

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AUROBINDO PHARMA USA, INC.
Petitioner,

v.

ANDRX CORPORATION,
ANDRX LABORATORIES, INC.
ANDRX LABORATORIES (NJ), INC.
ANDRX EU LTD.
ANDRX PHARMACEUTICALS, LLC,
TEVA PHARMACEUTICAL INDUSTRIES LTD.
Patent Owner(s)

Case IPR2017-01648
Patent 6,866,866 B1

Before SUSAN L.C. MITCHELL, JO-ANNE M. KOKOSKI, and
DEVON ZASTROW NEWMAN, *Administrative Patent Judges*.

NEWMAN, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
35 U.S.C. § 318(a); 37 C.F.R. § 42.73

I. INTRODUCTION

This is a Final Written Decision in an *inter partes* review challenging the patentability of claims 1–25 of U.S. Patent No. 6,866,866 B1 (Ex. 1001, “the ’866 patent”). We have jurisdiction under 35 U.S.C. § 6. The evidentiary standard is a preponderance of the evidence. *See* 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d). We issue this Final Written Decision pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73.

Having reviewed the arguments of the parties and the supporting evidence, we determine that Petitioner has not demonstrated by a preponderance of the evidence that the challenged claims are unpatentable.

A. *Procedural History*

Aurobindo Pharma USA, Inc. (“Petitioner”) filed a Corrected Petition requesting an *inter partes* review of claims 1–25 of the ’866 patent. Paper 8 (“Pet.”). The Petition relies upon the Declaration of Dr. Fatemeh Akhlaghi. Ex. 1019 (“Akhlaghi Decl.”).

Andrx, LLC (“Patent Owner”) filed a Preliminary Response to the Petition.¹ Paper 11 (“Prelim. Resp.”). We instituted an *inter partes* review of challenged claims 1–25 on one ground of unpatentability, pursuant to 35 U.S.C. § 314. Paper 12 (“Inst. Dec.”), 21–22.

After institution and before the due date for Patent Owner’s Response, however, the U.S. Supreme Court issued its decision in *SAS Institute Inc. v. Iancu*, 138 S. Ct. 1348 (2018). *See* Paper 20. Pursuant to *SAS Institute*, a decision to institute an *inter partes* review under 35 U.S.C. § 314 may not

¹ No other party named in the Petition entered an appearance on behalf of Patent Owner in this matter.

institute trial on fewer than all claims challenged in the petition. *SAS Institute*, 138 S. Ct. at 1355–56, 1358. In this proceeding, we had instituted only on Petitioner’s ground based on § 103. *See* Inst. Dec. 22. Accordingly, we modified our Decision on Institution to include review of all challenged claims on all grounds presented in the Petition. Paper 20, 2–3. The parties subsequently submitted a Joint Motion to Limit the Petition, requesting that the Petition be limited to the ground based on § 103, for obviousness of claims 1–25 over Timmins² and Cheng.³ Joint Motion 2. We granted the motion. Paper 23.

Patent Owner filed a Response (Paper 25, “PO Resp.”), which relies upon the Declaration of Dr. Jennifer Dressman (“Dressman Decl.,” Ex. 2010). Petitioner filed a Reply (Paper 26, “Reply”).

An oral hearing was held on September 24, 2018, and a transcript of the hearing is included in the record. Paper 33 (“Tr.”).

B. Related Proceedings

Petitioner identifies a currently pending district court action filed by Patent Owner against the Petitioner, asserting infringement of the ’866 patent, *Shionogi Inc. v. Aurobindo Pharma Ltd.*, Civ. Act. No. 1:17-cv-00072-UNA (D. Del. 1-25-17), and identifies multiple previous litigations in the District of Delaware, the Federal Circuit (Ex. 1006), and in the District of New Jersey. Pet. 7–8. Patent Owner identifies five prior individual or

² Timmins, Peter et al., WO 99/47128, published September 23, 1999 (“Timmins” Ex. 1003).

³ Cheng, Xiu, Xiu et al., WO 99/47125, published September 23, 1999 (“Cheng” Ex. 1002).

consolidated actions that were filed and dismissed, including some by settlement. Paper 6, 3–4.

C. The '866 and Relevant Background

The '866 patent relates to “controlled release unit dose formulations containing an antihyperglycemic drug. . . . [specifically] an oral dosage form comprising a biguanide such as metformin.” Ex. 1001, 1:6–11. Metformin is used to manage non-insulin dependent diabetes mellitus (NIDDM). *Id.* at 1:56–58.

According to the Specification, various techniques have been used to provide controlled and extended-release pharmaceutical dosage forms that provide stable therapeutic serum levels of the drug, thereby minimizing the effect of missed doses. *Id.* at 1:14–18. Because metformin is a short-acting drug, it requires twice- or thrice-daily doses. *Id.* at 2:4–6. The '866 patent states that, due to adverse events associated with use of metformin, reducing the dosage or using an extended-release form would provide a benefit, in addition to reducing the frequency of administration and improving the drug's safety profile. *Id.* at 2:6–16.

