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Paper 72
Entered: August 29, 2023

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC.,
Petitioner,

v.

CHUGAI SEIYAKU KABUSHIKI KAISHA, GENENTECH, INC., and HOFFMANN-LA ROCHE INC.,
Patent Owner.

IPR2022-00579
Patent 10,874,677 B2

Before JOHN G. NEW, GEORGIANNA W. BRADEN, and, TINA E. HULSE, *Administrative Patent Judges.*

NEW, *Administrative Patent Judge*.

JUDGMENT
Final Written Decision
Determining All Challenged Claims Unpatentable
Dismissing Petitioner's Motion to Exclude
35 U.S.C. § 318(a)

I. INTRODUCTION

We have jurisdiction to hear this *inter partes* review under 35 U.S.C. § 6. This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. For the reasons set forth below, we determine that Petitioner Celltrion, Inc. ("Petitioner") has established, by a preponderance of the evidence of record, that challenged claims 1–8 of Patent Owners Chugai Seiyaku Kabushiki Kaisha, Genentech, Inc., and Hoffmann-La Roche Inc. (collectively "Patent Owner") U.S. Patent No. 10,874,677 B2 (Ex. 1001, the "'677 patent") are unpatentable. Furthermore, because we find that Petitioner has established that claims 1–8 are unpatentable, we dismiss Petitioner's Motion to Exclude Evidence (Paper 59) as moot.

A. Procedural History

On February 21, 2022, Petitioner filed its Petition (Paper 2, "Pet.") seeking *inter partes* review of claims 1–8 of the '677 patent. Patent Owner waived filing a Preliminary Response (*see* Paper 8). On August 31, 2022, and pursuant to 35 U.S.C. § 314, we instituted *inter partes* review of challenged claims 1–8 of the '677 patent (Paper 9).

After institution of trial, Patent Owner filed a Response (Paper 22, "PO Resp."), to which Petitioner filed a Reply (Paper 41, "Pet. Reply"), and Patent Owner, in turn, filed a Sur-Reply (Paper 57, "PO Sur-Reply"). Petitioner also fined a Motion to Exclude Patent Owner's Exhibits 2005, 2006, 2009, 2034, 2065, 2080, 2081, and 2083 (Paper 59, "Mot. Exclude"), having timely objected to those exhibits. Patent Owner filed an Opposition

to Petitioner's Motion to Exclude (Paper 61, "Opp. Mot.") and Petitioner filed a Reply to the Opposition (Paper 66, "Reply Opp.").

Oral argument was held on May 31, 2023. A transcript of the oral argument is included in the record. (Paper 71, "Hearing Trans.").[1]

B. Related Proceedings

Petitioner identifies as a related matter *Celltrion, Inc. et al. v. Chugai Seiyaku Kabushiki Kaisha et al.*, IPR2022-00578 challenging related patent US 8,580,264 B2 (the "'264 patent"). Pet. 24–25. Petitioner further identifies *Fresenius Kabi USA, LLC, et al. v. Chugai Seiyaku Kabushiki Kaisha et al.*, IPR2021-01336, also challenging the '677 patent (terminated October 17, 2022), and *Fresenius Kabi USA, LLC, et al. v. Chugai Seiyaku Kabushiki Kaisha et al.*, IPR2021-01288 (terminated October 17, 2022) and *Fresenius Kabi USA, LLC, et al. v. Chugai Seiyaku Kabushiki Kaisha* et al., IPR2021-01542 (terminated October 17, 2022), both challenging the '264 patent as related matters. Pet. 25.

Patent Owner also identifies IPR2022-00578 (cited above) and *Fresenius Kabi USA, LLC, et al. v. Chugai Seiyaku Kabushiki Kaisha* et al., IPR2022-00201 challenging US 9,750,752 B2 (terminated October 17,

[1] Oral argument was simultaneously heard in this *inter partes* review and in *Celltrion, Inc. et al. v. Chugai Seiyaku Kabushiki Kaisha et al.*, IPR2022-00578, which was conducted in parallel, but not consolidated, with the present proceeding.

2022) as related matters. Paper 4, 1–2. Patent Owner additionally identifies the following U.S. Patent applications and issued patents that relate to U.S. Patent Application No. 16/254,105, which issued as the '677 patent:

- U.S. Patent Application No. 61/411,015, filed November 8, 2010, and now expired, is a provisional application from which U.S. Patent Application No. 16/254,105, which issued as U.S. Patent No. 10,874,677, claims the benefit of priority.

- U.S. Patent Application No. 61/542,615, filed October 3, 2011, and now expired, is a provisional application from which U.S. Patent Application No. 16/254,105, which issued as U.S. Patent No. 10,874,677, claims the benefit of priority.

- U.S. Patent Application No. 14/062,026, filed October 24, 2013, and now issued as U.S. Patent No. 9,750,752, is a patent application from which U.S. Patent Application No. 16/254,105, which issued as U.S. Patent No. 10,874,677, claims the benefit of priority.

- U.S. Patent Application No. 17/115,391, filed December 8, 2020, and now pending, is a patent application that claims priority to U.S. Patent Application No. 16/254,105, which issued as U.S. Patent No. 10,874,677.

Id. at 1–3.

C. Real Parties-in-Interest

Petitioner identifies Celltrion, Inc., Celltrion Healthcare Co. Ltd., and Celltrion Healthcare U.S.A., Inc. as real parties-in-interest. Pet. 24. Patent Owner identifies Chugai Seiyaku Kabushiki Kaisha (also called Chugai Pharmaceutical Co., Ltd.), Genentech, Inc., and Hoffmann-La Roche Inc. as

the real parties-in-interest. Paper 4, 1. There is no dispute over the identities of the real parties-in-interest in this proceeding.

D. The Instituted Challenges

Petitioner contends that challenged claims 1–8 of the '677 patent are unpatentable, based upon the following grounds, all of which have been instituted in this proceeding:

Ground	Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
1	1, 5	102[2]	NCT '653[3]
2	1–8	103	NCT '653, Morichika[4], Kivitz[5]

[2] 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 '538 patent have an effective filing date prior to the effective date of the applicable AIA amendments, we refer to the pre-AIA versions of 35 U.S.C. §§ 102 and 103 this Decision. Our conclusions herein, however, would not change regardless of which version of the Patent Act applies.

[3] U.S. Nat'l Library of Medicine, *History of Changes for NCT00965653: A Study of Subcutaneously Administered Tocilizumab in Patients with Rheumatoid Arthritis*, ClinicalTrials.gov ("NCT '653") Ex. 1004.

[4] Morichika et al. (WO 2009/084659 A1, July 9, 2009) ("Morichika") Ex. 1110.

[5] A. Kivitz et al., *HUMIRA® Pen: a Novel Autoinjection Device for Subcutaneous Injection of the Fully Human Monoclonal Antibody Adalimumab*, 4(2) EXPERT REV. MED. DEVICES 109–16 (2007) Ex. 1050.

Petitioner also relies on the Declarations of Prescott M. Lassman, Esq. (Ex. 1137), Dr. Dhaval K. Shah (Ex. 1032; Ex. 1138), Dr. Maarten Boers (Ex. 1034; Ex. 1139), and Dr. Paul A. Dalby (Ex. 1036; Ex. 1140). Patent Owner relies on the Declarations of Dr. Steven R. Little (Ex. 2005), Dr. Emil Samara (Ex. 2006), and Dr. Gregg J. Silverman (Ex. 2009). We have reviewed the credentials of Petitioner's and Patent Owner's declarants and consider them each to be qualified to provide the opinions for which their testimony has been submitted.

E. The '677 Patent

In one aspect, the '677 patent relates to methods for treating interleukin-6 (IL-6) related diseases, such as rheumatoid arthritis (also referred to as "RA"), with subcutaneously administered antibody that binds interleukin-6 receptor (anti-IL-6R antibody). Ex. 1001, col. 1, ll. 29–35. The '677 patent also relates to "devices useful for subcutaneous administration of an anti-IL-6R antibody." *Id.* at col. 1, ll. 39–40, cols. 4–5, ll. 65–3.

IL-6 is a "proinflammatory, multifunctional cytokine produced by a variety of cell types," and "exerts its effects through a ligand-specific receptor (IL-6R) present both in soluble and membrane-expressed forms." Ex. 1001, col. 2, ll. 1–2, 16–18. It has been known in the art that "[e]levated IL-6 levels have been reported in the serum and synovial fluid of [rheumatoid arthritis ("RA")] patients, indicative of production of IL-6 by the synovium." *Id.* at col. 2, ll. 19–21. It is also known in the art that "IL-6

levels correlate with disease activity in RA … and clinical efficacy is accompanied by a reduction in serum IL-6 levels." *Id.* at col. 2, ll. 23–25.

Tocilizumab (also referred to as "TCZ") is a recombinant humanized monoclonal antibody of the immunoglobulin IgG1 subclass which binds to human IL-6R. Ex. 1001, col. 2, ll. 27–29. Tocilizumab has been approved for use in treating a number of diseases, including rheumatoid arthritis and juvenile idiopathic arthritis. *See id.* at col. 2, ll. 34–43. In one aspect, the '677 patent relates to identification of a fixed dose of anti-IL-6R antibody such as tocilizumab. *Id.* at col. 1, ll. 35–36.

F. Representative Claim

Claims 1 and 5 are independent and are representative of the challenged claims. Claim 1 recites:

> 1. An article of manufacture comprising a subcutaneous administration device, which contains and delivers to a patient a 162 mg fixed dose of tocilizumab.

Ex. 1001, col. 63, ll. 45–47. Claim 5 recites:

> 5. An article of manufacture comprising a subcutaneous administration device, which contains and delivers to a patient a 162 mg fixed dose of an anti-IL-6R antibody, wherein the anti-IL-6R antibody comprises the light chain and heavy chain amino acid sequences of SEQ ID NOs:1 and 2, respectively.

Id. at cols. 63–64, ll. 56–47.

II. ANALYSIS

A. Level of Ordinary Skill in the Art

The level of skill in the art is a factual determination that provides a primary guarantee of objectivity in an obviousness analysis. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 1323 (Fed. Cir. 1999) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966)); *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991)).

Petitioner asserts that a person of ordinary skill in the art at the time of the invention "would in fact have been a team of individuals possessing the different skill sets typically employed on such a project." Pet. 18. Petitioner asserts that the "team would have included individuals skilled in the relevant area(s) of clinical medicine (e.g., rheumatologists), pharmacokineticists, formulators and project leads" working together as needed. *Id.* (citing Ex. 1034 ¶ 48; Ex. 1032 ¶ 27; Ex. 1036 ¶¶ 25–26).

Patent Owner agrees with Petitioner's definition of a person of ordinary skill being a team of individuals possessing the different skill sets typically employed on such a project. PO Resp. 7. According to Patent Owner, a person of ordinary skill in the art can have the knowledge and experience of multiple individuals working across different arts. *Id.* at 8 (citing *Daiichi Sankyo Co. v. Apotex, Inc.*, 501 F.3d 1254, 1256–57 (Fed. Cir. 2007)). Patent Owner disagrees with the definition adopted by the Board in its Decision to Institute, *viz.*:

> [A]n individual with an M.D. specializing in the treatment of autoimmune disorders and having several years of experience treating patients with such disorders, including rheumatoid

> arthritis; or an individual with an M.D. and/or Ph.D. having several years of experience researching treatments for autoimmune disorders, including rheumatoid arthritis, wherein the M.D. and/or Ph.D. would have had access to individuals skilled in clinical medicine, pharmacokinetics and formulation.

