UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

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

IPR2021-01542
IPR2021-01288

U.S. Patent No. 8,580,264

PATENT OWNER'S RESPONSE UNDER 37 C.F.R. § 42.120

TABLE OF CONTENTS

I. INTRODUCTION

The Board's separate Decisions instituting trial on all twelve claims in U.S. Patent 8,580,264 relied heavily on declaration testimony of Dr. Zizic, Petitioners' technical expert, who now concedes he lacks any specialized knowledge in antibody formulation, pharmacokinetics, or pharmacodynamics. That expertise is critical to evaluating whether the challenged claims to methods of treating rheumatoid arthritis with a fixed (162 mg) dose of tocilizumab every week or two weeks are anticipated and/or obvious. At the Board's invitation, Patent Owners have supplied testimony from experts in these arts that fills the evidentiary gaps the Board identified and makes clear that all twelve of the challenged claims were properly issued.

Among other things, Patent Owners' experts establish that (i) formulating the claimed dosage of this antibody, highly concentrated and suitable for subcutaneous administration, is complicated and not remotely enabled by the references Petitioners cite; and (ii) determining the proper dosage for a subcutaneously administered antibody typically requires extensive study and experimentation and cannot be responsibly selected through the simplistic arithmetic Dr. Zizic proposes. Hindsight, as it always does, permits reverse-engineering the claimed invention with relative simplicity. For the POSA, however, it was not so easy.

Besides these substantive scientific points, the Institution Decisions decided claim construction without mentioning a definition in the specification that contradicts it, and gave a meaning to the term "method of treatment" that Petitioners' expert now rejects. The Board also misapplied Federal Circuit precedent relating to disclosed ranges in the prior art and their impact on the obviousness analysis.

For these reasons and the others set out below, the claims challenged in both Petitions should be confirmed.[1]

II. BACKGROUND

A. Tocilizumab for Subcutaneous Administration

Tocilizumab, a humanized antibody, treats rheumatoid arthritis by inhibiting interleukin-6 ("IL-6"), an inflammatory cytokine found in joints of patients suffering from the disease. Ex. 2055 (*Silverman Decl.*) ¶¶10-17. Actemra®, Chugai's product comprising tocilizumab, was initially approved by FDA only for intravenous ("IV") administration with variable dosing depending on a patient's weight. Ex. 1069 (*2010 Actemra® Label*) at 1. The IV formulation had a modest tocilizumab concentration of 20 mg/mL. *Id.* at 1. Beginning in 2009, Patent

[1] For the Board's convenience, Patent Owners are filing a single consolidated Response to both Petitions.

Owners conducted clinical testing on whether RA patients could receive tocilizumab in a fixed dose and "subcutaneously," or directly under the skin tissue. This required solving several significant challenges. Ex. 2055 (*Silverman Decl.*) ¶¶18-19; Ex. 2056 (*Samara Decl.*) ¶¶32-34.

1. The Formulation Problem

The central challenge to formulating antibodies for subcutaneous administration is squaring the "large dose requirements" with injection-volume limitations. Ex. 2013 (*Wang 2007*) at 27. As of the priority date, "[d]evelopment of formulations for high-concentration protein drugs [was understood to] be quite challenging." Ex. 2014 (*Krishnan 2010*) at 26; (*Wang 2007*) at 21-22 (describing "major issues"). Formulating the antibodies at concentrations high enough to deliver a large dose in a small volume of fluid tended to cause "stability, manufacturing, and delivery" problems due to "the propensity of proteins to aggregate at [these] higher concentrations." Ex. 2015 (*Shire 2004*) at 2. These aggregates in turn created the risk of "increased immunogenicity"—i.e., a potentially dangerous immune reaction to foreign proteins. Ex. 2013 (*Wang 2007*) at 8-9, 14; Ex. 2055 (*Silverman Decl.*) ¶¶20-25.

As of the priority date, only two monoclonal antibodies—adalimumab and golimumab—had FDA approval for subcutaneous injection in RA patients. Both were "fully human" antibodies less likely to trigger an immune response than

"humanized" antibodies like tocilizumab, *see* Ex. 2016 (*Weiner 2006*) at 1; Ex. 1087 (*Lobo 2004*) at 9, and that required far lower concentrations. *Compare* Ex. 1023 (*Humira® Label*) at 14 (50 mg/mL) and Ex. 1083 (*Simponi® Label*) at 1 (100mg/mL) *with* Ex. 1001 (*'264 Patent*) at 39:9-11 (180 mg/mL); Ex. 2055 (*Silverman Decl.*) ¶31.

2. The Dosing Problem

Even today designing dosing regimens still requires careful study of the drug's pharmacokinetics ("PK") and pharmacodynamics ("PD"). Especially for biologic drugs administered subcutaneously, absorption and bioavailability were critical factors known to be highly variable, making generalization "difficult or impossible." Ex. 2017 (*Turner 2018*) at 11. "[E]stimating effective absorption and bioavailability" in humans remains "[o]ne of the biggest hurdles to development of SC therapeutic proteins." *Id.* at 11; *see also* Ex. 2018 (*Dirks 2010*) at 5 (noting "great deal of uncertainty" regarding "absorption of IgG following subcutaneous . . . administration."). Ex. 2056 (*Samara Decl.*) ¶¶10-31.

III. THE '264 PATENT

A. The Specification

The inventors relied on data from four separate clinical trials to designed the claimed subcutaneous dosing regimens. Ex. 1001 (*'264 Patent*) at Table 1. Figures 1 through 4 report preliminary results from two of those trials and disclose that patients administered a single injection containing 162 mg subcutaneous

tocilizumab weekly or every two weeks exhibited efficacy and PK/PD profiles similar to those of patients who, in a separate study, had received the established IV regimen. These subcutaneous dosing regimens were associated with significant reductions in disease activity and raised no serious safety concerns. The inventors concluded that "[t]aken altogether, these data suggest that the use of a fixed dosing regimen is acceptable." *Id.* at 31:58-60. The "observed PK, PD, efficacy, and safety data" from these studies also supported subcutaneously administering 162 mg of tocilizumab "every 2 weeks (Q2W) rather than every week (QW)" in a study evaluating tocilizumab's ability to inhibit progression of joint damage.

The specification also describes several exemplary subcutaneous tocilizumab formulations suitable for the claimed methods. *Id.* at 38:26-42:4. It explains which excipients and pH ranges are suitable for stabilizing tocilizumab in such formulations, *id.* at 38:45-64, and how a "target tocilizumab concentration" was selected and achieved through careful consideration of competing factors such as antibody concentration, formulation viscosity, and injection force, *id.* at 38-65-39:11. The specification further describes the PK, PD, and safety results from clinically testing these subcutaneous formulations at ascending doses of tocilizumab and reports that the SC injections were well tolerated with no serious adverse events. *Id.* at 42:9-47:14, Figures 8-13.