The '866 patent discloses a controlled release dosage form of metformin that is suitable for once-a-day dosing in the “fed” state, preferably at dinner. *Id.* at 8:54–56. The '866 patent states that, when administered in this manner, the bioavailability of the drug is improved relative to the fasted state, which is opposite of the commercially available form of metformin, GLUCOPHAGE®. *Id.* at 8:56–59. In addition, when dosed at dinnertime, the controlled release formulations provide a T_{max} between 5.5 and 7.5 hours after oral administration (which is delayed relative to the T_{max} provided by GLUCOPHAGE®), “such that the level of

the drug is greatest at the time when human patients are manufacturing glucose at highest levels.” *Id.* at 8:66–9:6.

D. Challenged Claims and Reviewed Ground of Unpatentability

As discussed above, the sole ground of review at issue is whether claims 1–25 are unpatentable under 35 U.S.C. § 103 based on the combination of Timmins and Cheng. *See* Inst. Dec. 22; Paper 23 (granting Parties’ Joint Motion to Limit Petition).

Claim 1 of the ’866 patent, the only independent claim, is representative and is reproduced below, with the limitation at issue italicized:

1. A controlled release oral dosage form for the reduction of serum glucose levels in human patients with NIDDM, comprising an effective dose of metformin or a pharmaceutically acceptable salt thereof and a controlled-release carrier to control the release of said metformin or pharmaceutically acceptable salt thereof from said dosage form, said dosage form being suitable for providing once-a-day oral administration of the metformin or pharmaceutically acceptable salt thereof, wherein following oral administration of a single dose, *the dosage form provides a mean time to maximum plasma concentration (T_{max}) of the metformin from 5.5 to 7.5 hours after administration* following dinner.

Dependent claims 2–25 recite additional or more restricted limitations with respect to those in claim 1, including narrower T_{max} ranges (claims 2, 3, 23, and 24), specified dissolution profiles (claims 4 and 5), specified heights of the mean plasma concentration/time curve at specific hours after dosing (claims 6 and 7), and specified C_{max} , AUC_{0-24} , $AUC_{0-\infty}$, and/or $t_{1/2}$ values when certain dosing parameters are followed (claims 8–22). Claim 25 additionally recites

that the dosage form contains a membrane with at least one passageway.

II. ANALYSIS

A. *Principles of Law*

A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which that subject matter pertains.⁴ *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved based on underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness, if present. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

“[T]he [obviousness] analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.” *KSR*, 550 U.S. at 418. Moreover, “any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed.” *Id.* at 420. Accordingly, a party that petitions the

⁴ The Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) (“AIA”), amended 35 U.S.C. §§ 102 and 103. Because the challenged claims of the ’866 patent have an effective filing date before the effective date of the applicable AIA amendments, throughout this Final Written Decision we refer to the pre-AIA versions of 35 U.S.C. §§ 102 and 103.

Board for a determination of unpatentability based on obviousness must show that “a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.” *In re Magnum Oil Tools Int’l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016) (citations omitted). This burden of persuasion never shifts to Patent Owner. See *Dynamic Drinkware, LLC v. Nat’l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015) (discussing the burden of proof in *inter partes* review).

We analyze the ground of unpatentability in accordance with these principles.

B. Level of Ordinary Skill in the Art

In determining the level of ordinary skill in the art, various factors may be considered, including the “type of problems encountered in the art; prior art solutions to those problems; rapidity with which innovations are made; sophistication of the technology; and educational level of active workers in the field.” *In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995) (internal quotation and citation omitted).

In our Institution Decision, we summarized the parties’ contentions, notably that Petitioner proposes that the person of ordinary skill would have had “a Pharm.D. and/or Ph.D. with experience in pharmaceutical sciences, dosage forms, clinical pharmacology or related fields, such as pharmacology,” and asserts that a person of ordinary skill in the art would have “experience in the research or development of pharmaceuticals and have the ability to gather and interpret pharmacokinetic data and the relationship between drug release from a dosage form and its effect on

pharmacokinetic parameters.” Inst. Dec. 5 (citing Ex. 1019 ¶¶ 91–96).
Petitioner also contends that “pharmaceutical development is an inherently collaborative process,” and that the skilled artisan would have had “access to, or be part of a team including, other skilled individuals, such as an M.D. with experience in the field of diabetes treatment.” *Id.*

We observed that Patent Owner proposes that a person of ordinary skill in the art at the time of the invention would have “held a degree in pharmacy, chemistry, chemical engineering, or a related field with at least three to five years of pharmacokinetics, biopharmaceutics, medicinal chemistry, pre-formulation, or formulation experience, research, or training [and would have been familiar] with the methods used in formulating oral dosage forms, modified release dosage forms, and osmotic delivery, and [understand] fundamental principles as to how osmotic dosage forms behave and function.” *Id.* at 6 (citing Prelim. Resp. 15–16).

As we noted in the Institution Decision, we do not “discern an appreciable difference in the parties’ respective definitions of the level of ordinary skill in the art.” *Id.* Because the parties agreed “that a person of ordinary skill in the art would have had experience with and knowledge of the development of pharmaceuticals and the ability to analyze pharmacokinetic data including the relationship between oral dosage forms and osmotic delivery,” and we found “that the prior art itself demonstrates the level of skill in the art at the time of the invention,” we determined it was unnecessary to resolve any perceived differences in the parties’ definitions of the level of ordinary skill in the art for purposes of the Institution Decision. *Id.* (citing *Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001)).