Dec. 6. Patent Owner contends that such an individual would have been "unable to develop those inventions without assistance from other individuals." PO Resp. 8 (citing Ex. 1001, cols. 29–32, ll. 19–37, cols. 38–42, ll. 59–14, Figs. 1–4).

Petitioner replies that there is little difference between the definition set forth in the Decision to Institute and the definition essentially agreed upon by the parties, as both definitions include a team of individuals. Pet. Reply 6. Petitioner contends, however, that the prior art of record demonstrates the amount of experience a skilled artisan would have had, which is quite substantial. *Id.* (citing *Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001)).

We are not persuaded that a person of ordinary skill in the art could be thought of as a "team of individuals." We find no support in *Sankyo* for Patent Owner's contention that "a person of ordinary skill in the art can have the knowledge and experience of multiple individuals working across different arts." *See* PO Resp. 8. Rather, in *Sankyo*, the Federal Circuit looked to the qualifications of the inventors of the patent at issue, all of whom were specialists in drug and ear treatments and noted that others working in the same field as the inventors were of the same skill level. *Sankyo*, 501 F.3d at 1257. Finding that such specialty training was a

requisite for ordinary skill in the art, the court defined the level of ordinary skill in the art in that case as "a person engaged in developing pharmaceutical formulations and treatment methods for the ear or a specialist in ear treatments such as an otologist, otolaryngologist, or otorhinolaryngologist who also has training in pharmaceutical formulations." *Id.*

We conclude that there is, as Petitioner acknowledges, little substantial difference between the qualifications of the "team" proposed by the parties, and those of the individual skilled artisan defined in our Decision to Institute. Such an individual would have had not only several years of experience researching treatments for autoimmune disorders, including rheumatoid arthritis, but would additionally have access to individuals skilled in clinical medicine, pharmacokinetics and formulation. Indeed, Petitioner's expert, Dr. Shah, acknowledges that an individual person of skill in the art "would have had access to individuals skilled in clinical medicine, pharmacokinetics and formulation." Ex. 1032 ¶ 27. This is consistent with our prior definition. We consequently adopt, for this Final Written Decision, the definition of a person of ordinary skill in the art as defined in our Decision to Institute and quoted above because it appears consistent with the problems addressed in the '677 Patent and the prior art of record. *See* Dec. 6. Furthermore, the prior art itself can reflect the appropriate level of ordinary skill in the art. *Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001). Regardless of the level of skill adopted, our analysis and findings would remain the same.

B. Claim Construction

The Board applies the same claim construction standard used to construe claim terms in a civil action under 35 U.S.C. § 282(b). *See* 37 C.F.R. § 100(b) (2020). Under that standard, claim terms "are generally given their ordinary and customary meaning" as understood by a person of ordinary skill in the art at the time of the invention. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc). "In determining the meaning of the disputed claim limitation, we look principally to the intrinsic evidence of record, examining the claim language itself, the written description, and the prosecution history, if in evidence." *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 469 F.3d 1005, 1014 (Fed. Cir. 2006) (citing *Phillips*, 415 F.3d at 1312–17). Extrinsic evidence is "less significant than the intrinsic record in determining 'the legally operative meaning of claim language.'" *Phillips*, 415 F.3d at 1317 (quoting *C.R. Bard, Inc. v. U.S. Surgical Corp.*, 388 F.3d 858, 862 (Fed. Cir. 2004)).

1. "Fixed dose"

Petitioner asserts that the claim term "fixed dose" is defined in the Specification as "a dosage of a drug, such as an anti-IL-6R antibody which is administered without regard to the patient's weight or body surface area (BSE), i.e., it is not administered as either a mg/kg or mg/m^2 dose." Pet. 27 (quoting Ex. 1001, col. 15, ll. 15–18). Patent Owner does not dispute this definition. PO Resp. 9 n.9. Because the term "fixed dose" is defined by the

Specification and is not disputed by the parties, we determine, based on the current record, that this term requires no further construction.

2. "Delivers to a patient"

In our Decision to Institute, we found that, for the purposes of that Decision, the claim phrase "delivers to a patient" does not limit the claims, which "are directed to a device and not to a method of treatment." Dec. 8. We found that the claim recitation that the device "delivers to a patient" the recited fixed dosage of tocilizumab is "merely an intended use of the subcutaneous administration device, as defined by the Specification." *Id.* (citing Ex. 1001, col. 20, ll. 7–11).

Patent Owner takes issue with our preliminary holding that the phrase "delivers to a patient" is not limiting upon the claim. PO Resp. 12. According to Patent Owner, a "wherein" clause containing functional language that informs the structural requirements of a claimed device is limiting on the scope of the claimed invention. *Id.* (citing, e.g., *K-2 Corp. v. Salomon S.A.*, 191 F.3d 1356, 1363 (Fed. Cir. 1999)). Patent Owner asserts that the clause reciting "which contains and delivers 162 mg of tocilizumab to a patient" dictates that the structure of the claimed device "must be able to contain 162 mg of tocilizumab and safely and effectively deliver that amount of drug subcutaneously to a patient with an IL-6-mediated disorder." *Id.* (citing Ex. 2009 ¶¶ 57–59).

Patent Owner argues further that the alleged risk of immunogenic reactions due to aggregation and viscosity of the subcutaneous formulation

was considerable for patients suffering from IL-6 mediated disorders like RA. PO Resp. 12 (citing Ex. 2009 ¶¶ 58, 84–88). Consequently, argues Patent Owner, the device structure must therefore accommodate these challenges, as well as the obstacles of aggregation instability, injection difficulties, and patient discomfort. *Id.* (citing Ex. 2005 ¶¶ 10–20).

Petitioner maintains its position that the limitation should not be accorded patentable weight because it recites an intended use of the claimed device. Pet. Reply 9 (citing *In re Casey*, 370 F.2d 576, 580 (C.C.P.A. 1967)). However, argues Petitioner, even if the phrase is limiting upon the claim, Patent Owner's proposed definition reads too much into the phrase. *Id.* According to Petitioner, to "deliver" a drug means to introduce into or on some part of the body. *Id.* at 9–10 (citing Ex. 1140 ¶ 6). Petitioner asserts that a person of ordinary skill in the art would have understood that the claimed "subcutaneous delivery device" must be capable of "delivering" the tocilizumab subcutaneously, i.e., introducing it into the subcutaneous layer of the skin, regardless of its disposition or effect thereafter. *Id.* at 10 (citing Ex. 1140 ¶ 6).

Petitioner argues further that an ordinarily skilled artisan would have understood that the plain meaning of the claim term "to a patient" means "to a human or other animal that is under medical care." Pet. Reply 10 (citing Ex. 1139 ¶ 31). Petitioner asserts that this claim term is not limited to patients with a particular disease, nor does the term inform a person of ordinary skill in the art as to a particular threshold of safety or efficacy that must be met. *Id.* Petitioner disputes Patent Owner's assertion that the claim

refers to patients "in need of treatment," pointing out that the language does not appear in the claims. Pet. Reply 10 (citing PO Resp. 12). Petitioner argues that, even if the phrase "delivers to a patient" contains functional language, it does not "dictate[] that the structure of the claimed device must be able to…safely and effectively deliver that amount of drug subcutaneously to a patient with an IL-6R-mediated disorder," as argued by Patent Owner. *Id.* at 10–11 (quoting PO Resp. 12) (alterations in original). At most, argues Petitioner, it could only require that the "subcutaneous delivery device" be capable of "delivering" the dose to a "patient," which is the very purpose of any subcutaneous drug delivery device. *Id.*

Patent Owner responds that its proposed construction does not seek to import a method-of-treatment limitation requiring that the claimed dose to be safe and effective. PO Sur-Reply 3. Rather, contends Patent Owner, it merely requires that a person of skill in the art prepare a device intended to deliver the claimed dose to someone she would expect to benefit from it. *Id.* In other words, Patent Owner asserts, the device, and not its contents, must be designed in a manner considered safe and effective to accomplish that task, and must account for the risks associated with subcutaneous administration to those with IL-6 mediated diseases. *Id.*

The claim phrase "delivers to a patient" is contained within the limitation of claims 1 and 5 reciting "a subcutaneous administration device, which contains and delivers to a patient a 162 mg fixed dose of [tocilizumab]." Although this language is not, as Patent Owner suggests, contained within a "wherein" clause, we nevertheless find that the most

natural reading of this claim language shows a functional limitation that simply requires that the claimed subcutaneous administration device be capable of containing and delivering to a patient a fixed dose of the drug. As such, we conclude that this functional language is limiting upon the claim. *See, e.g.*, *K-2 Corp. v. Salomon S.A.*, 191 F.3d 1356, 1363 (1999) (holding that functional language is limiting upon an apparatus claim).

We decline to adopt, however, Patent Owner's construction of a patient as being a person "with an IL-6-mediated disorder" or requiring the claimed device to "safely and effectively deliver that amount of drug subcutaneously to a patient" and to accommodate the risk of serious immunogenic reactions due to aggregation and viscosity[,] … as well as the obstacles of aggregation instability, injection difficulties, and patient discomfort." *See* PO Resp. 12. To adopt these definitions is to impermissibly extend the scope of the claims through claim construction beyond the language of the claims, which do not recite this language. To require that the patient be in need of treatment for an IL-6 mediated disease, as suggested by Patent Owner, is to place an additional limitation on the device that is not functional, but rather relates to the nature of the individual receiving the subcutaneous administration.

To the contrary, we interpret this functional language as requiring the claimed device to be capable of delivering the contained dosage to any "patient" whether or not they have a specific medical condition or without respect to ancillary conditions or concerns that may apply. If the device is capable of delivering the dosage subcutaneously to *any* patient, that is

sufficient for this functional limitation, and we decline to import additional limitations into the claim, as Patent Owner urges us to do. We therefore construe the claim phrase "delivers to a patient" as a functional limitation of the claims that requires that the claimed device be capable of subcutaneously delivering the dose contained within it to a person.

3. "A subcutaneous administration device, which contains and delivers to a patient a 162 mg fixed dose of tocilizumab"

Patent Owner next argues that a person of ordinary skill in the art would have understood that the "162 mg fixed dose of tocilizumab" recited in claims 1 and 5 must be contained in, and delivered to, a patient by a single subcutaneous administration device. PO Resp. 9 (citing Ex. 2009 ¶¶ 57–59). Patent Owner acknowledges that, although it is possible to administer a fixed dose of drug using more than one subcutaneous administration device, the Specification of the '677 patent never describes that. *Id.* at 9–10 (citing Ex. 2009 ¶ 57). Rather, contends Patent Owner, the Specification consistently describes containing and delivering to patients the entire 162 mg fixed dose of tocilizumab using a single device. *Id.* at 10 (citing Ex. 1001, col. 49, ll. 54–55, col. 34, ll. 34–35, col. 43, ll. 43–65, Table 2).