B. Claims

The '264 Patent has twelve claims. Petitioners' first IPR (IPR2021-01288) challenged claims 1-3 and 6-11. Claim 1 is illustrative of the claims challenged in that proceeding.

> 1. A method of treating rheumatoid arthritis (RA) in a patient comprising subcutaneously administering an anti-IL-6 receptor (IL 6R) antibody to the patient, wherein the anti-IL-6R antibody is administered as a fixed [dose] of 162 mg per dose every week or every [two][2] weeks, and wherein the anti-IL-6R antibody comprises the light chain and heavy chain amino acid sequences of SEQ ID Nos. 1 and 2, respectively.

Claim 10, the only other independent claim challenged in IPR2021-01288, is substantially the same as claim 1 except that it specifically recites "tocilizumab" as the anti-IL-6R antibody. *See* Ex. 1001 at claim 10.

Petitioners' second IPR (IPR2021-01542) challenges the remaining three claims. Claims 4 and 5 depend from claim 1, specifying that the RA patient treated in claim 1 is either a "TNF-inhibitor-inadequate responder" or "methotrexate (MTX) naïve or has discontinued MTX." Independent Claim 12 recites:

---

[2] As Petitioners note, Pet. 15 n. 5, the certificate of correction omits the words "dose" and "two" from claim 1, but those words appear in the original claim 1.

12. A method of inhibiting progression of structural joint damage in a rheumatoid arthritis patient comprising subcutaneously administering a fixed dose of 162 mg of tocilizumab to the patient every two weeks, wherein structural joint damage at week 24 or week 48 is found to be inhibited.

IV. PERSON OF ORDINARY SKILL IN THE ART

Petitioners propose that the POSA need only have *medical* expertise, '01288 Pet. at 20,[3] a definition that matches Dr. Zizic's qualifications but conspicuously omits expertise in antibody formulation, pharmacokinetics, and pharmacodynamics.

The Board should reject Petitioners' definition and adopt Patent Owners': the level of ordinary skill in the art includes several years of experience in treating RA patients, analyzing antibody pharmacokinetics/pharmacodynamics, and creating antibody formulations.

[3] They define the POSA as "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 having several years of experience researching treatments for autoimmune disorders, including rheumatoid arthritis." '01288 Pet. at 20.

As the Federal Circuit has made clear, these skills need not all be found in any single individual. The POSA is a hypothetical person who can have the knowledge and experience of multiple individuals working across different arts. *Daiichi Sankyo Co. v. Apotex, Inc.*, 501 F.3d 1254, 1256–57 (Fed. Cir. 2007). Although Petitioners' POSA would prescribe the claimed inventions in the '264 Patent, she typically would be unable to develop those inventions without assistance from other individuals. As Dr. Zizic acknowledged in his deposition, it would require "a multidisciplinary approach," one that included a "pharmacokineticist," "pharmacologist," and "formulation expert," to converting the known intravenous, weight-based tocilizumab dosing regimen to the claimed subcutaneous fixed-dose regimen. Ex. 2066 (Zizic Tr.) at 44:4-20; *see also id*. 69:12-70:4; 251:12-252:4; Ex. 2055 (*Silverman Decl.*) ¶¶45-51; Ex. 2057 (*Little Decl*.) ¶¶30-3; Ex. 2056 (*Samara Decl.*) ¶¶37-40.

The same point is clear in the specification's description of the extensive clinical testing, Ex. 1001 ('264 Patent) at 28:55-32:5, pharmacokinetic modeling, *id.* and Figs.1-4, and formulation development work, *id.* at 38:25-42:4, that led to the claimed inventions. The POSA in Petitioners' definition—a single practicing rheumatologist—would be incapable of performing all of these required tasks. Dr. Zizic acknowledges that he couldn't. Ex. 2066 (Zizic Tr.) at 64:19-65:19, 70:5-8, 79:2-10, 90:10-91:2, 110:19-111:5.

Patent Owners have supplied the Board with this expertise, through three declarants: Dr. Gregg Silverman, a rheumatologist and professor at NYU's Langone School of Medicine; Dr. Emil Samara, a pharmacokineticist who has advised global pharmaceutical companies on PK/PD issues for decades; and Dr. Steven Little, who teaches antibody formulation at the University of Pittsburgh and leads a lab there dedicated to the science of drug-delivery. These experts explain at length why there were no obvious solutions to the clinical, scientific, and practical challenges to developing the claimed subcutaneous dosing regimen.

V. CLAIM CONSTRUCTION

Two claim terms require construction: "a fixed dose of 162 mg per dose" and "[a] method of treating rheumatoid arthritis in a patient/treats rheumatoid arthritis."[4] These limitations appear in all claims except claim 12.

A. The Claims Require 162 mg of Tocilizumab Per Injection.

The POSA would understand that "a fixed dose of 162 mg per dose" means delivering that amount of tocilizumab in a single injection. Ex. 2055 (Silverman Decl.) ¶¶53-54. Petitioners have not argued otherwise, and for good reason. "A

[4] For purposes of these proceedings, Patent Owners do not dispute Petitioners' definition of "fixed dose," "TNF-inhibitor-inadequate responder," or "a method of inhibiting progression of structural joint damage in a rheumatoid arthritis patient."

fixed dose of 162 mg *per dose*" would be redundant if "per dose" were construed to mean something besides "per injection." A claim construction should give "meaning to all of a claim's terms," *Apple, Inc. v. Ameranth, Inc.*,842 F.3d 1229, 1237 (Fed. Cir. 2016), and not "render[ ] other parts of the claim superfluous," *Merck & Co., Inc. v. Teva Pharm. USA, Inc*, 395 F.3d 1364, 1372 (Fed. Cir. 2005). If the method could be practiced by administering 162 mg of tocilizumab over multiple injections, as sometimes occurs with therapeutic antibodies, Ex. 2057 (*Little Decl*.) ¶42; Ex. 2055 (*Silverman Decl.*) ¶106, there would have been no need to include "per dose" as part of the claim; "a fixed dose of 162 mg" would have sufficed.