In the Patent Owner Response, Patent Owner acknowledged the Board’s characterization of the knowledge of an ordinarily skilled artisan as consistent with the proposals of both parties (PO Resp. 12–13), and neither party further addressed the proper level of ordinary skill in the art or disagreed with our characterization from the Institution Decision. See PO Resp., Reply. Our determination regarding the patentability of the challenged claims does not turn on the differences between the parties’ definitions. We adopt Petitioner’s assessment, but note that our conclusions would be the same under Patent Owner’s assessment.

C. Testimony of Dr. Akhlaghi

Patent Owner argues that Dr. Akhlaghi’s testimony “should be given minimal [or no] weight” because the opinions vary, are inconsistent, and reveal a lack of understanding of the subject matter of the claims of the ’866 patent. PO Resp. 13–17. Patent Owner further argues that Dr. Akhlaghi is not an expert in formulation development, including formulations of the types relevant to this proceeding. *Id.* at 14.

Petitioner responds that Patent Owner’s selective quotations mischaracterize Dr. Akhlaghi’s deposition testimony and are responsive to deposition questions asked in a confusing manner. Pet. Reply 1–4. Petitioner reiterates Dr. Akhlaghi’s substantial expertise and experience with pharmaceutical formulations. *Id.* at 1–2.

We agree with Petitioner that Dr. Akhlaghi’s qualifications and deposition testimony, when read in context, indicate that Dr. Akhlaghi is sufficiently experienced to opine on the knowledge of one of skill in the art at the time of the ’866 patent. As noted in the August 13, 2018 update to our Trial Practice Guide:

An expert witness must be qualified as an expert by knowledge, skill, experience, training, or education to testify in the form of an opinion. Fed. R. Evid. 702. There is, however, no requirement of a perfect match between the expert's experience and the relevant field. *SEB S.A. v. Montgomery Ward & Co.*, 594 F.3d 1360, 1373 (Fed. Cir. 2010). A person may not need to be a person of ordinary skill in the art in order to testify as an expert under Rule 702, but rather must be "qualified in the pertinent art." *Sundance, Inc. v. DeMonte Fabricating Ltd.*, 550 F.3d 1356, 1363–64 (Fed. Cir. 2008).

See Notice of Update to Office Patent Trial Practice Guide, 83 Fed. Reg.

156, (Aug. 13, 2018) (text of update available at

https://www.uspto.gov/sites/default/files/documents/2018_Revised_Trial_Practice_Guide.pdf). In addition, we are well able to consider the value of an expert opinion and afford it appropriate weight. *Perreira v. Secretary of the Dept. of HHS*, 33 F.3d 1375, 1377 n.6 (Fed. Cir. 1994) ("An expert opinion is no better than the soundness of the reasons supporting it.")

D. Claim Interpretation

In an *inter partes* review, the Board currently interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear.⁵ 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016) (affirming applicability of broadest reasonable construction standard to *inter*

⁵ The Office recently changed the claim construction standard applicable to an *inter partes* review. See Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board, 83 Fed. Reg. 51,340 (Oct. 11, 2018). The rule changing the claim construction standard, however, does not apply to this proceeding because Petitioner filed its Petition before the effective date of the final rule, i.e., November 13, 2018. *Id.* at 51,340 (rule effective date and applicability date), 51,344 (explaining how the Office will implement the rule).

partes review proceedings). Under that standard, and absent any special definitions, we give claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. See *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. See *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

We address the construction of only certain claim terms raised by the parties, and we do so only to the extent necessary to determine whether Petitioner has demonstrated unpatentability by a preponderance of the evidence. See 35 U.S.C. § 316(e); *Nidec Motor Corp. v. Zhongshan Borad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (“[W]e need only construe terms ‘that are in controversy, and only to the extent necessary to resolve the controversy.’”) (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

T_{max}

In our Institution Decision, we noted that the term “ T_{max} ” appears in each of the challenged claims, and that both parties agreed that T_{max} should be construed as stated in the Specification: “the time period which elapses after administration of the dosage form at which the plasma concentration of the drug attains the highest plasma concentration of drug attained within the dosing interval (i.e., about 24 hours).” Inst. Dec. 7 (citing Pet. 24; Prelim Resp. 18; Ex. 1001, col. 7, ll. 49–53). We concluded that the proposed definition was consistent with the Specification and defined the claim term with reasonable clarity, deliberateness, and precision, and we adopted the parties’ construction.

Neither party addressed the issue of construction of T_{max} in further briefing, but the parties disagree about how Dr. Akhlaghi applied the definition in her testimony. *See, eg.*, Pet. Reply 9–10. For purposes of analyzing the patentability of the challenged claims, we continue to interpret the term as “the time period which elapses after administration of the dosage form at which the plasma concentration of the drug attains the highest plasma concentration of drug attained within the dosing interval (i.e., about 24 hours),” because that definition is consistent with the Specification, and because the parties themselves agreed to the definition of T_{max} . Inst. Dec. 7.