Patent Owner also points to the Specification's description of the inventor's efforts to develop 162 mg fixed dose subcutaneous tocilizumab formulations capable of being "contain[ed]" in and "deliver[ed]" by a single subcutaneous administration device by grappling with competing demands of a "higher concentration of tocilizumab, 180 mg/mL," "high viscosity,"

low injection volumes of "1 mL or less", and "increase[d] ejection force." PO Resp. 10 (citing Ex. 1001, col. 40, ll. 9–17) (alteration in original). These challenges, Patent Owner asserts, would have been obviated by a dose contained in and delivered *via* more than one subcutaneous injection device. *Id.* at 11.

Petitioner disagrees that the claimed device must administer all of the fixed dose in one injection. Pet. Reply 8. Petitioner contends that syringes and other injection devices, as well as infusion pumps, are generally capable of administering their contents to patients in more than one injection, e.g., if the user decides to administer the contents of the device in several injections rather than one. *Id.* (citing Ex. 1140 ¶¶ 4–5). Petitioner emphasizes that the challenged claims are device claims, not method claims, and do not place any restrictions on how the device may be used. *Id.*

Patent Owner replies that Petitioner's declarant, Dr. Boers, opined that a person of ordinary skill in the art "would have been unaware of any reason why the clinical investigator would need to use more than one injection," and that it "would be very, very strange, in fact, and maybe even unethical, to do it another way." PO Sur-Reply 1–2 (citing Ex. 1139 ¶ 33; Ex. 2080, 49). Patent Owner also points again to the Specification, which, Patent Owner argues, discloses evidence supporting Patent Owner's construction, and Dr. Silverman's opinion, including consistent descriptions of a single device containing and delivering subcutaneously the claimed fixed dose to patients, and efforts to develop a 162 mg fixed formulation suitable for that purpose. *Id.* at 2–3.

Patent Owner also argues that the prosecution history of the '677 patent underscores this interpretation. PO Resp. 11. According to Patent Owner, the word "contains" was added to the claims as part of an amendment, indicating that the requirement that the administration device "contains" tocilizumab is separate from, and in addition to, the requirement the device "delivers" tocilizumab. *Id.* (citing Ex. 1068, 328–29). Patent Owner contends that the claims this rule out the possibility of administration from a pre-filled vial, which would contain the drug but could not deliver it without the use of another administration device like a syringe. *Id.*

We are not persuaded that the language of the claims reciting "a subcutaneous administration device, which contains and delivers to a patient a 162 mg fixed dose of tocilizumab" necessarily requires that the dose delivered to the patient be delivered in a single injection. As an initial matter, the claim term "fixed dose" is defined by the Specification of the '677 patent as meaning "a dosage of a drug, such as an anti-IL-6R antibody which is administered without regard to the patient's weight or body surface area (BSA), i.e.[,] it is not administered as either a mg/kg or mg/m^2 dose." Ex. 1001, col. 15, ll. 15–18. There is no dispute between the parties over this portion of the claim language, and we have adopted this definition as part of our construction. *See* Section II.B.1, *supra*. Moreover, the Specification provides no further definition of the term "dose."

The claim language also recites that the "subcutaneous administration device, … contains and delivers to a patient" the 162 mg fixed dose of tocilizumab. The claim places no further restrictions or limitations on how

the device delivers the fixed dose, i.e., the language places no limits *requiring* that the fixed dose be administered in a single injection. Nor does the plain meaning of the word "dose" require that the medicament be delivered *via* a single injection. The Merriam-Webster Medical Dictionary defines the term "dose," in relevant part, as "the measured quantity of a therapeutic agent to be taken at one time." *See* Ex. 3003.[6] However, "taken at one time" does not necessarily mean given as a single injection or other singular means of delivery, but rather that the total amount be taken at the same time. By way of example, a 20 mg dose of medicine could be given as two 10 mg tablets to be taken together. That is to say, the definition is temporal in nature, rather than specifying a means or route of administration.

To be sure, the Specification discloses examples of the medication being delivered as a single injection. *See* Ex. 1001, col. 49, ll. 54–55, col. 34, ll. 34–35, col. 43, ll. 43–65, Table 2. But the common language of claims 1 and 5 does not require that the device deliver the fixed dose *in a single injection*. Indeed, the language of the claims would also include within its scope a "subcutaneous administration device, which … delivers to a patient a 162 mg fixed dose" of tocilizumab *via* two or more sequential subcutaneous injections. The language of the claims requires only that the device be capable of containing and delivering the fixed dose. It is silent

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[6] Merriam-Webster, *Dose*, *available at*: https://www.merriam-webster.com/dictionary/dose#medicalDictionary (last visited July 18, 2023). Ex. 3003.

with respect to the method by which the dose should be delivered (other than subcutaneously), and we decline to read further limitations into the plain and ordinary meaning of the claim language. Patent Owner's argument that the addition of the term "contains" to the claim during prosecution does not change our interpretation, because the word contains does not require, expressly or implicitly, that the fixed dose be administered as a single injection.

We consequently construe the language of independent claims 1 and 5 reciting a "subcutaneous administration device, which contains and delivers to a patient a 162 mg fixed dose" of tocilizumab to mean that the claimed apparatus must be "capable of containing and delivering the 162 mg fixed dose subcutaneously," without specifying the method by which the dose is to be delivered (e.g., single or multiple injections) or reading any further method limitations into the device claim.

C. *Principles of Law*

1. Burden of Proof

"In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016 (citing 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify "with particularity … the evidence that supports the grounds for the challenge to each claim")). Therefore, in an *inter partes* review, the burden of proof is on the Petitioner to show that the challenged

claims are unpatentable; that burden never shifts to the patentee. *See* 35 U.S.C. § 316(e); *In re Magnum Oil Tools Int'l, Ltd*., 829 F.3d 1364, 1375 (Fed. Cir. 2016) (citing *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015)).

2. Anticipation

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373 (Fed. Cir. 2003) (quoting *Verdegaal Bros., Inc. v. Union Oil Co. of Cal.*, 814 F.2d 628, 631 (Fed. Cir. 1987)). It is well settled that "a reference can anticipate a claim even if it 'd[oes] not expressly spell out' all the limitations arranged or combined as in the claim, if a person of skill in the art, reading the reference, would 'at once envisage' the claimed arrangement or combination." *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015) (quoting *In re Petering*, 301 F.2d 676, 681 (C.C.P.A. 1962)).

3. Obviousness

To ultimately prevail in its challenge to Patent Owner's claims, Petitioner must demonstrate by a preponderance of the evidence[7] that the

[7] The burden of showing something by a preponderance of the evidence requires the trier of fact to believe that the existence of a fact is more probable than its nonexistence before the trier of fact may find in favor of

claims are unpatentable. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d). A patent claim is unpatentable under 35 U.S.C. § 103 if the differences between the claimed subject matter 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 said subject matter pertains. *KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of 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. *Graham v. John Deere Co*., 383 U.S. 1, 17–18 (1966).

In determining obviousness when all elements of a claim are found in various pieces of prior art, "the factfinder must further consider the factual questions of whether a person of ordinary skill in the art would be motivated to combine those references, and whether in making that combination, a person of ordinary skill would have had a reasonable expectation of success." *Dome Patent L.P. v. Lee*, 799 F.3d 1372, 1380 (Fed. Cir. 2015); *see also WMS Gaming, Inc. v. Int'l Game Tech.*, 184 F.3d 1339, 1355 (Fed. Cir. 1999) ("When an obviousness determination relies on the combination of two or more references, there must be some suggestion or motivation to

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the party who carries the burden. *Concrete Pipe & Prods. of Cal., Inc. v. Constr. Laborers Pension Tr. for S. Cal.*, 508 U.S. 602, 622 (1993).

combine the references."). "Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure." *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988); *see also In re Magnum Oil Tools*, 829 F.3d at 1381 (finding a party that petitions the 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.").

An 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; *see In re Translogic Tech, Inc.*, 504 F.3d 1249, 1259 (Fed. Cir. 2007). In *KSR*, the Supreme Court also stated that an invention may be found obvious if trying a course of conduct would have been obvious to a person of ordinary skill in the art:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

550 U.S. at 421. "*KSR* affirmed the logical inverse of this statement by stating that § 103 bars patentability unless 'the improvement is more than

the predictable use of prior art elements according to their established functions.'" *In re Kubin*, 561 F.3d 1351, 1359–60 (Fed. Cir. 2009) (citing *KSR*, 550 U.S. at 417).

We analyze the asserted challenges to patentability in accordance with the above-stated principles.

D. Ground 1: Alleged Anticipation of claims 1 and 5 by NCT '653

1. Overview of the Prior Art

a. NCT '653

NCT00965653 ("NCT '653") is a clinical trial study, entitled "A Study of Subcutaneously Administered Tocilizumab in Patients with Rheumatoid Arthritis." Ex. 1004, 1. The summary states, "This open-label randomized [2 arm] study will investigate the pharmacokinetics, pharmacodynamics, efficacy and safety of subcutaneously administered tocilizumab in patients with rheumatoid arthritis who have shown an inadequate response to methotrexate." *Id.* at 6. The summary explains further that "[p]atients will be randomized to receive tocilizumab 162 mg sc [subcutaneously] either weekly or every other week, in combination with methotrexate, for 12 weeks." *Id.*

2. Petitioner's arguments

a. "An article of manufacture comprising a subcutaneous administration device"

Petitioner acknowledges that NCT '653 does not describe the specific device (e.g., a syringe or an autoinjector) used in the study; however, a

person of ordinary skill in the art would have understood that a "subcutaneous administration device" was necessary to administer the tocilizumab subcutaneously. Pet. 30–31 (citing Ex. 1034 ¶ 204). According to Petitioner, this implicit disclosure is sufficient for anticipation. *Id.* at 31 (citing *In re Baxter Travenol Labs.*, 952 F.2d 388, 390–91 (Fed. Cir. 1991)).

b. "which contains and delivers to a patient a 162 mg fixed dose of tocilizumab" (claim 1)

Petitioner argues that NCT '653 discloses that "[p]atients will be randomized to receive tocilizumab 162 mg sc[8] either weekly or every other week, in combination with methotrexate, for 12 weeks." Pet. 31 (citing Ex. 1004, 6). Petitioner asserts that the 162 mg dose is "fixed," i.e., it did not vary from patient to patient regardless of body weight or body surface area. *Id.* (citing Ex. 1004, 6). According to Petitioner, a person of ordinary skill in the art would have understood that the "subcutaneous administration device" used in the study contained and delivered a 162 mg fixed dose of tocilizumab to the patient. *Id.* (citing Ex. 1034 ¶ 205).

c. "which contains and delivers to a patient a 162 mg fixed dose of an anti-IL-6R antibody, wherein the anti-IL-6R antibody

[8] Subcutaneously.

> comprises the light chain and heavy chain amino acid sequences of SEQ ID NOs. 1 and 2, respectively" (claim 5)

Petitioner argues that tocilizumab, as employed in NCT '653, is an anti-IL-6R antibody comprising the light chain and heavy chain amino acid sequences of SEQ ID. Nos. 1 and 2, respectively. Pet. 32 (citing Ex. 1001, col. 5, ll. 29–30).