The specification, "'the single best guide to the meaning of a disputed term,'" *Phillips v. AWH Corp*., 415 F.3d 1303, 1315 (Fed. Cir. 2005) (*en banc*) (citation omitted), reinforces this construction. Clinical trial participants are described as receiving a "(180 mg/mL) SC formulation *single dose* of 0.9 mL corresponding to a dose of [] 162 mg [tocilizumab]" in a single "SC injection in the right or left anterior thigh." Ex. 1001 at 43:33-35, 52-54 (emphasis added). The specification also describes grappling with issues like "higher concentration[s] of tocilizumab," "ejection force," "viscosity," and low injection volumes in an effort to develop subcutaneous formulations capable of delivering this amount of tocilizumab in a single injection. *Id.* at 39:1-11. And it details a "subcutaneous

administration device" that "delivers to a patient a fixed dose of an anti-IL-6 receptor (IL-6R) antibody, wherein the fixed dose is . . . 162 mg. . . ." *Id*. at 28:21-25. The specification never describes tocilizumab being administered any other way.

B. The Claims Require More than Merely Administering Tocilizumab.

Petitioners insist that "a method of treating rheumatoid arthritis" / "treating rheumatoid arthritis" requires nothing more than administering tocilizumab, without regard to whether it even *might* be effective and safe. This construction, which the Board tentatively credited, disregards critical intrinsic evidence and what both parties' experts understand "treatment" means to someone practicing the claims.[5]

1. Treatment Refers to a Therapeutic Benefit.

The specification defines "treatment" as "*therapeutic* treatment" in a patient diagnosed with RA. Ex. 1001 ('264 patent) 13:59-14:12, 15:1-2. "Therapeutic"

---

[5] The Board also preliminarily credited Dr. Zizic's testimony that the claim term "does not require actually causing a therapeutic benefit *in a particular patient*." '01288 Decision at 11 (emphasis added). The phrase "particular patient" appears nowhere in the patent, much less in Claims 1 or 10. The specification and the claims refer only to "*a* patient."

means "having a good effect on the body or mind," particularly "relating to the healing of a disease," Ex. 2036 (*New Oxford American Dictionary*) at 3, or "serving to heal or cure." Ex. 2037 (*Webster's New World College Dictionary*) at 3. "Therapeutic treatment" therefore requires administering a drug that is known to be safe and effective, which necessarily includes safety and efficacy in treating "a patient" diagnosed with rheumatoid arthritis. Ex. 2055 (*Silverman Decl.*) ¶¶55-56.

Petitioners' construction ignores this definition, a cardinal sin in claim construction. They propose that "a method of treating RA in a patient" should be construed as "a method of *attempting* to treat RA in a patient," without, apparently, any regard to whether the treatment would work, *see* Pet. 22-23, and therefore rendering the specification's definition of "treatment" as "therapeutic treatment" meaningless. To get there, Petitioners rely on a dictionary to narrow how the inventors themselves defined their invention, *id.*, something that is never appropriate. *See*, *e.g., Nystrom v. TREX Co.*, 424 F.3d 1136, 1145 (Fed. Cir. 2005). The inventors made it clear that the "treatment" of a patient to tocilizumab must actually work.

At a minimum, the Board should interpret "treatment" to include *a reasonable expectation* of safety and efficacy, even if such success is not guaranteed for every patient. The specification also supports this narrower

construction. Example 1, which reports the results of studies evaluating the "PK, PD, safety, immunogenicity and efficacy" of various subcutaneous dosing regimens in RA patients, discloses that the claimed 162 mg weekly or biweekly dosing regimen was not only most effective among the subcutaneous dosing regimens tested but also most similar in therapeutic benefit to the existing IV dosing regimen. *See id.* at 29:66-30:46; 36:35-40. These results prompted the inventors' "selection" of the claimed subcutaneous dosing regimen over others evaluated in the studies but not recited in the claims (e.g., 81 mg). *Id.* at 29:48-49.

This construction comports entirely with the Federal Circuit's *Lilly* decision interpreting a "method of treating" claim to require "that a skilled artisan would have had a 'reasonable expectation' of success in treating vasamotor's symptoms, even if such success was not guaranteed in all cases." *Eli Lilly & Co. v. Teva Pharms. Int'l GmbH*, 8 F.4th 1331, 1345 (Fed. Cir. 2021). The Institution Decision distinguished *Lilly* on the basis that "the claim language [there] includes the built-in element of efficacy, requiring 'an effective amount.'" But *so too here*, when the specification is, as required, included in construing the term "treating rheumatoid arthritis."

2. The Experts Agree that Treatment Requires a Reasonable Expectation of Safety and Efficacy.

At deposition, Dr. Zizic clarified that the POSA would understand "treatment" to require "anticipating that [the drug] will be safe and reasonably

effective." Ex. 2066 (Zizic Tr.) at 47:12-48:13, an expectation a doctor could reasonably have only if a drug has previously been shown to be safe and effective in patients:

> **Q.** What do you mean by "treatment"?
>
> **A.** Treatment is to give them a medicine which in peer-reviewed studies has shown to be effective in some patients, number of patients, obviously, enough to be statistically significantly different from either your comparator or your placebo, depending on the study.
>
> **Q.** And that has also been shown to be safe?
>
> **A.** Oh, that goes without saying.

Id. He "absolutely" would never "treat a patient with a drug unless [he] believed it to be effective." *Id.* at 47:4-7.

Not surprisingly, Dr. Silverman agrees. For a rheumatologist, "treatment" of a patient with a therapeutic agent requires a reasonable expectation of safety and efficacy, Ex. 2055 (*Silverman Decl.*) ¶54 ; Ex. 2066 (Zizic Tr.) at 44:4-7, and would never include administering a drug without regard to its effects on the patients. Ex. 2055 (*Silverman Decl.*) ¶54; Ex. 2066 (*Zizic Tr.*) at 46:1-47:7. "Treatment" begins with the determination of what to administer, and how often. Dr. Silverman notes, for example, that although a nurse can administer a drug, only a doctor can decide whether to treat the patient with that drug, and how the drug

should be administered. Ex. 2055 (*Silverman Decl.*) ¶54. That is because making a decision about how to treat a patient requires balancing concerns about the drug's safety and efficacy. *Id.*; Ex. 2066 (Zizic Tr.) at 46:1-47:7.

3. Claims 6 and 11 Do Not Refute This Construction.

In its Institution Decisions, the Board focused on claims 6 and 11, which respectively claim "administering to the RA patient one or more additional drug which treats the RA," and "administering one or more additional drug which treats the [RA] wherein the additional drug is selected from the group consisting of non-biological DMARDs, NSAIDs, and corticosteroids." The Board noted that DMARDs and TNF inhibitors are described in the specification as drugs that "'have been used successfully to treat RA,' even though some patients 'fail to respond,' or have 'inadequate response' to these therapies." '01542 Decision at 12 (quoting '264 Patent at 1:47-50, 14:46-57).