E. Overview of the Prior Art

1. Timmins (Ex. 1003)

Timmins relates to a “biphasic controlled release delivery system for pharmaceuticals . . . such as the antidiabetic metformin HCl salt.” Ex. 1003, Abstract. Timmins discloses “a new dosage form for medicaments [such as] metformin, which provides for extended release of the drug and also for prolonged gastric residence which enables efficient delivery of drugs normally absorbed in the gastrointestinal tract,” and methods of preparing the dosage form. *Id.* at 1:5–11.

Petitioner alleges “Timmins['] disclosure covers Bristol-Myers Squibb’s product, GLUCOPHAGE XR®, which was approved for marketing (October 13, 2000) before the priority date of the ’866 patent.” Pet. 18.

Example 3 of Timmins discloses a 0.5 mg metformin hydrochloride tablet that revealed the following profile of *in vitro* release of metformin:

<u>Time (hours)</u>	<u>% metformin released</u>
1	33.1
2	47.6
3	57.5
4	65.1
6	76.5
8	84.3
10	88.6

The Table above shows the *in vitro* release profile of metformin by hour intervals. Ex. 1003, 32:20–33:9.

Example 5 of Timmins discloses a T_{max} range of 4–8 hours, with a median (not mean) T_{max} of 5 hours for a single dose after dinner administration:

Formulation	Cmax (ng/ml)	AUC (inf) (ng.hr/ml)	Tmax* (hr)	%UR
Glucophage	1226 (16)	10128 (14)	3.5 (1, 5)	43.3 (20)
Example 3	978 (13)	10483 (21)	5 (4, 8)	42.7 (18)

The Table above shows the “interpatient variability in pharmacokinetic parameters” as illustrated by the provided parameters. *Id.* at 34:11–30.

Timmins does not report a mean T_{max} for its disclosed formulation, the tablet of Example 3.

2. Cheng (Ex. 1004)

Cheng relates to “an oral dosage form comprising a biguanide such as metformin . . . or a pharmaceutically acceptable salt thereof.” Ex. 1004, 1:7–9. Cheng has the same inventive entity as the ’866 patent. *Id.* at [75].

Cheng discloses a controlled release pharmaceutical tablet comprising 1) a core, including an antihyperglycemic drug, a binding agent, and an absorption enhancer; 2) a semipermeable membrane coating that is permeable to water and biological fluids but impermeable to the antihyperglycemic drug that covers the core; and 3) at least one passageway in the membrane for the release of the antihyperglycemic drug. *Id.* at 9:61–10:6. Cheng discloses that “the term passageway includes an aperture, orifice, bore, hole, weaken[ed] area or an erodible element such as a gelatin plug that erodes to form an osmotic passageway for the release of the antihyperglycemic drug from the dosage form.” *Id.* at 5:8–11.

Example 2 of Cheng is reproduced below:

I Core	
metformin HCl	88.555%
povidone ³ , USP	6.368%
sodium lauryl sulfate	4.577%
magnesium stearate	0.5%

³approximate molecular weight = 1,000,000, dynamic viscosity (10% w/v solution at 20° C.) = 300–700 m Pa s.

Example 2 discloses the formula of “a controlled release tablet containing 850 mg of metformin HCl.” *Id.* at 7:35–44. Cheng discloses that “an additional hole was drilled on the plain side of the coated tablet.” *Id.* at 9:1–2. A depiction of the “in vivo plasma profile” of the product is shown below in Figure 8:

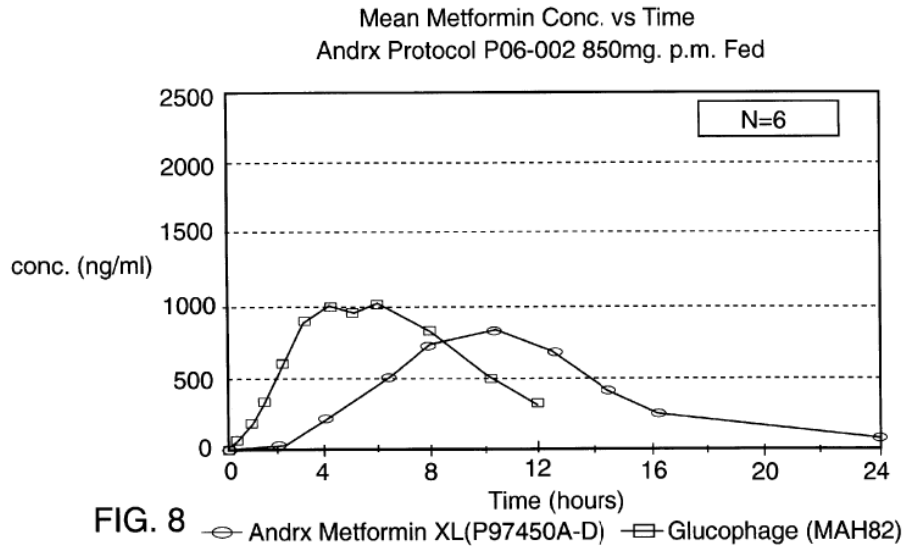


Figure 8 depicts the in vivo plasma profiles of the sustained release metformin product and the GLUCOPHAGE® product when administered “shortly after dinner.” *Id.* at 9:28–32.