Petitioner also argues that NCT '653 is enabled and that efficacy is not a limitation in claims 1 and 5. Pet. 34–36.

3. Analysis

We are not persuaded by Petitioner's arguments that it has met its burden of showing, by a preponderance of the evidence, that NCT '653 anticipates claims 1 and 5 of the '677 patent.

"For a claim to be anticipated, each claim element must be disclosed, either expressly or inherently, in a single prior art reference, and the claimed arrangement or combination of those elements must also be disclosed, either expressly or inherently, in that same prior art reference." *Therasense, Inc. v. Becton, Dickinson and Co.*, 593 F.3d 1325, 1332–33 (Fed. Cir. 2010); *see also Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1082 (Fed. Cir. 2008) (holding that a claim is unpatentable under 35 U.S.C. § 102 only when "every element and limitation of the claim was previously described in a single prior art reference, either expressly or inherently, so as to place a person of ordinary skill in possession of the invention").

Petitioner acknowledges that NCT '653 does not describe the specific device (e.g., a syringe or an autoinjector) used in the study, nor can we discern one. *See* Pet. 30–31. NCT '653 states merely that "[p]atients will be randomized to receive tocilizumab 162 mg sc either weekly or every other week, in combination with methotrexate, for 12 weeks." Ex. 1004, 6. NCT '653 thus discloses the route of tocilizumab administration (subcutaneous), but does not identify any device that is used to deliver the drug subcutaneously.

Lacking an express disclosure of "a subcutaneous administration device, which contains and delivers to a patient a 162 mg fixed dose" of tocilizumab within the four corners of NCT '653, we next inquire whether NCT '653 inherently discloses the claimed device. A reference may anticipate inherently if a claim limitation that is not expressly disclosed "is necessarily present, or inherent, in the single anticipating reference." *Verizon Servs. Corp. v. Cox Fibernet Va., Inc.*, 602 F.3d 1325, 1337 (Fed. Cir. 2010); *see also Agilent Techs., Inc. v. Affymetrix, Inc.*, 567 F.3d 1366, 1383 (Fed. Cir. 2009) (holding that the "very essence of inherency is that one of ordinary skill in the art would recognize that a reference unavoidably teaches the property in question").

There can be little logical doubt that NCT '653 necessarily teaches "a subcutaneous administration device" for the simple reason that the reference teaches that randomized subjects receive "tocilizumab 162 mg [subcutaneously]" and a person of ordinary skill in the art would have understood that a suitable device is required to do this. But the claims also

require that the subcutaneous administration device also "contains and delivers to a patient a 162 mg fixed dose of tocilizumab." Petitioner contends that a person of ordinary skill in the art would have understood that the "subcutaneous administration device" used in the study contained and delivered a 162 mg fixed dose of tocilizumab to the patient. Pet. 31.

We are not persuaded, however, that an ordinarily skilled artisan would understand that NCT '653 necessarily discloses that the subcutaneous administration device was one capable of containing and delivering 162 mg of tocilizumab. Certainly, it would be logical for a person of ordinary skill in the art to assume that a device used to administer the dose was capable of delivering the whole dose in a single administered injection. But the reference does not rule out the possibility that another method could be used, e.g., two injections, each from a device capable of containing and delivering a dose only of 81 mg. Such an administration, though perhaps unlikely, is not categorically excluded by the disclosures of NCT '653. As such, we conclude that NCT '653 does not inherently disclose "a subcutaneous administration device, which contains and delivers to a patient a 162 mg fixed dose" of tocilizumab because it does not disclose that the subcutaneous administration device[s] *necessarily* "contains and delivers" the 162 mg fixed dose.

Because we find that NCT '653 neither expressly not inherently discloses all of the limitations of claims 1 and 5, we conclude that the reference does not anticipate independent claims 1 and 5. Consequently,

Petitioner has failed to meet its burden of showing, by a preponderance of the evidence, that claims 1 and 5 are unpatentable under 35 U.S.C. § 102.

E. Ground 2: Alleged Obviousness of claims 1 and 5 over NCT '653, Morichika, and Kivitz

1. Overview of the Prior Art

a. Morichika

Morichika describes antibody-containing formulations for subcutaneous administration. Ex. 1110, Abstr. Morichika explains that most known antibody formulations are used for intravenous injection, but that there is "growing demand" for antibody-containing formulations that can be self-injected subcutaneously. *Id.* ¶ 2. Morichika further explains that antibody-containing formulations for subcutaneous injection require increasing the concentration of the antibody in the injection solution because the antibody administered per dose is large, while the injection solution is generally limited for this dosage form. *See id.* ¶ 3.

Morichika discloses antibody-containing liquid formulations "especially suited for subcutaneous injection." *Id.* ¶ 53. The liquid formulations may contain 150–200 mg/mL antibody, 100–300 mM arginine and 10–50 mM methionine (stabilizers), 10–20 mM histidine (buffer), and 0.005–3% surfactants, such as polysorbates 20, 80 and poloxamer 188. *See id.* ¶¶ 15, 35, 40–41. In particular, Morichika describes a "highly concentrated antibody-containing preparation … that does not require reconstitution by lyophilization and does not require redissolution." *Id.* ¶ 10. The preparation "can be stably stored in solution for a long period of time

and can be manufactured without a lyophilization step in the manufacturing process, thus addition of a sugar or the like as a cryoprotectant agent is not necessary." *Id.*

Morichika exemplifies an antibody sample formulation containing an anti-IL-6R antibody referred to as "MRA."[9] *See* Ex. 1110 ¶¶ 29, 61. Morichika discloses examples A8 and A26, including 180 Mg/mL MRA (anti-IL6-R antibody), 100 mM arginine, 30 mM methionine, 0.5 Mg/mL polysorbate 80, and 20 mM histidine, with a pH of 6.0. *Id.* ¶¶ 64, 82. Morichika discloses stability data for examples A8 and A26, that "suggests that the combination of arginine and methionine has a synergistic effect" on inhibiting a dimer impurity. *See id.* ¶¶ 68–70, 83–84.

b. Kivitz

Kivitz discusses the Humira® adalimumab pen, which is described as "a novel, integrated, disposable autoinjection delivery system for the subcutaneous injection of adalimumab." Ex. 1050, 109 (Abstr.). Kivitz explains that "[s]elf-administered injectables offer several advantages over intravenous injections (i.e., portability, convenience and flexible scheduling)." *Id.* Kivitz further explains that "patients with chronic,

[9] Petitioner asserts that MRA refers to TCZ. Pet. 13 (stating Morichika "discloses a high-concentration formulation of tocilizumab (referred to as 'MRA' in the reference)"; *see also* Ex. 1034 ¶ 78; Ex. 1040, 2817 (referring to "tocilizumab (previously known as MRA)").

debilitating diseases may need a self-administered medication available in an easy-to-use and convenient delivery device that minimizes pain and facilitates adherence to therapy." *Id.* Kivitz states that, "[b]ased on the positive response from patients to the adalimumab pen, it is quite possible that biological therapies delivered by autoinjector pens may rapidly become the preferred treatment in RA and related diseases." *Id.* at 114.

2. Petitioner's Arguments

Petitioner argues that challenged claims 1 and 5 require only a subcutaneous administration device, without specifying what that device is. Pet. 36. Petitioner asserts that dependent claims 2–4 and 6–8 further limit claims 1 and 5 to embodiments that employ specific "subcutaneous administration devices," and that the narrowest claims (3 and 7) are limited to "a syringe, including a pre-filled syringe," and "an autoinjector," respectively. *Id.*

Petitioner again acknowledges that NCT '653 does not expressly describe the device to be used, but contends that a skilled artisan would have known that both pre-filled syringes and autoinjectors were conventional devices that were used in the art to deliver antibodies and other biologics subcutaneously to RA patients, and indeed were already in commercial use as of 2009. Pet. 37. By way of example, Petitioner points to Kivitz, which teaches the subcutaneous delivery of fixed doses of adalimumab (Humira®), etanercept (Enbrel®) and anakinra (Kineret®) via autoinjector and pre-filled

syringes to RA patients. *Id.* (citing Ex. 1050, 111; also citing Ex. 1034 ¶ 213).

Petitioner also argues that Morichika teaches how to formulate tocilizumab so that it, too, could be delivered to RA patients via an autoinjector or pre-filled syringe. Pet. 37. Petitioner contends that Morichika teaches a tocilizumab formulation that is "especially suitable" for subcutaneous administration, such as *via* injection. *Id.* (citing Ex. 1110 ¶ 53; Ex. 1034 ¶¶ 212, 214).

Petitioner argues that it would have been obvious to a person of ordinary skill in the art to use the tocilizumab formulation of Morichika in the pre-filled syringe or autoinjector of Kivitz to arrive at the claimed article of manufacture, i.e., a device comprising the 162 mg dose of tocilizumab of NCT '653 in a subcutaneous administration device such as a prefilled syringe or an autoinjector. Pet. 37 (citing Ex. 1034 ¶¶ 215, 227).

Petitioner argues that a skilled artisan would have been motivated to combine the teachings of the references to arrive at the claimed invention. Pet. 37–38. According to Petitioner, Kivitz explains that RA is a chronic disease in which long-term efficacy depends on patients adhering to their prescribed dosage regimen, which can endure for a lifetime. *Id.* at 38 (citing Ex. 1050, 110; Ex. 1048, 786–87). Petitioner contends that intravenous medications for RA usually require a patient to visit a clinic for each dose, so that a trained medical professional can administer the IV infusion, which can be burdensome, especially for elderly patients or those with debilitating disease, and may affect patient adherence. *Id.* (citing Ex. 1050, 110, 114).

Petitioner asserts that patients who fear the IV procedure or who have poor venous access may also have difficulty adhering to their prescribed dosage regimen. *Id.* (citing Ex. 1050, 110; Ex. 1049, 265; Ex. 1034 ¶¶ 62–65, 216).

In contrast, argues Petitioner, pre-filled syringes and autoinjectors for subcutaneous injections can be used by patients to self-administer at home, whenever convenient. Pet. 38 (citing Ex. 1050, 110). Petitioner points out that such devices are easy to use and minimize both the pain and duration of injection. *Id.* (citing Ex. 1050, 110). Petitioner notes that the cost of at-home, self-administration can also be lower than intravenous delivery, because no clinic or medical professional needs to be involved. *Id.* at 38–39 (citing Ex. 1050, 110). Petitioner notes that all of these advantages may increase patient adherence to their treatment regimen. *Id.* (citing Ex. 1050, 110, 114; Ex. 1034 ¶¶ 62–65, 115, 216).

Petitioner also contends that fixed subcutaneous dosing was known in the art to have therapeutic benefits over intravenous dosing, because the former avoids the calculations needed for body-mass dosing (e.g., calculating mg/kg), which must be done for each dose and can lead to dosing errors. Pet. 39 (citing Ex. 1034 ¶ 64). Petitioner states that subcutaneous doses are also generally smaller and administered more frequently than intravenous doses, that tend to avoid the large peaks and troughs in mean blood plasma concentration often seen with intravenous delivery. *Id.* (citing Ex. 1034 ¶ 64).