But the statements are entirely consistent with the requirement for efficacy, or at least a reasonable expectation of safety and efficacy. While these TNF inhibitors or DMARDs failed to achieve the desired clinical benefit for some patients, no one would deny the physician who administered them reasonably *expected* them to be safety and efficacious. If anything, the patent's discussion of inadequate responder patient populations demonstrates that successfully achieving efficacy *is* an objective of the claimed methods. Claim 4, for example, recites

treating RA patients who are "TNF-inhibitor-inadequate responder[s]," meaning that the POSA must reasonably expect the claimed tocilizumab dosing regimen to successfully achieve safety and efficacy where TNF-α inhibitors could not. The same is true of claims 6 and 11; they require the POSA to administer additional drugs to the patient with a reasonable expectation that doing so will improve the treatment regimen.

C. The Preamble Is Limiting.

As a back-up Petitioners urge the Board to find that "a method of treating rheumatoid arthritis in a patient" is not limiting at all. '01288 Pet. at 21. But preambles are "generally construed . . . as limiting" if, as with the challenged claims, they "embody the essence of the claimed invention" by stating "the intentional purpose for which the methods must be performed." *Lilly*, 8 F.4th at 1340-42. The preamble here easily satisfies that standard. It "embod[ies] the essence of the claimed invention," *id.* at 1342, because it recites the requisite purpose for which the subcutaneous administration step is performed: "treating rheumatoid arthritis in a patient." Were the preamble non-limiting, as Petitioners propose, then "the claimed method [would] reduce[] to nothing more than a process" of subcutaneously administering an anti-IL-6R antibody without "fathomable utility." *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1345 (Fed. Cir. 2003).

The preamble also provides "antecedent basis for a term appearing in the body of a claim." *In re Fought*, 941 F.3d 1175, 1178 (Fed. Cir. 2019). The Federal Circuit has "repeatedly held" such preambles to be limiting. *Id.* (collecting cases). In the claims of the '264 Patent, "administering to *the* patient" (claims 1 and 10), "*the RA* patient" (claims 3-5), and "administering to *the RA* patient one or more additional drug which treats *the RA*" (claim 6) all refer back to the preamble's "treating *rheumatoid arthritis (RA)* in *a* patient" language. *See Lilly*, 8 F.4th at 1343 (preamble reciting a method of treatment "in *an* individual" limiting where it provides antecedent basis claim term "administering to *the* individual").

Finally, unlike in *Bristol-Myers Squibb Co. v. Ben Venue Labs, Inc.*, 246 F.3d 1368, 1375 (Fed. Cir. 2001), or *In re Capaxone Consol. Cases*, 906 F.3d 1013 (Fed. Cir. 2018) (cited '01288 Pet. at 21), the preamble requires a "manipulative difference" in how the method steps are performed. Those cases involved method-of-treatment claims with administration steps specifying both the dosage amount and frequency, such that "the steps of the . . . method [were] performed in the *same way* regardless of whether or not the patient experiences" treatment of the condition recited in the preamble. 246 F.3d at 1375 (emphasis added); 906 F.3d at 1023. The claim language here, however, expressly varies the dosing regimen—either "every week *or* every [two] weeks"—based on patient response. *See* Ex. 1001 at 30:62-65, 34:46-49, 30:2-42.

VI. ARGUMENT

A. *NCT00965653* Does Not Anticipate Any Claim.

Exhibit 1028 (*NCT00965653*) is a 2016 webpage from ClinicalTrials.gov summarizing a proposed Phase-I study testing the safety and efficacy of 162 mg subcutaneous tocilizumab administered weekly or every two weeks. Ex. 1028 at 2. Petitioners contend it anticipates claims 1-3 and 6-11 (although not 4, 5, or 12). The Board preliminarily overruled Patent Owners' objection that Exhibit 1028 was neither prior art nor publicly accessible, relying on the declaration of Mr. Paarlberg, a regulatory consultant with no expertise to opine on how someone with the POSA's qualification could have located *NCT00965653* even assuming publication before the priority date. Ex. 2082 (*Paarlberg Tr.*) at 57:9-58:13.

NCT00965653 in any event does not disclose every limitation of the challenged claims. Nor does it disclose or enable the subcutaneous formulation the protocol proposes to test. On this last point, the Board applied a presumption of enablement to excuse the protocol's silence on the composition of the formulation but invited Patent Owners to submit evidence rebutting it. Dr. Little, an expert with specialized knowledge about antibody formulation, does that.

1. *NCT00965653* Does Not Disclose All Claimed Limitations.

Assuming it qualifies as prior art despite the deficiencies noted *infra* §6.F.2 *NCT00965653* does not disclose the subcutaneous administration of the claimed amount of tocilizumab in a single injection, as required by the claims. As Dr.

Little explains, large doses of antibody drugs were sometimes administered subcutaneously over multiple, smaller injections. Ex. 2057 (*Little Decl.*) ¶¶41-42. Subcutaneous administration requires low injection volumes, and because 100 mg/mL was considered the upper concentration limit for subcutaneous antibody formulations, the POSA would not have envisioned administering the entire 162 mg fixed dose in a single injection. Ex. 2057 (*Little Decl.*) ¶¶41-42. The possibility that patients in *NCT00965653* trial may have received their tocilizumab in multiple doses forecloses anticipation by this reference. Ex. 2055 (*Silverman Decl.*) ¶¶59-60.

NCT00965653 also contains no statement or suggestion on the efficacy of the subcutaneous dosing regimen. This is not surprising since this is a protocol for a *proposed* clinical trial whose results were not disclosed until well after the priority date. Under the proper construction of "a method of treatment," *see supra*, this is an element of the claim.

Petitioners argue efficacy is "inherent in the treatment disclosed in *NCT00965653*." Pet. 27-28. This simply is untrue. As Dr. Zizic concedes, the disclosed dosing regimen "is effective" only for "*some* patients." Ex. 1002 ¶105. But unless the regimen is inevitably effective, inherency does not exist. *See Bettcher Indus., Inc. v. Bunzl USA, Inc.*, 661 F.3d 629, 639-40 (Fed. Cir. 2011) (inherency requires more than "probabilities or possibilities" and the "mere fact

that a certain thing *may* result from a given set of circumstances is not sufficient"). *See also* Ex. 2055 (*Silverman Decl.*) ¶¶64-66.

2. *NCT00965653* (Ex. 1028) Is Not Prior Art.