F. Obviousness over Timmins and Cheng

Petitioner challenges claims 1–25 as unpatentable under 35 U.S.C. § 103 based on the combination of Timmins and Cheng. Pet. 20–23, 40–53. Pet. Reply. 2–24. Petitioner relies on the Akhlaghi Declaration in support of its contentions. *Id.* Patent Owner disagrees with Petitioner’s assertions, and relies on the Dressman Declaration. Prelim. Resp. 26–30; PO Resp. 1–55.

1. Claim 1

Petitioner argues that Cheng discloses a dosage form of metformin hydrochloride that “is essentially identical to that described in the ’866 patent in terms of the types and amounts of excipient components, and [that] releases metformin approximately the same as the tablets disclosed in the ’866 patent.” Pet. 20. Petitioner acknowledges two differences between the Cheng formulation and the claimed invention: 1) Example 2 of the ’866

patent shows two laser drilled holes in the dosage form rather than the single hole disclosed in Cheng; and 2) claim 1 of the '866 patent specifies a T_{max} range of 5.5 to 7.5 hours, while Cheng discloses a T_{max} of 8–12 hours. *Id.* at 20–22 (citing Ex. 1019 (Akhlaghi Decl.) ¶¶ 148, 155).

Petitioner argues that drilling a second hole in the dosage form to match the invention of the '866 patent is “trivial” and is an “option plainly suggested by the language of [Cheng].” *Id.* at 22 (citing Ex. 1019 ¶ 148). Petitioner argues that upon making this change, the skilled artisan “would expect the T_{max} of the altered product to be concisely within the T_{max} range recited in claim 1, and to match the other pharmacokinetic parameters recited in the claims dependent on claim 1 of the '866 patent (i.e., claim[s] 2–25).” *Id.*

With regard to the motivation of the skilled artisan, Petitioner relies on the Federal Circuit’s finding in *Sciele Pharma, Inc.*⁶ v. *Lupin Ltd.*, 684 F.3d 1253, 1261 (Fed. Cir. 2012) (Ex. 1006). In *Sciele*, the court reviewed the district court’s grant of a preliminary injunction precluding Lupin from selling its generic version of a pharmaceutical, Fortamet, which Sciele claimed was covered by the '866 patent. *Id.* at 5. Lupin denied infringement on the basis that the “'866 patent was invalid, unenforceable, and/or would not be infringed” by Lupin’s products because the combination of Cheng and Timmins rendered the claims obvious. *Id.*

On review, the Court vacated the preliminary injunction and remanded to the district court, finding that Cheng in view of Timmins raised a substantial question of invalidity for obviousness. *Id.* at 13. The Court

⁶ Sciele Pharma Inc. is a predecessor of Patent Owner Shionogi Pharma Inc. Ex. 1006, 2.

also found that the skilled artisan would have been motivated to combine Cheng and Timmins “to better match the T_{max} profile of Glucophage while providing the convenience of an extended release” and that the data provided in Timmins, while not in the form of a mean T_{max} as claimed, is “raw data from which one skilled in the art could compute the range of possible T_{max} values.” *Id.* at 14–15.

In reliance on these findings, which are reviewed and endorsed by Dr. Akhlaghi, Petitioner argues that the skilled artisan “would have used the teaching of Timmins . . . to lower the T_{max} value taught by Cheng . . . to reach a mean range of about 4.67–6.33 hours, well within the range claimed by [claim 1 of] the ’866 patent.” Pet. 22–23; Ex. 1019 ¶¶ 162–165.

Petitioner further argues that, following modification of the T_{max} to within the range of claim 1, the skilled artisan would expect that the altered tablet would exhibit the same pharmacokinetic parameters as those recited in the dependent claims, making those claims obvious as well. Pet. 22 (citing Ex. 1019 ¶ 177).

Patent Owner disputes these contentions and asserts that the skilled artisan would not have been motivated to combine the teachings of Cheng and Timmins, and that the combination of Cheng and Timmins fails to teach or suggest key limitations (*e.g.*, a mean T_{max} of 5.5 hours to 7.5 hours) recited in the claims of the ’866 patent. *See generally* PO Resp. Patent Owner argues that a skilled artisan would not have been motivated to derive a mean T_{max} from the data disclosed in Timmins (PO Resp. 17–19; 27–34), and that to the extent any mean T_{max} values were derived from the data of Timmins, the value would have been lower than the mean T_{max} range of

claim 1. See *e.g.*, *Id.* at 35–37. Patent Owner additionally provides evidence of objective indicia of nonobviousness. *Id.* at 50–54.