Given these considerations, Petitioner argues that the teaching of subcutaneous dosage regimen for RA by NCT ’653 would have motivated a

person of ordinary skill in the art to combine that protocol with the devices disclosed by Kivitz. Pet. 39–40 (citing Ex. 1034 ¶¶ 216–221). Petitioner also argues that Morichika's teaching of a stable formulation of tocilizumab suitable for use in an autoinjector or pre-filled syringe would have increased interest in NCT '653 and encouraged the use of one of those devices to deliver the fixed dose to RA patients. *Id.* at 41. The availability of a ready-made recipe for the formulation, Petitioner argues, would have saved an ordinarily skilled artisan time and expense in experimentation. *Id.* (citing Ex. 1034 ¶ 221).

Petitioner additionally points to other prior art that would have motivated the person of ordinary skill in the art to combine the references. Pet. 39. Petitioner points to clinical trials that had demonstrated that 4 mg/kg and 8 mg/kg of intravenous tocilizumab were effective at treating RA. *Id.* at 40 (citing Ex. 1034 ¶¶ 216–221). Petitioner notes that, in February 2009, Patent Owner announced that a subcutaneous version of subcutaneous tocilizumab (Actemra®) was in Phase II development and, in June 2009, announced that Actemra had "[c]ontinued strong efficacy data" and had "[d]emonstrated long-term safety with increasing efficacy over time." *Id.* (citing Ex. 1034 ¶ 69; Ex. 1071, 4; Ex. 1072, slide 12) (alterations in original).

Finally, argues Petitioner, a person of ordinary skill in the art would have had a reasonable expectation of success in presenting 162 mg of tocilizumab in an autoinjector or pre-filled syringe. Pet. 41 (citing Ex. 1034 ¶¶ 222–226). According to Petitioner, an ordinarily skilled artisan would

have been able to follow Morichika's teachings to create a concentrated formulation of tocilizumab that could be contained in an autoinjector or pre-filled syringe. *Id.* (citing Ex. 1034 ¶¶ 222–226). Petitioner notes that Morichika later entered national stage in the U.S. and issued as a U.S. patent prior to the filing date of the '677 patent, with claims to a "stable" formulation of tocilizumab "suitable for subcutaneous administration." *Id.* (citing Ex. 1034 ¶ 68; Ex. 1112; Ex. 1115, 96).

Petitioner contends that challenged claims 1–8 do not require that the "article of manufacture" be efficacious for a particular disease, including RA. Pet. 42. Petitioner points out that no disease is recited in the claims, and importing a specific disease as a limitation into the claims would be improper. *Id.* (citing *Acceleration Bay, LLC v. Activision Blizzard Inc.*, 908 F.3d 765, 771 (Fed. Cir. 2018)). Petitioner asserts that this is particularly so given that the '677 Specification mentions over 100 different diseases as "examples of IL-6-mediated disorders to be treated herein." *Id.* (citing Ex. 1001, col. 13, ll. 27–60). Therefore, argues Petitioner, no reasonable expectation of efficacy is required in order for the claims to be obvious. *Id.*

Even so, argues Petitioner, a person of ordinary skill in the art would have had a reasonable expectation from the prior art that a 162 mg fixed dose of tocilizumab, when delivered subcutaneously *via* a pre-filled syringe or autoinjector to an RA patient, and delivered at a sufficient frequency, would have efficacy against RA, in at least some patients. Pet. 43 (citing Ex. 1034 ¶ 224).

Petitioner points to the Declaration of its expert, Dr. Boers, who testifies that tocilizumab dosed 8 mg/kg intravenously had been approved in Japan and Europe for treating RA, and that there was an abundance of clinical trial results showing that both 4 mg/kg and 8 mg/kg IV doses were efficacious in RA patents. Pet. 43 (citing Ex. 1034 ¶¶ 55–56, 61, 224). Specifically, states Dr. Boers, the SAMURAI, LITHE, and RADIATE studies showed that 4 mg/kg and 8 mg/kg of IV tocilizumab were effective at treating RA, and tocilizumab (Actemra®) had been approved in Europe and Japan as a safe and effective treatment for RA. *Id.* (citing Ex. 1034 ¶ 224). Petitioner asserts that a skilled artisan would have understood that 162 mg of tocilizumab can be delivered subcutaneously at some total dose and frequency to approximate these effective IV doses. *Id.* (citing Ex. 1034 ¶ 224).

Petitioner further points out that Morichika also discloses that its high-concentration formulation of tocilizumab would be effective intravenously or subcutaneously, and that Patent Owner represented that subcutaneous administration was "preferred" for tocilizumab. Pet. 43–44 (citing Ex. 1034 ¶¶ 78, 219, 221, 225; Ex. 1110 ¶ 53; Ex. 1071, 4; Ex. 1072, slide 12, Ex. 1030, 4).

Petitioner also points to the Declaration of Dr. Shah, who testifies that a person of ordinary skill in the art would have been able to employ routine pharmacokinetic modeling to predict whether the 162 mg fixed dose in NCT '653 would have at least some efficacy against RA. Pet. 44 (citing Ex. 1032 ¶¶ 82, 119, 123). Dr. Shah opined that an ordinarily skilled artisan

would have understood from the prior art that maintaining a mean blood plasma level of tocilizumab at or above 1 μg/ml would be effective against RA. *Id.* (citing Ex. 1032 ¶¶ 104–109; 114; Ex. 1034 ¶ 59).

By way of example, Petitioner points to Nishimoto[10], which reported that 1 μg/mL was the minimum effective concentration ("MEC") at which tocilizumab would effectively block the activity of IL-6. Pet. 44 (citing Ex. 1008, 3961–63). Petitioner also notes that the Japanese Ministry of Health's Report on Deliberation Results for Actemra®[11]stated that 1 μg/mL was "the minimum effective blood concentration of MRA [tocilizumab]." *Id.* (citing Ex. 1024, 22–23).

Petitioner contends that a person of ordinary skill in the art, having comprehended this information, could have generated a routine pharmacokinetic model to assess whether 162 mg of tocilizumab would produce mean blood plasma levels at or above the MEC. Pet. 44 (citing Ex. 1034 ¶¶ 70–72, 179, 226; Ex. 1032 ¶¶ 115–123). Petitioner asserts that,

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[10] N. Nishimoto et al., *Mechanisms and Pathologic Significance in Serum Interleukin-6 (IL-6) and Soluble IL-6 Receptor after Administration of an Anti-IL-6 Receptor Antibody, Tocilizumab, in Patients with Rheumatoid Arthritis and Castleman Disease*, 112(10) BLOOD 3959–64 (2008) ("Nishimoto") Ex. 1008.

[11] Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare [Japan], *Report on the Deliberation Results* (March 6, 2008) (the "Deliberations Results Report") Ex. 1024.

by 2009, such models had become an essential and routine part of drug product development, and they were in wide use for precisely this type of analysis. *Id.* at 44–45 (citing Ex. 1034 ¶¶ 70–72). According to Petitioner, a person of ordinary skill in the art would have chosen a two-compartment pharmacokinetic ("PK") model for tocilizumab, guided in part by the two-compartment model taught by Ng[12] for efalizumab, an IgG1-kappa subtype antibody structurally similar to tocilizumab, and by the two-compartment model for tocilizumab that Patent Owner included in the FDA Review and EMA Report, submitted in support of the regulatory approval of tocilizumab (Actemra®). *Id.* at 45 (citing Ex. 1034 ¶¶ 104, 179; Ex. 1032 ¶¶ 80–82, 85; Ex. 1007, 1091–92, Fig 1A; Ex. 1010, 110–24; Ex. 1006, 41).

Petitioner asserts that the pharmacokinetic parameters needed to produce a reasonably predictive two-compartment model for tocilizumab were available in, or could have been estimated from, the FDA Review, the EMA Report, and/or Chernajovsky[13]. Pet. 45 (citing Ex. 1032 ¶¶ 84–85, 87–89, 90–91, 100–103; Ex. 1009, 154–55, Fig. 3; Ex. 1006, 41–42, Ex. 1010).

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[12] C.M. Ng et al., *Pharmacokinetic-Pharmacodynamic-Efficacy Analysis of Efalizumab in Patients with Moderate to Severe Psoriasis*, 22(7) PHARMACEUT. RES., 1088–1100 (2005) ("Ng") Ex. 1007.

[13] N. Nishimoto et al., *Humanized Antihuman IL-6 Receptor Antibody, Tocilizumab*, in THERAPEUTIC ANTIBODIES (Y. Chernajovsky et al., eds.) 151–60 (2008) ("Chernajovsky") Ex. 1009.

Petitioner acknowledges that two parameters for tocilizumab are not disclosed in the prior art (bioavailability (F) and rate of absorption (K_a)), but have been reported for structurally-similar antibodies. *Id.* (citing Ex. 1032 ¶¶ 92–98).

Petitioner points to Dr. Shah's Declaration, in which he testifies that a routine two-compartment model, when programmed with the prior-art pharmacokinetic parameters for tocilizumab found in the FDA Review, predicts that a 162 mg subcutaneous dose of tocilizumab, when administered weekly, will produce and maintain a mean blood plasma concentration well above the 1 μg/ml MEC for tocilizumab at steady state. Pet. 46 (citing Ex. 1032 ¶ 117, Fig, 14). Petitioner contends that essentially the same result is obtained when using the pharmacokinetic parameters obtained from EMA Report and Chernajovsky, and that a person of ordinary skill in the art would therefore have had a reasonable expectation that an autoinjector filled with a 162 mg dose of tocilizumab, when used by an RA patient once a week, would have at least some efficacy. *Id.* at 46–47 (citing Ex. 1032 ¶ 115, 119 Fig. 12; Ex. 1034 ¶ 226).

Petitioner also points to Patent Owner's sponsoring of NCT '653, its public statements about subcutaneous tocilizumab being "in development," that subcutaneous tocilizumab was the "preferred form," and that Patent Owner had performed pharmacokinetic/pharmacodynamic ("PK/PD") modeling and other analyses, as evidence that a skilled artisan would understand that a 162 mg dose in NCT '653 administered, e.g., once weekly,

would demonstrate at least some efficacy in at least some patients. Pet. 47 (citing Ex. 1034 ¶¶ 225–226).

3. Patent Owner's Response

Patent Owner argues that neither Kivitz nor Morichika cure the alleged deficiencies of NCT '653, because neither reference teaches how to make a subcutaneous device containing a formulation of a drug at the high antibody dose and concentration required by the claims. PO Resp. 21–22 (citing Ex. 2009 ¶¶ 98–102, 115–117). Patent Owner argues that a person of ordinary skill in the art would have had no motivation to combine the teachings of the references or a reasonable expectation of success in doing so.[14] *Id.* at 22.

Dr. Little, one of Patent Owner's declarants, opines that, as of the priority date of the '677 patent, the upper concentration limit for subcutaneously administered antibody formulations was "thought to be about 100 mg/mL." PO Resp. 14 (citing Ex. 2005 ¶ 41 (citing Ex. 1030 ¶ 3)). Patent Owner asserts that the prior art recognized that "[t]he most outstanding limitation" on subcutaneous administration "may be that large doses of antibody may not be feasibly injected IM or SC due to the relatively limited solubility of IgG (~ 100 mg/mL)." *Id.* (quoting Ex. 2020, 5).