Petitioners unequivocally identify Exhibit 1028 as their grounds for challenging the patent. As they describe it: "NCT00965653 (Ex. 1028) is a clinical trial protocol, titled 'A Study of Subcutaneous Administered Tocilizumab in Patients with Rheumatoid Arthritis,' which was publicly available on ClincalTrials.gov before November 2009."[6] '01288 Pet. at 25. Despite Petitioners' concession that Ex. 1028 was not published until 2016, Reply 7, the Board preliminarily determined that *NCT00965653* qualifies as prior art. In doing so, the Board "recognize[d] and accept[ed] Petitioner's clarification"— made *ex post* in the Reply—"that it relies on the 'First Posted' version of NCT00965653, that is referenced in Exhibit 1028, and is best represented in the History of Changes document submitted as Exhibit 1038." '01288 Decision at 19. The Petition, the Board reasoned, relies on the combination of "Exhibits 1028, 1038, [and] 1053," and consideration of "the Exhibit 1038 version of that study record as the best representation of the relied upon version of the *NCT00965653* study

[6] *See also* Pet. at viii (explaining that "NCT00965653" refers to Ex. 1028) and 25 (identifying "NCT00965653" as the "[b]asis" for Grounds 1 and 2).

record amounts only to a different, more accurate citation for the study version relied upon in the Petition and not some improper revision of the grounds for the challenges." *Id.* at 21-22.

This is error. The Petition never discusses or even cites to Exhibit 1038. This document is instead only mentioned in two paragraphs (¶¶36-37) of Mr. Paarlberg's declaration—neither of which are specifically cited in the Petition itself. But regulations prohibit Petitioners' belated attempt to add Exhibit 1038 to the basis for their grounds through a *post-hoc* "clarification" in the Reply. They require that "the *initial petition* identify with particularity the evidence that supports the grounds for the challenge to each claim," including the "[t]he *exhibit number* of the supporting evidence relied upon to support the challenge." *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1330 (Fed. Cir. 2019) (citing 37 C.F.R. § 42.104(b)(5)). Having specifically identified Ex. 1028 as the basis for their grounds, Petitioners cannot now change that basis to a different exhibit—especially one that was never cited in the Petition. *Qiagen N. Am. Holdings, Inc. v. HandyLab, Inc.*, — F. App'x —, 2021 WL 5024387, at *3 (Fed. Cir. Oct. 29, 2021) (affirming Board's refusal to consider exhibit that Petitioner "could have submitted . . . in its Petitions to support [its grounds] . . . but it did not").

Nor can Petitioners rely on Exhibit 1028's reference to the "First Posted" date to remedy this deficiency. As the Federal Circuit recently explained, "[t]he

'patents or printed publications' that form the 'basis' of a ground for *inter partes* review must *themselves* be prior art to the challenged patent." *Qualcomm Inc. v. Apple Inc.*, 24 F.4th 1367, 1374 (Fed. Cir. 2022) (emphasis added). Just as applicant admitted prior art cannot be "the basis of a ground in an *inter partes* review[] because it is not contained in a document that is a prior art patent or prior art printed publication," *id.* at 1375, the same is also true of the "prior art version of NCT00965653" Petitioners purport to rely on by proxy through Exhibit 1028—a reference they concede is not itself prior art to the challenged patent.

3. Petitioners Have Not Established Public Availability.

Now that he has been deposed, it is clear that Mr. Paarlberg cannot establish that *any* version of the *NCT00965653* protocol was publicly accessible as of the critical date.

First, he is the wrong expert. His declaration never addresses public accessibility from the viewpoint of the interested POSA even though the question turns on that. *See Bruckelmyer v. Ground Heaters, Inc*., 445 F.3d 1374, 1378 (Fed. Cir. 2006) (POSA exercising reasonable diligence must be able to locate the reference); Ex. 2055 (*Silverman Decl*.) ¶61. Mr. Paarlberg conceded at his deposition that he possesses none of the skills relevant to the POSA. Ex. 2082 (*Paarlberg Tr.*) at 57:9-58:13. His opinions about the *timing* of postings on clinicialtrials.gov also are not competent opinion testimony. He has "no

knowledge [of the] internal policies and procedures" relating to such disclosure at Chugai, Genentech, or Roche, and so has no idea what they posted and when. Ex. 2082 (Paarlberg Tr.) at 54:16-56:22; *see also id*. at 88:10-17, 90:4.

The Board accepted Mr. Paarlberg's reliance on provisions of the FDA Amendments Act of 2007 to demonstrate public availability on ClinicalTrials.gov. Decision 22. But he conceded at deposition that several of those provisions were not always followed. *Id.* at 90:12-15, 94:4-8; *see also* Ex. 1004 (*Paarlberg Decl*.) at ¶29 (the "first posted date" is only an "*estimate*" and "the original study record was *most likely* publicly available by August 25, 2009).

Mr. Paarlberg's declaration also never reveals what search parameters the POSA would have used to locate *NCT00965653* or what other clinical trial registries were available to the POSA for searching at the time.[7] He attests that "one would have been able to search for and access" *NCT00965653* on the ClinicalTrials.gov website and that he was able to "locate[] the record for clinical study number NCT00965653," Ex. 1004 at ¶24, but he never explains *how* he did so or *how many* results he had to review to find this particular study. And for good

[7] At his deposition, Mr. Paarlberg acknowledged that as of 2009, there were "probably more than 30" and "maybe" even more than 50 clinical trial registries other than ClinicalTrials.gov. Ex. 2082 (Paarlberg Tr.) at 30:4-9.

reason. When questioned about this statement at deposition, Mr. Paarlberg conceded that he "[j]ust put the NCT number in the search function" to locate *NCT00965653*—a number the interested POSA certainly would not have known unless she, like Mr. Paarlberg, had the document in the first place. *Id.* at 101:2-102:1. He conceded he did not locate *NCT00965653* through the type of search the POSA might have conducted, for example by searching for keywords such as "rheumatoid arthritis" or "tocilizumab." *Id.* at 102:2-4, 103:22-104:3. Nor did he know how many results those searches would give.

Id. at 103:14-21. Such testimony, coupled with his deficient declaration, fails to establish that the interested POSA could have located *NCT00965653* with reasonable diligence from among the thousands of clinical trial protocols on ClinicalTrials.gov as of 2009. *See SRI Int'l*, *Inc. v. Internet Sec. Sys., Inc.*, 511 F.3d 1186, 1194-97 (Fed. Cir. 2008); *see also Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1349-50 (Fed. Cir. 2016); *Microsoft Corp. v. Bradium Techs. LLC.*, IPR2015-01435, Paper 15 at 11 (P.T.A.B. Dec. 23, 2015).

The mere existence of a search function does not suffice to fill the gaps in Mr. Paarlberg's opinion. "Even if keyword searches could be performed quickly" on sites such as ClinicalTrials.gov, they are "not always reliable because of *lack of standardization of drug names* and health conditions," which directly "contributed

to the difficulty of using [those] websites." Ex. 2084 (*Manheimer 2002*) at 3 (emphasis added). Mr. Paarlberg's deposition illustrated the problems this "difficulty" would have posed for a POSA searching for *NCT00965653*. He testified that he believed *NCT00965653* could be located by searching for "rhPM-1," a synonym for tocilizumab used in early studies. *Id.* at 105:10-12. But his speculation was wrong. Searching for "rhPM-1" in fact returns *no* results on ClinicalTrials.gov. Ex. 2083 (ClinicalTrials.gov "rhPM-1" search results).