Petitioner’s arguments with respect to the sole disputed limitation of claim 1 – the mean T_{max} range of 5.5 to 7.5 – including Dr. Akhlaghi’s relevant declaration statements, are premised entirely on the findings of the Federal Circuit in *Sciele*. The Petition and evidence of record provide no independent factual basis for the argument that the combination of Timmins and Cheng renders this limitation obvious. Rather, the Petition relies on Dr. Akhlaghi’s review of the relevant findings in the *Sciele* decision and her statements that generally she agrees with the findings. See Pet. 19–23; 40–53; Ex. 1019 ¶¶ 72–75, 162–165, 182–184, 191, 192, 194, 196. The sole information in the record regarding Dr. Akhlaghi’s own efforts to calculate the mean T_{max} using the information provided in Example 5 of Timmins is from her deposition testimony, in which she concludes that her calculation was “around 5.75, or something like that . . . [depending on] . . . how you set your confidence values.” Ex. 2011, 70:8–72:12. Dr. Akhlaghi testifies that her calculations are “very close” to the numbers reported in the *Sciele* decision. *Id.* at 72:13–20. However, neither the calculations that resulted in the Court’s opinion in *Sciele* that “Timmins discloses a range of possible mean T_{max} between 4.67 and 6.33 hours” (Ex. 1006, 14), nor those performed by Dr. Akhlaghi, are of record in this proceeding.⁷ Dr. Akhlaghi

⁷ Although the parties at oral argument addressed a purported agreement to file Dr. Akhlaghi’s calculations in the record, because neither party ultimately did so, we rely only upon Dr. Akhlaghi’s deposition testimony describing that she used an “equal distribution between 4, 5, 6, 7, and 8” to reach “5.75, or around that number” as her calculation of the mean T_{max} disclosed by Timmins. See *e.g.*, Tr. 42:6–16; 43:9–20; 47:17–2; Ex. 2011 70:8–72:12; 73:7–13.

admitted at her deposition that her Declaration, filed in support of the Petition, did not address her calculation of a mean T_{max} of 5.75:

Q: Okay. Now, there's no place in your declaration where you report the calculation of the 5.75 hours. Right?

A: No, I haven't. I just, like, went through what the Federal Circuit said.

Ex. 2011, 75:2–6. Dr. Akhlaghi also testified she understood that the Federal Circuit had not calculated a particular mean T_{max} , but rather the possible range for the mean T_{max} as between 4.67–6.33 hours, and that her knowledge of those calculations was limited to the *Sciele* decision, which does not state any of the assumptions made regarding the data that formed the basis for the calculated range. *Id.* at 75:7–78:22.

Based on our review of the record, we determine that Petitioner has not shown sufficiently that combining the teachings of Timmins and Cheng as Petitioner contends would have resulted in a dosage form that provides a mean T_{max} of metformin from 5.5 to 7.5 hours after administration.

As an initial matter, we are not bound by the *Sciele* court's factual findings, as the issue heard was a matter of injunctive relief. *See Univ. of Tex. v. Camenisch*, 451 US 390, 395 (1981) (“[T]he findings of fact and conclusions of law made by a court granting a preliminary injunction are not binding at trial on the merits.”); *Abbott Labs v. Andrx Pharm.*, 473 F.3d 1196, 1206–1207 (Fed. Cir. 2007) (no collateral estoppel where the district court's preliminary injunction proceeding addressed only whether the party challenging the patent demonstrated a likelihood of success in proving invalidity, and did not make conclusive findings); *Momenta Pharm. v. Teva Pharm.*, 809 F.3d 610 (Fed. Cir. 2015). Patent Owner, therefore, is entitled

to a full trial on the merits on the issue of invalidity, given our decision to institute.

Nevertheless, we need not disagree with the Court’s holding to find that Petitioner has not carried its burden. The Court’s finding that “Timmins discloses a range of possible mean T_{max} between 4.67 and 6.33 hours” does not mean that the Timmins mean T_{max} would be within the range of 5.5–7.5 hours as recited in claim 1. Ex. 1006, 14. As Patent Owner’s expert Dr. Dressman explains, although the possible T_{max} values from the data of Example 5 of Timmins fall between 4.67–6.33, “[t]his does not suggest that Timmins discloses an actual mean T_{max} of either 4.67 hours or 6.33 hours, or any other single mean T_{max} value. . . . Instead, a POSA could only determine that, statistically, the mean T_{max} of Timmins falls somewhere between these two values, but neither Dr. Akhlaghi nor the Federal Circuit offered any information on where in the range that would occur.” Ex. 2010 ¶ 73. Fully *half* of the potential range, 4.67–5.49, does not fall within the range of 5.5–7.5 hours recited in claim 1. Moreover, Dr. Ahklaghi stated that if additional patients were “basically randomly” assigned not using the equal distribution she used, that a range of numbers could result. Ex. 2011, 73:7–17.