[14] Patent Owner also argues that Kivitz teaches away from the proposed combination. PO Resp. 22. At oral argument, however, Patent Owner essentially conceded this argument. *See* Hearing Trans. 41.

According to Patent Owner, the necessity of low injection volumes constrained subcutaneous administration of biologic medicines in particular, because subcutaneous injection volumes had to be preferably 1 mL or less to prevent additional tissue damage or inflammation from the injection itself. *Id.* (citing Ex. 2005 ¶ 15; also citing Ex. 2015, 2; Ex. 2032, 2). Consistent with this, argues Patent Owner, neither of the monoclonal antibodies approved for subcutaneous administration to RA patients at the time utilized an injection volume greater than 1 milliliter. *Id.* (citing Ex. 2005 ¶¶ 21–25).

Patent Owner argues that, given the "small volume" limits on subcutaneous administration, "treatments with high doses," such as "100 mg" or more, would "require development of formulations at concentrations exceeding 100 mg/mL," which would have been a "challenging" feat as of the priority date. PO Resp. 15 (citing Ex. 2015, 2; Ex. 2005 ¶¶ 35–41). Patent Owner points to Haller[15] as teaching that rheumatologists would circumvent this problem by administering multiple shots. *Id.* (citing Ex. 2032, 2; also citing Ex. 2020, 5).

Patent Owner contends that a person of ordinary skill in the art, armed with this understanding, would not have envisioned the subjects in NCT '653 receiving the entire 162 mg fixed dose from a single administration device. PO Resp. 15 (citing Ex. 2005 ¶ 42). Patent Owner

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[15] M.F. Haller, *Converting Intravenous Dosing to Subcutaneous Dosing with Recombinant Human Hyaluronidase*, 31(10) PHARM. TECH. 1–5 (2007) ("Haller") Ex. 2032.

notes that, among the therapeutic monoclonal antibodies approved for RA, the highest dose administered in a single injection was 50 mg (at a concentration of 100 mg/mL), which is well below the 162 mg fixed dose the claims require. *Id.* Petitioner points to the testimony of Drs. Silverman and Little that an ordinarily skilled artisan, reading NCT '653, would have understood that the patients in that trial could, and probably did, receive 162 mg of tocilizumab through multiple administration devices, each containing lower doses and concentrations. *Id.* at 15–16 (citing Ex. 2005 ¶¶ 42–47; Ex. 2009 ¶¶ 111–114).

Patent Owner also argues that the Petitioner has failed to demonstrate that NCT '653 was publicly accessible on or before the priority date. PO Resp. 16. Patent Owner asserts that the Declaration of Mr. Lassman (the "Lassman Declaration"), upon which Petitioner relies to prove public accessibility of NCT '653, is deficient in several respects. *Id.*

Specifically, Patent Owner contends that: (1) Mr. Lassman is unqualified; (2) the Lassman Declaration never identifies the specific search parameters a person of skill in the art would have used to locate NCT '653 on the ClinicalTrials.gov website; and (3) other clinical trial registries existed in addition to ClinicalTrials.gov. PO Resp. 17–20.

With respect to (1), Patent Owner notes that Mr. Lassman is a regulatory lawyer who has never been employed by NIH, the National Library of Medicine, FDA, nor any other entity responsible for managing the ClinicalTrials.gov database. PO Resp. 17. Patent Owner asserts that Mr. Lassman possesses none of the skills relevant to those of ordinary skill in the

art and, in forming his opinion, did not consult anyone possessing those skills to discern how an ordinarily skilled artisan would have searched for NCT '653. *Id.* at 17–18 (citing Ex. 2012, 41–42, 44–45, 66).

With respect to (2), Patent Owner argues that Mr. Lassman attests that he was able to "locate[] the record for clinical study number NCT00965653," but never explains how he did so or how many results he had to review to find this particular study. PO Resp. 18–19 (citing Ex. 1035 ¶ 29) (alteration in original). Patent Owner asserts that, rather than locate NCT '653 through the type of search a person of ordinary skill in the art might have conducted, e.g., by searching for keywords such as "tocilizumab" or "rheumatoid arthritis," Mr. Lassman located the study by searching for its number, *viz.*, NCT00965653. *Id.* at 19 (citing Ex. 2012, 63, 66).

Patent Owner adds that the existence of a search function on ClinicalTrials.gov does not cure this alleged deficiency. PO Resp. 19. According to Patent Owner, keyword searches on sites such as ClinicalTrials.gov were "not always reliable because of *lack of standardisation of drug names* and health conditions," which directly "contributed to the difficulty of using [those] websites." *Id.* (quoting Ex. 2035, 3). Patent Owner states that searching for synonyms in ClinicalTrials.gov sometimes returned inconsistent results or none at all. *Id.* (citing Ex. 2009 ¶ 62, Ex. 2010, 136).

Addressing (3), Patent Owner notes that Mr. Lassman testified that as of 2009, "a lot of companies had their own registries" hosted on independent

websites or "source[s] other than ClinicalTrials.gov," and that other jurisdictions, such as Europe, also had their own registries. PO Resp. 20 (citing Ex. 2012, 27, 29–30). Patent Owner argues that it is therefore uncertain that a skilled artisan, searching for clinical trials, would have necessarily looked to ClinicalTrials.gov as opposed to one of the many other registries available at the time. *Id.* at 21.

With respect to Kivitz, Patent Owner contends that the subcutaneous administration devices taught by the reference administered only 40 mg of adalimumab in a volume of 0.8 ml or 50 mg of etanercept in a volume of 1 ml. PO Resp. 22. Patent Owner points out that the challenged claims require a tocilizumab dose and concentration of more than three times greater than that disclosed by Kivitz. Patent Owner asserts that the lesson of Kivitz and NCT '653 to those of ordinary skill in the art would be to divide the 162 mg fixed dose of tocilizumab among at least two subcutaneous administration devices, and not the single device claimed. *Id.*

Patent Owner next points to the testimony of its expert, Dr. Silverman, who testifies that subcutaneous dosing regimens were riskier than intravenous ("IV") dosing regimens because of both (i) the high concentrations required, and (ii) injecting a biological drug beneath the skin, increased the likelihood of an immunogenic reaction, tissue damage, and formation of neutralizing anti-drug antibodies. PO Resp. 22–23 (citing Ex. 2009 ¶¶ 24–25, 84–88 (citing Ex. 2030, 3, 6); Ex. 2020, 9).

Patent Owner contends that, as of the priority date, "immunogenicity

[was] not well understood, and the immunogenicity of a therapeutic protein [could] not be reliably predicted." PO Resp. 23 (quoting Ex. 2020, 9) (alteration in original). Petitioner asserts that the prior art taught that tocilizumab could induce "anti-tocilizumab antibodies" in patients causing "hypersensitivity reactions leading to withdrawal" from a clinical trial. *Id.* (quoting Ex. 1069, 9).

Patent Owner argues that, given the risk of an immunogenic response, the art taught that proteins like tocilizumab should be administered "(i) by … iv. [intravenous] injection rather than sc. [subcutaneous], (ii) as infrequently as possible, and (iii) in amounts just sufficient to maintain effective levels." PO Resp. 24 (citing Ex. 2009 ¶ 87 (quoting Ex. 2030, 6)) (alterations in original). Patent Owner notes, however, that NCT '653 proposes the opposite, i.e., administering tocilizumab subcutaneously, more frequently (weekly or every other week instead of monthly), and at the same high concentration for all patients. *Id.*

Turning to Morichika, Patent Owner argues that, although the reference sets out exemplary high-concentration tocilizumab formulations, it discloses no information about what kind of device should be used to administer 162 mg of tocilizumab in a single injection, or whether administration would be well tolerated and comfortable for the patient. PO Resp. 24. Patent Owner notes that Petitioner's formulation expert, Dr. Dalby, acknowledged in his deposition that different administration devices can lead to different aggregation levels and different PK profiles. *Id.* (citing Ex. 2011, 84–85).

Patent Owner argues that Morichika is also ambiguous on the topic of viscosity, which is a concern for reasons of both patient comfort and ease of administration. PO Resp. 25 (citing Ex. 2005 ¶ 19). Patent Owner additionally contends that increased viscosity also may cause the drug to "pool" at the injection site, leading to adverse reactions, reduced bioavailability, and increased immunogenicity. *Id.* (citing Ex. 2005 ¶ 19; Ex. 2071, 1–2). According to Patent Owner, the claimed 162 mg dose was formulated with viscosity in mind; the Specification of the '677 patent notes that "due to the higher concentration of tocilizumab" required by subcutaneous administration (180 mg/ml) compared to IV administration (20 mg/ml), "the SC formulation was developed with regard to the effect of protein concentration on the injection force and [] viscosity [for] a standard syringe." *Id.* (quoting Ex. 1001, col. 40, ll. 9–12) (alteration in original). Patent Owner asserts that Morichika mentions viscosity, but does so only in passing, stating that the viscosity of the solutions it lists are "[p]referably" "about 2~15 mPa-s, more preferably about 4~10 mPa-s." *Id.* (quoting Ex. 1110 ¶ 55) (alteration in original). However, Patent Owner contends, Morichika does not teach how to achieve these viscosities, and does not explain what effect different viscosities in the broad ranges it discloses would have on ease of administration of patient comfort. *Id.* at 25–26.

Patent Owner next argues a person of ordinary skill in the art would not have had a realistic expectation of success that the recited 162 mg fixed dose would successfully treat an IL-6 mediated disease like RA. PO Resp. 26. Patent Owner argues that its own declarant, Dr. Samara, testified

that he has never seen subcutaneous dosing regimen selected using the sort of composite data Petitioner's declarant Dr. Shah, suggests. *Id.* (citing Ex. 2006 ¶¶ 43–59). And Patent Owner points out that Dr. Boers, Petitioner's rheumatology expert, agreed in his deposition that Dr. Shah's averaging approach was not standard, and that he was unable to identify any antibody dosing regimen developed based on that sort of analysis. *Id.* at 27–28 (citing Ex. 2010, 110–111). Patent Owner asserts that the modeling work it announced conducting involved proprietary PK data specific to tocilizumab, and did not rely on the sort of composite information that Dr. Shah uses. *Id.* at 28 (citing Ex. 2006 ¶¶ 46–48).

Dr. Samara further testifies that utilizing an averaging approach, as Dr. Shah does, would be especially unsuitable for tocilizumab, because the non-linear PK profile it produces would mean that the correlation between dose and response is unpredictable. PO Resp. 28. Dr. Samara also opines that Dr. Shah adds to this uncertainty by using averaging to derive PK properties that are themselves unpredictable. *Id.* (citing Ex. 2006 ¶ 50).