4. *NCT00965653* Does Not Enable the Claimed Subcutaneous Dosing Regimen.

An anticipation reference must be more than just prior art and publicly accessible. It also "must enable a person of ordinary skill to make and use the [claimed] invention." *In re Kumar*, 418 F.3d 1361, 1368 (Fed. Cir. 2005); *Helifix Ltd. v. Blok-Lok, Ltd*., 208 F.3d 1339, 1348 (Fed. Cir. 2000) (no anticipation where prior art did not enable making "a tool capable of being used in the claimed method"). The Institution Decision applied a presumption of enablement to excuse the absence in *NCT00965653* of any disclosures about the tocilizumab formulation necessary to practice the claims,'01288 Decision at 26, but invited Patent Owners to submit "persuasive evidence to demonstrate that

NCT0096563 is not enabling," including an analysis of "the *Wands* factors" relating to undue experimentation. *Id*. at 26.[8]

On the first point, Patent Owners stand by their position, '01288 Sur-reply at 6, that no binding Federal Circuit precedent applies the presumption of enablement to a non-patent publication asserted in a petition for *inter partes review*. Petitioners initially conceded their obligation to establish enablement before disclaiming it in the Reply. *See* '01288 Pet. at 64 ("NCT00965653 discloses *and enables* each and every limitation of all of the claims of the '264 patent.) (emphasis added).

In any event, the declaration testimony from Drs. Little and Silverman is more than adequate to supply the "persuasive evidence" the Board found missing at institution. With respect to the first *Wands* factor, it is undisputed on the current record that developing a suitable subcutaneous formulation would have required

[8] The *Wands* factors include "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

substantial experimentation. Dr. Little, a formulations expert, explains how antibodies must be stabilized in a suitable formulation before they can be administered to patients, and that accomplishing this is no easy task. Ex. 2057 (*Little Decl.*) ¶¶37-38 (explaining that "failing to properly stabilize mAbs can cause the drug to be ineffective, not be available in the appropriate tier, and/or trigger inflammatory responses" and that "[s]ide effects of an improperly formulated antibody product can be severe"); *see also id.* at ¶¶10-13.

The prior art confirms this. Antibodies are "prone to a variety of physical and chemical degradation pathways"—including aggregation, deamidation, cross-linking, isomerization, and fragmentation—that cause significant losses in activity and trigger immunogenic reactions in patients. Ex. 2013 (*Wang 2007*) at 8-14; *see also id.* at 11, 14.

Dr. Little also explains that the POSA would not have reasonably expected a formulation known to stabilize one antibody to also stabilize a different antibody with a different sequence. Ex. 2057 (*Little Decl.*) ¶¶44-46 ("the chemical structure of each antibody is unique," resulting in "antibodies behav[ing] in solution in unpredictable ways," "mean[ing] that stabilization strategies could not be generalized across different antibodies"); ¶¶46-47 (explaining why the formulations for Humira®, Simponi®, Enbrel®, and Cimzia® would not enabled the claims); *see also* Ex. 2055 (*Silverman Decl.*) ¶¶108-109. Dr. Zizic acknowledged

the same point during his deposition. He agreed that the "different chemical structure" of different antibodies means that "[e]ach particular pharmaceutical product is a formulation unique unto itself." Ex. 2066 (Zizic Tr.) at 94:18-95:1. This unpredictability meant that as of the priority date—and still today—"generalization of universal stabilization strategies ha[d] not been successful," and "[v]ery often, proteins ha[d] to be *evaluated individually* and *stabilized on a trial-and-error basis*." Ex. 2024 (*Wang 1999*) at 2 (emphasis added); Ex. 2057 (*Little Decl.*) ¶38 ("determining which formulation will achieve acceptable stability is and was considered the *most formidable challenge* in formulation a liquid protein pharmaceutical"). Petitioners conceded exactly this point in a patent application they filed six years after the priority date here when attempting to claim their own formulation for tocilizumab. They told the Patent Office that "[a]lthough the use of excipient(s) [may be] known to increase the stability of a given protein, the stabilizing effects of these excipients is *highly dependent on the nature of the excipients and of the bioactive protein itself*." Ex. 2025 (*U.S. Patent No. 10,961,314*) at 2:3-7 (emphasis added).

Because there was little known in November 2010 about the behavior of tocilizumab when formulated for subcutaneous administration, this process presented a formidable challenge. The POSA possessing only *NCT00965653* would have had no choice but to make and test individual formulations to

determine whether they could be used to stabilize tocilizumab. (*Wands* factor 1.) Ex. 2057 (*Little Decl*.) ¶¶39-41, 46.

The nature of the invention, the state of the prior art, the relative skill of those in the art, and the unpredictability of monoclonal antibodies all increase the amount of experimentation that would have been necessary to create the specific 162 mg subcutaneous dose claimed in the '264 Patent. (*Wands* factors 4-7.) As Dr. Little explains, subcutaneous fixed-dose regimens posed especially difficult formulation challenges because administering antibodies this way requires a large amount of antibody to be contained within a small volume. Ex. 2057 (*Little Decl*.) at ¶¶14-16. Dr. Little explains that this high-concentration requirement is considered one of the most challenging problems in antibody formulation. Ex. 2057 (*Little Decl*.) ¶18.

The literature from the time confirms this. As of November 2010, the art taught that "[f]rom the perspective of stability etc., the concentration limit for IgG-type antibody formulations is in general thought to be about 100 mg/ml," Ex. 1011 (*Igawa*) at ¶0003, a little more than half the concentration in the '264 patent (180 mg/ml). The only monoclonal antibodies approved by FDA for subcutaneous administration as of November 2010—Humira® and Simponi®— used concentrations at or well below 100 mg/ml. *See* Ex. 1023 at 15 (adalimumab: 50 mg/ml); Ex. 1083 at 1 (golimumab: 100 mg/ml). Ex. 2057 (*Little Decl*.) ¶¶15, 20-

25. The POSA learned nothing from *NCT00965653* about making a subcutaneous formulation of tocilizumab at nearly twice the "concentration limit" generally understood in the art. *Id.* at ¶¶48-49.