We find the evidence of record establishes that it is just as probable that the mean T_{max} taught by Example 5 of Timmins would fall between 4.67–5.49, and, therefore, below range required by claim 1. To begin, the median T_{max} disclosed by Example 5 of Timmins is 5. Ex. 1003, 34:11–29. While the median is not the mean, it does show that the most common T_{max} value of the 24 patients was below 5.5. *Id.* Patent Owner, relying on Dr. Dressman’s testimony, argues that to the extent the skilled artisan sought to determine the mean T_{max} of the data of Example 5 of Timmins, that artisan would have believed the data would be close to the median of 5 and below

the range of claim 1: Dr. Dressman explains that the skilled artisan “would have found it reasonable to assume that the majority of the patients [of Timmins] will have had T_{max} values at or close to 5 hours (*i.e.*, 4, 5, or 6 hours)” and that, assuming a bell-shaped distribution, the mean T_{max} would be 5.29 hours, which falls outside of the range recited in claim 1. Ex. 2010 ¶¶ 80–84. We find Dr. Akhlaghi’s stated reasoning for choosing an equal distribution as being “the simplest scenario,” which led to the calculation of 5.75 hours, is not as persuasive as Dr. Dressman’s fact-based assumption based on Timmins’ reported data of a median of 4.

We note that Dr. Akhlaghi and Dr. Dressman agree that ordinarily skilled artisans at the time would have assumed a normal bell-shaped distribution of the data from Example 5 of Timmins. See Ex. 2011, 67:10–16 (“Well, if you’re referring to [a] person of ordinary skill in the art, as we have defined in our declarations between us . . . I think those persons of ordinary skill in the art probably would assume normal distribution, because that’s the most - - that’s the easiest distribution.”); Ex. 2010 ¶ 75 (“[I]t is my opinion that a POSA reviewing Example 5 in Timmins is likely to associate the data with an approximately normal distribution of T_{max} , as is commonly observed in the field.”).

While Dr. Akhlaghi does testify that the T_{max} is a discrete variable not subject to normal distribution (Ex. 2011, 64:21–65:3), Petitioner does not explain why this fact alone establishes that the mean T_{max} of Timmins Example 5 would be between 5.5 and 7.5 hours. In fact, Dr. Akhlaghi states that the “FDA guideline actually suggest reporting median for T_{max} values.” *Id.* at 65:1–3. As discussed above, the Timmins reported median of 5 hours is below the range recited in claim 1. Thus, we are not persuaded that the

skilled artisan would have understood Timmins to disclose a mean T_{max} between 5.5 and 7.5 hours.

We further find persuasive Dr. Dressman's testimony that the distribution of T_{max} values required to provide a mean T_{max} at the upper end of the possible values of Timmins (e.g., 6.33) could only be produced by a non-normal distribution of values. Ex. 2010 ¶ 78. Dr. Dressman opines that this distribution would have been implausible to the skilled artisan as inconsistent with a bell-shaped T_{max} distribution as observed in most pharmacokinetic studies of oral dosage forms, and is inconsistent with Timmins' own teaching of minimal interpatient variability in pharmacokinetic parameters observed using its formulation. *Id.* at ¶¶ 75, 79, 80. While we recognize that this analysis is constrained to provide the data required for the very upper end of the Federal Circuit's provided range, 6.33, rather than at 5.5, the bottom range of claim 1, the value 6.33 nonetheless falls at the lower half of claim 1's range of 5.5–7.5 and suggests that the data of Timmins does not support the entire range of claim 1. Ex. 1001, 21:60–63. Petitioner has not persuasively explained why Dr. Dressman's analysis is incorrect.

We are also unpersuaded that Petitioner has established that the skilled artisan, in view of Timmins and Cheng, would have specifically targeted a T_{max} range of 5.5–7.5 hours. While we agree with the Federal Circuit's conclusion that the skilled artisan would have been motivated to lower the T_{max} based on the teachings of Timmins (Ex. 1006, 14–15), Petitioner does not persuasively explain why the skilled artisan would have targeted the specific mean T_{max} range recited in claim 1. Rather, Petitioner and Dr. Akhlaghi appear to argue that the entire range of 4.67–6.33 would have been targeted. *See, e.g.*, Pet. Reply, 12 (“Akhlaghi also fully agrees

with the Federal Circuit’s following reasoning in *Sciele*, which would lead the POSA to match the mean T_{max} range of Timmins.”). Because Timmins does not disclose a mean T_{max} range, we infer that Petitioner’s comment indicates that Dr. Akhlaghi believes the entire mean T_{max} range found in *Sciele*, 4.67–6.33 hours, is what the POSA would have been led to match. We note that 4.67–6.33 hours does not include 6.34–7.5 hours, which is over half of the range recited in claim 1.

We further note that the stated reasons that the *Sciele* court found would have motivated a skilled artisan to lower the Timmins T_{max} included “reduction in dosing frequency, providing patient convenience that would probably improve compliance,” as well as “an extended time period over which therapeutically beneficial plasma levels of drug were maintained.” Ex. 1006, 14–15. But the *Sciele* court linked these motivations to the extended release version of the drug disclosed in Timmins that could be given as a single post-dinner administration (*id.*), not to a specific mean T_{max} of 5.5–7.5 hours. Petitioner has not explained sufficiently why that portion of the range of a mean T_{max} of 4.67–6.33 hours would have been targeted to achieve the stated benefits. Petitioner endorses and relies upon the findings of the *Sciele* court without explaining why those findings guarantee that the mean T_{max} range would be higher than 5.5.