Patent Owner contends that, to a person of ordinary skill in the art, subcutaneous dosing regimens for antibodies like tocilizumab are the product of extensive empirical testing by a team of scientists aiming to balance safety, efficacy, patient convenience, and other factors. PO Resp. 29 (citing Ex. 2006 ¶ 34). Patent Owner contends that even when empirical testing produces reliable data on an antibody's PK and PD profile, success in designing a subcutaneous dosing regimen is hardly guaranteed, as demonstrated by the examples of rituximab and trastuzumab illustrate the

point. *Id.* at 31 (citing Ex. 2006 ¶ 49). Patent Owner argues that, collectively, the IV to SC bridging studies from these drugs demonstrate the unpredictability and extensive experimentation necessary for developing a successful subcutaneous dosing regimen. *Id.* (citing Ex. 2006 ¶¶ 49, 52). Patent Owner notes that Dr. Samara opines that a skilled artisan would have been well aware of the potential for such complications in November 2010. *Id.* (citing Ex. 2006 ¶¶ 49, 53).

4. Petitioner's Reply and Patent Owner's Sur-Reply

Petitioner replies, with respect to NCT '653's public availability, that based upon his testimony, it is indisputable that Mr. Lassman has personal knowledge of how the ClinicalTrials.gov website function in 2010. Pet. Reply 11. Petitioner also argues that Mr. Lassman described in detail how ClinicalTrials.gov facilitated public access to clinical trial records and proffered a wealth of evidence establishing that NCT '653 was published on ClinicalTrials.gov more than one year prior to the earliest possible filing date of the '264 patent. *Id.* at 12 (citing Ex. 1035; Ex. 1137 ¶¶ 3–12).

Petitioner asserts that Patent Owner's argument that searching on ClinicalTrials.gov could be unreliable "because of a lack of standardization of drug names" is irrelevant, because the name Actemra® had already been approved, and its non-proprietary name of "tocilizumab" had already been standardized internationally by the applicable regulatory authorities. Pet. Reply 13 (citing Ex. 1010, 2; Ex. 1024, 1; Ex. 1006, 24). Petitioner notes that its expert, Dr. Boers, testified that a person of ordinary skill in the art

would have "adjust[ed] the keywords" and "play[ed] around with the specifics of the search machine to get what you want" but "after a while" would "come up with satisfactory conclusions." *Id.* (citing Ex. 2010, 136).

Petitioner also contends that Patent Owner's argument that a skilled artisan may have used registries other than ClinicalTrials.gov to search for clinical trials using subcutaneous tocilizumab is irrelevant to the analysis. Pet. Reply 14. According to Petitioner, the Lassman Declaration establishes that ClinicalTrial.gov was established for the express purpose of facilitating public access to clinical trial records. *Id.* (citing Ex. 1035 ¶ 14; Ex. 1137, ¶ 4).

Turning to the combination of NCT '653, Kivitz, and Morichika, Petitioner argues that Patent Owner's argument ignores the fact that the claims do not require any specific concentration of antibody, or a specific formulation, and that the Specification of the '677 patent discloses a variety of formulations, suggesting that it would require only routine skill to arrive at a usable formulation. Pet. Reply 18 (citing Ex. 1140 ¶¶ 7–9; Ex. 1001, cols. 22–25, ll. 5–17; Ex. 1135, 14–15; Ex. 1134, 15–17).

Petitioner reiterates that Kivitz is relied upon to show the reasons, backed by a clinical study, why many RA patients favored subcutaneous auto-injectors like the Humira Pen and Sure-Click device over any other device for delivering weekly and biweekly antibody (and other biologic) treatments for RA. Pet. Reply 19. Petitioner argues that the detailed explanations of the advantages of auto-injectors to RA patients would have motivated a person of ordinary skill in the art to use an auto-injector as the

"subcutaneous administration device" in the protocol of NCT '653, which involved the treatment of RA patients. *Id.*

With respect to Morichika, Petitioner argues that, contrary to Patent Owner's arguments, there is no "single injection" limitation in the claims, nor are the devices limited to those that are "well tolerated" or "comfortable" for the patient. Pet. Reply 19. Petitioner asserts that Morichika discloses a 180 mg/ml formulation of tocilizumab, which equates to 0.9 ml, that Patent Owner acknowledges can readily be administered *via* an auto-injector in a single injection. *Id.* at 20 (citing PO Resp. 7; *see* Ex. 1110 ¶ 53). Petitioner notes that Kivitz teaches that patients rated the auto-injector highly because it caused less pain, had a lower injection time, was safer and easier and more convenient, i.e., better tolerated and more comfortable to use than subcutaneous syringe devices. *Id.* (citing Ex. 1050, 112–114, Fig. 3).

Petitioner also argues that Patent Owner's arguments that a person of ordinary skill in the art would not be motivated to use the Morichika high-concentration formulation in an auto-injector out of concern that instability (e.g., aggregation) and high viscosity would create dangerous immunogenicity when the formulation is administered subcutaneously relies on prior-art teachings that have nothing to do with tocilizumab. Pet. Reply 20. Petitioner points out the only prior-art reference of record that discusses the stability and viscosity of high-concentration formulations of tocilizumab is Morichika, which teaches that the formulation is both highly

stable and has a viscosity that is ideally suited to subcutaneous administration. *Id.* (citing Ex. 1140 ¶¶ 15–30).

Petitioner also points out that Patent Owner's argument a skilled artisan would not have had a "reasonable expectation" that the Morichika formulation would be stable, i.e., not aggregate, when stored in a subcutaneous administration device contradicts its earlier representations to the USPTO. Pet. Reply 21. Petitioner states that Morichika is Patent Owner's own patent publication, and Patent Owner is effectively contending that its own Specification would not have enabled a person of ordinary skill in the art to make a stable, high-concentration formulation of tocilizumab that would not aggregate, despite the fact that Patent Owner sought, and obtained, claims in the U.S. to a "stable liquid formulation" of tocilizumab (a.k.a. MRA) "suitable for subcutaneous administration comprising 180 mg/ml" antibody using the same specification as Morichika. *Id.* (citing Ex. 1112, 16). Petitioner contends that Patent Owner is also effectively asserting that a skilled artisan would not believe the test data presented by its own inventors in Morichika showing that the formulation was stable and did not aggregate (dimerize) under typical accelerated storage test conditions, despite Morichika's statement that the disclosed formulations were "especially suited for subcutaneous administration" to "humans." *Id.* (citing Ex. 1115, 322–24; Ex. 1110 ¶ 53).

Petitioner asserts that Patent Owner similarly argues that a person of ordinary skill in the art would have been concerned that the Morichika formulation would be too viscous. Pet. Reply 22 (citing PO Resp. 25–26).

Again, Petitioner argues that Patent Owner's own inventors stated in Morichika that the "preferable" viscosity of the disclosed formulations was "about 2-15 mPa-s" and the "more preferabl[e]" viscosity was "about 4–10 mPa-s." *Id.* (citing Ex. 1110 ¶ 55). Petitioner asserts that a person of skill in the art would have had no reason to doubt that the disclosed formulations and examples achieve, or could be adapted with routine optimization to achieve, these viscosities. *Id.* (citing Ex. 1140 ¶¶ 26–27).

Finally, argues Petitioner, Patent Owner ignores its own public statements that a subcutaneous version of Actemra® was "in development," and that in its view the "preferred" form of Actemra® was "thought to be subcutaneous formulation." Pet. Reply 23 (citing Pet. 40). Petitioner also points to the other two clinical trial protocols for subcutaneous tocilizumab that it published prior to the priority date, both of which administer 162 mg of tocilizumab weekly or biweekly in 0.9 ml "pre-filled syringes." *Id.* (citing Ex. 1131; Ex. 1132; Ex. 1139 ¶ 52). Petitioner maintains that these statements and publications by Patent Owner would have supported the expectation of a skilled artisan that an auto-injector (and other subcutaneous administration devices) containing 162 mg of tocilizumab formulated for subcutaneous injection could successfully be made. *Id.*

Patent Owner responds that Morichika does not test the safety or efficacy of its formulations in humans, animals, or even cells. PO Sur-Reply 8. Patent Owner further contends that NCT '653 does not disclose any data with the 162 mg SC dose. *Id.* Patent Owner argues that Petitioner's position that a skilled artisan would have prepared an untested,

highly concentrated subcutaneous formulation, for an untested dosage and administration route, and combined it with an administration device that contains and delivers that formulation to patients is illogical. *Id.*

Patent Owner also argues that Petitioner's formulation expert, Dr. Dalby, never addresses the potential pharmacokinetic issues (such as bioavailability and absorption) that concededly arise from even small changes in a formulation. PO Sur-Reply 11. He acknowledges that Morichika does not discuss the bioavailability or absorption of the formulations disclosed, and that his only basis for concluding a person of ordinary skill in the art would dismiss all of the known concerns about subcutaneous formulations is Morichika's statement that its formulations can be "prepared for administration to animals such as humans," *Id.* at 11–12 (citing Ex. 2081, 105–107:2; Ex. 1140 ¶ 17 (citing Ex. 1110 ¶ 13)).

5. Analysis

We conclude that Petitioner has demonstrated, by a preponderance of the evidence, that claims 1–8 of the '677 patent would have been obvious over the combination of NCT '653, Kivitz, and Morichika.

As an initial matter, we find that NCT '653 was publicly accessible as of the priority date of the '677 patent. Whether a reference qualifies as a "printed publication" is a legal conclusion based on underlying factual findings. *Nobel Biocare Servs. AG v. Instradent USA, Inc.*, 903 F.3d 1365, 1375 (Fed. Cir. 2018) (citing *Jazz Pharm., Inc. v. Amneal Pharm., LLC*, 895 F.3d 1347, 1356 (Fed. Cir. 2018)). The underlying factual findings include

whether the reference was publicly accessible. *Nobel*, 903 F.3d at 1375 (citing *In re NTP, Inc.*, 654 F.3d 1279, 1296 (Fed. Cir. 2011)).

We find that Mr. Lassman credibly testifies that he is extensively familiar with the ClinicalTrials.gov website and, additionally, worked on drafting the statute that expanded and governed Clinicaltrials.gov. Ex. 1137 (citing Ex. 1035 ¶¶ 6, 9). Mr. Lassman testifies that "Clinicaltrials.gov is a site designed to be used by members of the public, not by experts. The site is designed to require less skill in searching clinical trial records than a POSA would have had." *Id.* ¶ 4 (emphasis omitted). More to the point:

> On February 29, 2000, Clinicaltrials.gov was launched by NIH in fulfillment of the above-described statutory requirement for a clinical trials registry. When it was launched, the site was described by NIH as "a consumer-friendly database … with information on more than 4,000 federal and private medical studies involving patients and others at more than 47,000 locations nationwide." NIH confirmed that the site was intended to "provide[] patients, families and members of the public easy access to information about the location of clinical trials, their design and purpose, criteria for participation, and, in many cases, further information about the disease and treatment under study."

Ex. 1035 ¶ 14 (quoting Ex. 1063, internal citation omitted) (alteration in original).

We do not agree with Patent Owner's argument that Mr. Lassman is not qualified to opine with respect to this subject matter, given Mr. Lassman's intimate knowledge of, and experience with, the ClinicalTrials.gov website. See Ex. 1035 ¶ 6. Moreover, the NIH press release quoted in the passage above, expressly states that the website

provides easy access to information concerning clinical trials to "patients, families and members of the public." *See* Ex. 1063. We thus credit Mr. Lassman's testimony that NCT '653 was publicly accessible on the ClinicalTrials.gov website as of the priority date of the '677 patent.