Attempting an ultra-high concentration formulation would have confronted the POSA with two particularly significant problems: increased viscosity and aggregation. Ex. 2057 (*Little Decl*.) ¶¶17-20; Ex. 2066 (Zizic Tr.) at 141:22-142:11. Viscosity, which measures the "thickness" of a formulation's consistency, is a concern for reasons of both patient comfort and ease of administration. Ex. 2057 (*Little Decl*.) ¶19. Viscous formulations often clog needles and require greater injection force, something that makes the drug more difficult to administer and less comfortable for patients to receive. Increased viscosity also may cause the drug to "pool" at the injection site, leading to adverse reactions, reduced bioavailability, and increased immunogenicity. Ex. 2057 (*Little Decl*.) ¶19. The claimed 162 mg dose was formulated with viscosity in mind; the specification 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.*

at 39:1-11.[9] *NCT00965653* contains no similar guidance on how to account for viscosity, and in fact does not even acknowledge the problem.

Aggregation posed an additional obstacle. Ex. 2057 (*Little Decl.*) ¶18; Ex. 2066 (Zizic Tr.) at 99:11-100:1, 139:20-140:4. Aggregates in antibody formulations could reduce activity (and therefore efficacy) and make immunogenic reactions more likely. As Dr. Silverman explains, immunogenicity would have been a particular concern for subcutaneous tocilizumab. Unlike TNFα, the IL-6 cytokine was understood to have both "pro- and anti-inflammatory activity," meaning that therapies targeting this cytokine possibly could aggravate RA symptoms rather than mitigate them. Ex. 2026 (*Kelley's 2001*) at 5-6, 25. Antibodies targeting IL-6 directly might actually extend that cytokine's activity. *Id.* at 25. This meant that inhibiting IL-6 directly, for example, the same way

[9] Because the "[v]olume of subcutaneous injection is ideally 1 mL or less," a "high concentration of protein is needed in [the] drug product." Ex. 1001 at 39:5-7. But on the other hand, a "high concentration of protein" will cause "high viscosity," thereby necessitating "increase[d] injection force." *Id.* at 39:7-9. The specification then explains that it arrived at "the target tocilizumab concentration [of] 180 mg/mL" by balancing the "protein concentration and viscosity" requirements. *Id.* at 39:9-11.

adalimumab targets TNFα, could in theory worsen the patient's RA symptoms. *See id.*; Ex. 2055 (*Silverman Decl.*) ¶16. Without careful experimentation to select the right formulation, the POSA would risk worsening patients' symptoms. Ex. 2055 (*Silverman Decl.*) ¶¶63, 67. Indeed, Dr. Zizic agreed that concentration-dependent aggregation "is the greatest challeng[e]" to developing high-concentration protein formulation." Ex. 2066 (Zizic Tr.) 122:10-17. Yet *NCT00965653* contains no information whatsoever that could guide the POSA's efforts to avoid aggregation.

Other *Wands* factors reinforce the conclusion that *NCT00965653* is not enabling. Ex. 2057 (*Little Decl.*) ¶49; Ex. 2055 (*Silverman Decl.*) ¶¶62-63. It is undisputed that *NCT00965653* provides absolutely no guidance whatsoever on how to make a 162 mg subcutaneous tocilizumab formulation. (*Wands* factor 2.) *See* Ex. 2066 (Zizic Tr.) at 248:21-251:1. *NCT00965653* likewise is completely devoid of examples of subcutaneous tocilizumab formulations. (*Wands* factor 3.) The contrast with the Patents' specification is stark. The latter contains a wealth of information enabling the formulation of tocilizumab for subcutaneous administration. Example 4 teaches several exemplary formulations of tocilizumab suitable for subcutaneous administration and the special considerations that went into developing those formulations. *See* Ex. 1001 at 38:25-42:5, Tables 2 and 3. The specification explains which excipients will work to stabilize tocilizumab in a

subcutaneous formulation and how to achieve the appropriate pH range. *Id.* at 38:39-64. Without similar guidance, *NCT00965653* cannot enable the POSA to practice the claimed subcutaneous dosing regimen, and it cannot anticipate the claims.

B. *NCT00965653* Does Not Render the Challenged Claims Obvious.

Even were *NCT00965653* enabling prior art, its limited disclosure would not have given the POSA a reasonable expectation of success at creating the claimed 162 mg subcutaneous dosing regimen.

1. The POSA Would Not Have Used Petitioners' Proposed Multiplication Approach.

Petitioners contend that the POSA reasonably would have expected the 162 mg fixed dose of subcutaneous tocilizumab described in *NCT00965654*, administered weekly or every other week, to be "equivalent" to the IV dosing regimen disclosed in *Emery* and *Maini*, i.e., 4 mg/kg or 8 mg/kg of tocilizumab every four weeks. According to Petitioners, the POSA would simply have converted the IV dose into a subcutaneous dose by multiplying the IV dose by a purported average patient weight of 70 kg. The POSA would then have adjusted this calculation to account for the antibody's subcutaneous bioavailability to produce a range of possible subcutaneous doses. The Board preliminarily credited Dr. Zizic's unrebutted testimony on this issue, '01288 Decision at 38, but the

record—including Dr. Zizic's deposition testimony—now confirms the error in doing so.

Dr. Samara, Patent Owners' expert and a Ph.D. pharmacokineticist with decades of experience in drug development, identifies multiple fundamental errors in Dr. Zizic's proposition that the POSA would simply multiply the IV dosage by an average weight calculation goes against fundamental pharmacokinetic principles. Ex. 2056 (*Samara Decl.*); *see also* Ex. 2055 (*Silverman Decl*.) ¶¶96-97.

First, Dr. Zizic incorrectly relies on average patient-weight figures. As Dr. Samara explains, a pharmacokineticist designing a subcutaneous dosing regimen would understand that what matters is not the average patient weight, but the *distribution* of weights across the potential patient population. Ex. 2056 (Declaration of Dr. Emil Samara), ¶¶45-47 (*Samara Decl.*). Only by considering the weight distribution could a pharmacokineticist account for variation in weight across patients. *See, e.g.*, Ex. 2066 (Zizic Tr.) at 178:5-16 (patient weight is a source of drug response variability). Dr. Samara explains that accounting for such variation is necessary to avoid the risk of over or under-dosing patients. Ex. 2056 (*Samara Decl.*) ¶¶26-28; Ex. 2055 (*Silverman Decl.*) ¶75. The same fixed dose that might prove therapeutically beneficial for one patient with a given weight may prove ineffective in another, heavier patient, and toxic in a third, lighter patient. Relying on average weights, like Dr. Zizic proposes, would not account for the

serious risk of over- or under-dosing patients. This is particularly true for tocilizumab, as it was already known in November 2010 its PK and PD were affected by body size. Ex. 2056 (*Samara Decl*.) ¶¶53-54. Without population-level weight data, it would have been impossible for the POSA to know how to convert an intravenous weight-based dose into a subcutaneous fixed dose that would achieve the same efficacy. Ex. 2056 (*Samara Decl*.) ¶¶45-47.