For the foregoing reasons, we determine that Petitioner has not made a sufficient showing that a person having ordinary skill in the art would have been motivated to make a dosage form that provides a mean T_{max} of metformin from 5.5 to 7.5 hours after administration based on the combined teachings of Timmins and Cheng. Accordingly, we find that Petitioner has not shown by a preponderance of the evidence that claim 1 of the ’866

patent is unpatentable under 35 U.S.C. § 103 as obvious over the combined teachings of Timmins and Cheng.

2. *Dependent Claims 2–25*

Petitioner’s arguments with respect to the dependent claims fall into three categories. We address these by groups of claims argued below.

Claims 2, 3, and 25

Claim 2 depends from claim 1 and further recites a mean T_{max} range of 6.0 to 7.0 hours. Ex. 1001, 21:60–63. Claim 3 depends from claim 1 and further recites a mean T_{max} range of 5.5 to 7.0 hours. *Id.* at 21:64–67. Claim 25 depends from claim 1 and further recites that the dosage form should have a core with specific features. *Id.* at 24:33–42.

Petitioner relies on its arguments with respect to claim 1 to support its contention that the combination of Timmins and Cheng discloses all of the elements of claims 2, 3, and 25. Pet. 45–46, 53. As discussed above, we find that Petitioner has not established by a preponderance of the evidence that Timmins teaches a mean T_{max} value between 5.5 and 7.5. For the same reasons, Petitioner has not established by a preponderance of the evidence that dependent claims 2, 3, and 25 would have been obvious over the combined teachings of Timmins and Cheng.

Claims 4 and 5

Claims 4 and 5 specify percentages of the metformin or metformin salt that are released within specific time periods after administration. Ex. 1001, 22:1–52.

Petitioner relies on its arguments with respect to claim 1 to support its contention that the combination of Timmins and Cheng discloses all of the elements of claims 4 and 5. Pet. 46–47. In addition, Petitioner asserts that “[t]he claim limitations are those needed for an in vitro release rate to

produce a T_{max} in the range claimed, and would be routinely established by an artisan of ordinary skill in the art, modifying the dosage forms of [Cheng] according to the instruction of Timmins.” *Id.* at 52. Petitioner further asserts that Patent Owner, during the prosecution of the ’866 patent, stated that the ordinary artisan “would easily alter the controlled release formulations of the prior art to produce the in vivo T_{max} range specified in the ’866 patent.” *Id.* at 3–4 (citing Ex. 1010, 8–9).

Patent Owner, relying on Dr. Dressman’s testimony, responds that the cited portion of the prosecution history “described the flexibility of formulation *within the same claimed controlled release formulation* that could be drawn upon to achieve a target T_{max} value,” meaning that, with the teachings of the ’866 patent, a skilled artisan could have adjusted the mean T_{max} to within the range of 5.5 to 7.5 hours. PO Resp. 24. Patent Owner argues this was “not an admission that the claimed invention would have been obvious to a POSA without the benefit of hindsight.” *Id.*

Petitioner does not respond on this issue, other than to reiterate its original statement. Pet. Reply 6, 13. Nevertheless, we find that Petitioner’s reliance on its arguments discussed above regarding claim 1 remain problematic because no separate basis for unpatentability has been established for these claims; even if the skilled artisan had been able to use available technology to adjust the mean T_{max} , Petitioner has not established that the mean T_{max} range of 5.5 to 7.5 hours would have been targeted in the first place. We find that Petitioner has not established by a preponderance of

the evidence that claims 4 and 5 would have been obvious over the combined teachings of Timmins and Cheng.

Claims 6–24

Claims 6–24 include additional limitations that characterize the release of the metformin or metformin salt at specific time periods after administration. Ex. 1001, 22:53–24:32.

Petitioner relies on its arguments with respect to claim 1 to support its contention that the combination of Timmins and Cheng discloses all of the elements of claims 6–24. Pet. 47–53. For each claim, Petitioner also asserts that “[h]aving routinely modified release rate of the dosage forms of Cheng et al. to meet the T_{max} values taught by [Timmins], the modified dosage form would inherently meet the limitations of [the claim].” *Id.*; Ex. 1019 ¶¶ 196–197. Petitioner does not make any separate arguments for any of these claims, relying entirely on its arguments for claim 1 and the inherent ability of the dosage form to meet the limitations once the dosage form of claim 1 is established.

As discussed above, we find that Petitioner has not established that the skilled artisan, in view of Timmins and Cheng, would have specifically targeted a T_{max} range of 5.5–7.5 hours as recited in claim 1. Because a separate basis for unpatentability has not been established for these claims, even if the dosage form had the limitations of each of these dependent claims, Petitioner has not established that the mean T_{max} range of 5.5 to 7.5 hours would have been targeted. We find that Petitioner has not established

by a preponderance of the evidence that claims 6–24 would have been obvious over the combined teachings of Timmins and Cheng.

III. CONCLUSION

After reviewing the record and weighing the evidence offered by both parties, we determine that Petitioner has not demonstrated, by a preponderance of the evidence, that claims 1–25 of the '866 patent are unpatentable.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that Petitioner has not shown by a preponderance of the evidence that claims 1–25 of the '866 patent are unpatentable; and

FURTHER ORDERED that, because this is a Final Written Decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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