T3 between the 10 milligrams and 3 milligrams of mannitol compositions is small, which represents a difference in degree rather than kind, because the improved stability is incremental and is in line with what would be expected by reducing the amount of mannitol.[48] *In re Harris*, 409 F.3d 1339, 1344 (Fed. Cir. 2005) (finding increased stress rupture life by 32-43% to be a difference of degree and not of kind); EX1004, ¶¶367–69. Indeed, as Dr. Kipp explains, it "actually only represents a difference in improvement by a fraction of a percent," which was not "unexpected" given mannitol's propensity to degrade levothyroxine sodium composition. EX1004, ¶368-369. Also, the actual difference is so small that, if information regarding the test method and statistical error were available and considered, the alleged improvement would be even more insignificant. EX1004, ¶368.

[48] The difference between the amount of T3 for the composition containing 10 milligrams of mannitol (0.286% T3) and the composition containing 3 milligrams of mannitol (0.131% T3) is 0.155% T3.

2. Commercial Success

Any alleged commercial success requires a patentee to provide data establishing, for example, market share, market growth, or comparative sales volume; and, more importantly, "[a] nexus must be established between the merits of the claimed invention and the evidence of commercial success before that issue becomes relevant to the issue of obviousness." *Vandenberg v. Dairy Equip. Co.*, 740 F.2d 1560, 1567 (Fed. Cir. 1984). There is no evidence linking the claims to any alleged commercial success. Tellingly, the product label of Patent Owner's levothyroxine sodium composition does not even state or reference any of the alleged improvements related to the reduced amount of mannitol. *See* EX1034. Indeed, the product label states "Initial U.S. Approval: 1969" and provides no information about the amount of mannitol—essentially a tacit admission that the claimed product is the same as the prior art composition that existed prior to the '289 patent and that contained 10 milligrams mannitol. EX1034, 1, 6–7.

X. CONCLUSION

Petitioner has demonstrated by a preponderance of the evidence that Claims 1–21 of the '289 patent are unpatentable as obvious.

RESPECTFULLY SUBMITTED,

ALSTON & BIRD LLP

Date: January 19, 2017

/Jitendra Malik/

Jitendra Malik (Reg. No. 55823)
4721 Emperor Boulevard, Suite 400
Durham, North Carolina 27703
Telephone: 919-862-2210
Fax: 919-862-2260
Jitty.Malik@alston.com

Lead Counsel for Petitioner
Mylan Institutional Inc.

CERTIFICATION OF WORD COUNT

Pursuant to 37 C.F.R. §§ 42.24, the undersigned certifies that the argument section of this Petition (Sections I–II, V–X) has a total of 13,757 words, less than 14,000 words, according to the word count tool in Microsoft Word™.

Respectfully submitted,

ALSTON & BIRD LLP

By: /Jitendra Malik/
Jitendra Malik, Ph.D.
Reg. No. 55,823

CERTIFICATION OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e), 42.8(b)(4) and 42.105, the undersigned certifies that on the 19th day of January 2017, a complete copy of the foregoing Petitioner's Petition for *Inter Partes* Review of U.S. Patent No. 9,006,289, Power of Attorney, and all supporting exhibits were served via Express Mail to the Patent Owner by serving the correspondence address of record for the '289 patent:

Jonathan M. Blanchard
P.O. Box 51295
Knoxville, TN 37950-1295

Courtesy copies of the foregoing were also served via UPS® to the counsel of Patent Owner in related district court litigation:

Jonathan M. Blanchard
PITTS & LAKE, P.C.
1319 Old Weisgarber Rd.
Knoxville, TN 37909
(865) 584-0105

Imron T. Aly
SCHIFF HARDIN LLP
233 South Wacker Drive, Suite 6600
Chicago, Illinois 60606
(312) 258-5500

Donald A. Robinson
ROBINSON MILLER LLC
One Newark Center, 19th Floor
Newark, NJ 07102
(973) 690-5400

Brian E. Farnan
FARNAN LLP
919 North Market Street, 12th Floor
Wilmington, Delaware 19801
(302) 777-0300

Respectfully submitted,

ALSTON & BIRD LLP

By: /Jitendra Malik/

Jitendra Malik, Ph.D.
Reg. No. 55,823