Turning to the merits, we find that independent claims 1 and 5, as well as dependent claims 2–4 and 6–8 are not limited by any requirement for a showing of the efficacy or safety of administering tocilizumab. The claims are expressly directed to an article of manufacture, specifically a subcutaneous administration device, and *not* a method of treatment or even administration of the drug. As we explained in our claim construction (*see* Section II.B.3 *supra*) the functional portion of the language of the claims requires only that the claimed device be "capable of containing and delivering the 162 mg fixed dose subcutaneously" without further limitation. Whether or not the dose delivered is efficacious in the treatment of RA is immaterial to this apparatus claim. Consequently, we need not reach the parties' arguments with respect to whether the claims require a certain level of efficacy.

As we explained in Section II.D.3 above, NCT '653 teaches subcutaneous administration of a 162 mg fixed dose of tocilizumab, but does not expressly identify any device that is used to deliver the drug subcutaneously. *See* Ex. 1004, 6. Kivitz teaches the use of an autoinjection pen delivery system for the subcutaneous injection of adalimumab, a fully human monoclonal antibody for the treatment of rheumatoid arthritis that is similar to tocilizumab. Ex. 1050, Abstr. Kivitz teaches that:

> The long-term efficacy of any therapy, particularly a biological therapy, is significantly influenced by the degree of adherence to the therapeutic regimen. However, adherence rates tend to be low in chronic diseases, such as RA, and the route of administration can affect adherence to therapy. Therefore, patients with RA and similar diseases need an easy-to-use and convenient delivery device that minimizes pain and facilitates adherence, ultimately helping to maximize therapeutic outcomes.

Ex. 1050, 110 (internal references omitted). Kivitz teaches that its HUMIRA® autoinjection pen is an FDA-approved device and contains a fixed dose of adalimumab 40 mg in a 0.8 ml solution, a volume suitable for subcutaneous injection. *Id.* at 110, 111–112. Kivitz teaches that "the adalimumab Pen appears to be a suitable option for the delivery of safe and effective long-term treatment for RA, psoriatic arthritis and ankylosing spondylitis" and concludes that:

> The adalimumab autoinjection Pen represents the newest advance in delivery systems available for the administration of biological therapy. Despite the few limitations of the data provided in the TOUCH study, the fact that such a large majority of patients favored the Pen provides more than enough evidence to support its use as an important delivery option for adalimumab therapy. Moreover, patients can choose a delivery device that suits their personal needs and preferences, owing to the continued availability of both the prefilled syringe and the Pen. This opportunity for individualized treatment may encourage adherence to therapy, which is likely to have a positive impact on long-term clinical outcomes.

Id. at 114.

Kivitz thus teaches a popular subcutaneous delivery device for self-injection that is capable of containing and delivering a fixed dose of 40 mg

of adalimumab subcutaneously. Independent claims 1 and 5 of the '677 patent require a considerably larger fixed dose of tocilizumab, *viz.*, 162 mg. A person of ordinary skill in the art, seeking to combine the teachings of NCT '563 and Kivitz, would have modified the subcutaneous delivery device taught by Kivitz to deliver the larger, 162 mg fixed dose of tocilizumab recited in the claims.

Morichika is an International Patent Application, WO 2009/084659 A1, assigned to Patent Owner, and is prior art to the '677 patent. Ex. 1110, code (71). Morichika is directed to "a stable, highly concentrated antibody-containing formulation suitable for subcutaneous administration, in in which dimer formation and deamidation are suppressed during long-term storage." Ex. 1110 ¶ 7. Morichika teaches that adding arginine or its salt, which is an amino acid, as a stabilizer can produce a stable antibody-containing solution formulation at a high concentration. *Id.* ¶ 8. Morichika teaches that its concentrated highly antibody-containing preparation does not require reconstitution by lyophilization and does not require redissolution and that can be stably stored in solution for a long period of time and can be manufactured without a lyophilization step. *Id.* ¶ 10. Morichika teaches that:

> The highest concentration of the antibody concentration of the antibody-containing solution formulation of the present invention is generally 300 mg/mL, preferably 250 mg/mL, and even more preferably 200 mg/mL, from the viewpoint of manufacturing. Therefore, the antibody concentration of the highly concentrated antibody solution formulation of the present invention is preferably 50–300 mg/mL, and even more

> preferably 100–300 mg/mL, and even more preferably 120–250 mg/mL, and *especially 150–200 mg/mL*.

Id. ¶ 15 (emphasis added).

Morichika also teaches exemplary embodiments of its claimed compositions, specifically, it discloses a stable formulation containing an anti-IL-6 receptor humanized antibody (tocilizumab is one such) at a concentration of 180 mg/ml. Ex. 1110 ¶¶ 61–87. Morichika also teaches that its compositions have a viscosity of 2 to 15 mPa-s, "[p]referably" "about 2~15 mPa-s, more preferably about 4~10 mPa-s." *Id.* ¶¶ 9, 55.

We agree with Petitioner that it would have been obvious to a person of ordinary skill in the art to modify the autoinjector pen of Kivitz, which is designed to deliver a subcutaneous dose of a fully human monoclonal antibody for the treatment of RA to contain and subcutaneously deliver the fixed dose of 162 mg tocilizumab, as taught by NCT '653. *See* Pet. 36–38. We further agree with Petitioner that a person of ordinary skill in the art would have been motivated to thus modify Kivitz, because Kivitz teaches that its device is popular with patients and easy to use and consequently increases compliance with the treatment regimen. *See id.* at 38–41.

We also agree with Petitioner that an ordinarily skilled artisan would also have had a reasonable expectation of success in combining the references, because Morichika teaches formulations of anti-IL-6 receptor human antibodies (such as tocilizumab) that are suitable for subcutaneous injection and at concentrations that meet or exceed the 162 mg fixed dose recited in the challenged claims. *See* Ex. 1110, 2.

Patent Owner disagrees that a person of ordinary skill in the art would have been motivated to combine the references, or have had a reasonable expectation of success in doing so. *See* PO Resp. 21–26. Patent Owner contends that subcutaneous injection of a high concentration of antibodies at the low volumes required for subcutaneous injection (approximately 1.0 milliliter) would have posed significant problems that would have discouraged a person of ordinary skill in the art from attempting to combine the references to arrive at the invention claimed in the '677 patent.

Specifically, Patent Owner contends that a skilled artisan would have been deterred by problems well-known in the art, including "aggregation, stability, immunogenicity, and delivery at antibody concentrations above 100 mg/mL." *See* PO Resp. 22. Patent Owner's expert, Dr. Silverman, opines that subcutaneous dosing regimens were riskier than IV dosing regimens because both (i) the high concentrations required, and (ii) injecting that drug beneath the skin, increased the likelihood of an immunogenic reaction, tissue damage, and formation of neutralizing anti-drug antibodies. *See* Ex. 2009 ¶¶ 24–25, 84–88.

Patent Owner also argues that Morichika's teachings are ambiguous. *See* PO Resp. 24. According to Patent Owner, Morichika sets out exemplary high-concentration tocilizumab formulations, but discloses no information about what kind of device should be used to administer 162 mg of tocilizumab in a single injection, or whether administration using that (unnamed) device would be well tolerated and comfortable for the patient. *Id.* Similarly, Patent Owner argues, Morichika's teachings on viscosity are

equally vague. *Id.* at 25. Patent Owner acknowledges that Morichika teaches that its composition's viscosities are "[p]referably" "about 2~15 mPa-s, more preferably about 4~10 mPa-s," but argues that Morichika says nothing about how to achieve these viscosities, and it does not explain what effect different viscosities in the broad ranges it discloses would have on ease of administration of patient comfort. *Id.* at 25–26 (quoting Ex. 1110 ¶ 55) (alteration in original).

We do not agree with Patent Owner's arguments. Although we agree with Patent Owner that the prior art taught subcutaneous administration of high-concentrations of antibodies posed some risk of aggregation and immunogenicity, nevertheless, NCT '653 expressly teaches the subcutaneous injection of 162 mg tocilizumab in a clinical trial. As we explained in our claim construction, we do not limit the language reciting the claimed device to require only a single injection in delivering the 162 mg fixed dose. *See* Section II.B.3 *supra*. Nor do we construe the claims to require the injection to be comfortable for the patient. *Id.* Although that would have been desirable, the plain language of the claims do not support such a construction.

In summary, subcutaneous injection of a 162 mg fixed dose of tocilizumab had been performed in the NCT '653 clinical trial prior to the priority date of the '677 patent. Subcutaneous injection self-evidently requires a device designed to contain and deliver the 162 mg fixed dose. Kivitz and Morichika together support the Petitioner's position that a person of ordinary skill in the art would understand that a subcutaneous injection

device could deliver a high concentration of human anti-IL-6 human antibodies in a volume suitable for subcutaneous injection (approximately 1 milliliter). We consequently conclude that Petitioner has met its burden of showing, by a preponderance of the evidence of record, that claims 1–8 of the '677 patent are obvious over the combined teachings of NCT '653, Kivitz, and Morichika.

F. Petitioner's Motion to Exclude Evidence

Petitioner has also moved to exclude Patent Owner's Exhibits 2005, 2006, 2009, 2034, 2065, 2080, 2081, and 2083. Mot. Exclude 1. Because we find that Petitioner has met its burden of showing, by a preponderance of the evidence, that claims 1–8 are unpatentable, we need not reach Petitioner's arguments in support of its Motion to Exclude, and we dismiss the Motion as moot.

III. CONCLUSION

For the reasons we have set forth above, and after having analyzed the entirety of the record and assigning appropriate weight to the evidence cited by Petitioner and Patent Owner, we determine that Petitioner has established, by a preponderance of the evidence, that claims 1–8 of the '677 patent are unpatentable. Furthermore, because we conclude that Petitioner has met its burden in this *inter partes* review, we dismiss Petitioner's Motion to Exclude Evidence as moot.

IV. ORDER

Accordingly, it is

ORDERED that Petitioner has shown by a preponderance of the evidence that claims 1–8 of the '677 patent are unpatentable;

FURTHER ORDERED that Petitioner's Motion to Exclude is dismissed as moot;

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.[16]

[16] Should Patent Owner wish to pursue amendment of the challenged claims in a reissue or reexamination proceeding subsequent to the issuance of this Final Written Decision, we draw Patent Owner's attention to the April 2019 *Notice Regarding Options for Amendments by Patent Owner Through Reissue or Reexamination During a Pending AIA Trial Proceeding*. *See* 84 Fed. Reg. 16,654 (Apr. 22, 2019). If Patent Owner chooses to file a reissue application or a request for reexamination of the challenged patent, we remind Patent Owner of its continuing obligation to notify the Board of any such related matters in updated mandatory notices. *See* 37 C.F.R. § 42.8(a)(3), (b)(2).

Claims	35 U.S.C. §	Reference(s) /Basis	Claims Shown Unpatentable	Claims Not Shown Unpatentable
1, 5	102	NCT '563		1, 5
1–8	103	NCT '563, Kivitz, Morichika	1–8	
Overall Outcome			1–8	

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