Second, Dr. Zizic fails to consider the problem of absorption, the process by which a subcutaneously administered drug travels from the site of administration through the circulatory system. Ex. 2056 (*Samara Decl*.) ¶¶48-50. As Dr. Samara notes, in 2010 "little [was] known about the mechanism of absorption of mAbs administered via subcutaneous or intramuscular injection." Ex. 2056 (*Samara Decl*.) ¶17 (quoting Ex. 2027 (*Mould 2010*) at 6); *see also* Ex. 2017 (*Turner 2018*) at 1 ("While several avenues for treatment utilizing biotherapeutics are being explored, there is still a sufficient gap in knowledge regarding the interplay of formulation conditions, immunogenicity, and pharmacokinetics (PK) of the absorption of these compounds when they are given SC."). Dr. Zizic concedes this. Ex. 2066 (Zizic Tr.) at 220:20-221:7. What the POSA *did* know was that absorption rates vary depending on the particular antibody being administered, the volume of the injection, aggregation, and, most relevant here, patient weight. Ex. 2056 (*Samara Decl*.) ¶48. Dr. Zizic now concedes this as well. *Id.* at 119:2-6

(patient weight), 221:16-22 (protein molecular weight), 102:3-6 (aggregation). The POSA would understand that all of these factors would have to be accounted for to design a safe and effective subcutaneous dosing regimen. Yet Dr. Zizic does not consider absorption effects at all as part of his calculation, and cannot do so because he relies on a contrived average patient weight rather than the kind of population modeling analysis Dr. Samara explains would actually be used.

Third, Dr. Zizic's multiplication approach largely ignores the issue of antibody clearance, that is, the rate at which the drug is removed from the body. Dr. Zizic concedes that clearance (and thus, the patient's total exposure to the drug) depends on patient weight, Ex. 1002 (Zizic '01288 Declaration) ¶161, but concludes the POSA would not have spent time to understand the relationship because tocilizumab was known to have a "wide therapeutic window." *Id.* at ¶156. For this proposition, Dr. Zizic relies on an EMA Assessment Report indicating that total exposure, or "AUC," "was also known to vary significantly when tocilizumab was administered as a weight-based dose." *Id.* (citing Ex. 1019).

Dr. Samara corrects Dr. Zizic's inaccurate reading of the EMA report, pointing out that the portion of the EMA Assessment Report Dr. Zizic cites addresses the pharmacokinetics of *IV* tocilizumab at a particular dosage. Ex. 2056 (*Samara Decl.*) ¶54. The POSA would not have assumed that these results could be used to design a subcutaneous dosing regimen using a different dosage. *Id.*.

Indeed, the Assessment Report itself cautions that "[a] major conclusion is that due to the concentration-dependent PH, the total CL [*i.e.*, clearance] and/or apparent half-life estimated is only valid for a given dose and dosing interval and *should not be translated to other dosing regimens*." Ex. 1019 at 23 (emphasis added). At his deposition, Dr. Zizic fully agreed with the EMA's cautionary warning even though his declaration did not cite it. Ex. 2066 (Zizic Tr.) at 164:19-165:9.

Dr. Samara also explains that Dr. Zizic is wrong to claim tocilizumab has a "wide therapeutic window." In fact, the prior art taught that IV tocilizumab was optimally effective only at the 8 mg/kg dosage. Ex. 2056 (*Samara Decl*.) ¶63. Other tested dosages were deemed minimally effective (4 mg/kg) or not effective at all (2 mg/kg). *Id*. Given these results, Dr. Samara explains, the POSA would consider the therapeutic window of tocilizumab to be relatively narrow, not wide. *Id.*

Fourth, Dr. Zizic's multiplication approach flies in the face of real-world efforts to design subcutaneous dosing regimens for therapeutic antibodies like tocilizumab. In his many years of experience, Dr. Samara has never seen subcutaneous dosing regimen calculated in the manner Dr. Zizic suggests. Ex. 2056 (*Samara Decl*.) ¶ 56. Instead, 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.

See id.. If finding an appropriate subcutaneous dose were easy as Dr. Zizic claims, the inventors of the '264 Patent would not have wasted hours laboriously conducting human studies testing various subcutaneous dosing regimens. *See* Ex. 1001 (*'264 Patent*), Table 1; *id.* at 39:13-18.

Adalimumab is one such example. As Dr. Silverman explains, after establishing efficacy through *intravenous weight-based* dosing, subcutaneous development began with an initial study on the "safety and tolerability of subcutaneous injections of adalimumab" to determine whether a new route of administration was even feasible. Ex. 2081 (*Rau 2002*) at 3. The feasibility study once again utilized *weight-based* dosing and generated subcutaneous PK/PD, bioavailability, efficacy, and safety data. Based on this data, two subcutaneous dose-finding studies were designed, evaluating a total of six different *fixed-dose* regimens (20 mg, 40 mg, or 80 mg every week or every other week) that led to selection of the 40 mg every other week dose as safe and effective for subcutaneous administration. Ex. 2081 (*Rau 2002*) at 3, Table 1; Ex. 1023 (*Humira® Label*) at 1. Taken together, these clinical trials illustrate the considerable empirical testing necessary to develop a successful subcutaneous dosing regimen, particularly when changing *both* the route of administration (intravenous to subcutaneous) and dosing methodology (weight-based to fixed dosing). No such data existed in the prior art to guide the POSA in designing a

subcutaneous fixed-dose regimen for tocilizumab, which instead published for the first time in the '264 Patent.

Even when empirical testing produces reliable data on an antibody's PK and PD profile, success in designing a subcutaneous dosing regimen is not guaranteed. The examples of rituximab and trastuzumab illustrate the point. Ex. 2056 (*Samara Decl*.) ¶60. Rituximab was initially approved for IV dosing on a body-surface-area basis. Ex. 2056 (*Samara Decl*.) ¶ 60. A dose-finding study intended to determine a comparable subcutaneous dosage had to be revised after interim analysis revealed that scientists had underestimated the variability in subcutaneous rituximab's bioavailability. Ex. 2056 (*Samara Decl*.) ¶ 60. Likewise, in a subcutaneous dose-finding study for trastuzumab, the original protocol was amended to add an additional dosing cohort after interim pharmacokinetic analysis revealed that the existing dosing cohorts were insufficient to cover the broad range of bioavailability observed between subjects. Collectively, these IV to SC bridging studies demonstrate the unpredictability and extensive experimentation necessary for developing a successful subcutaneous dosing regimen. Drs. Samara and Silverman opine that the POSA would have been well aware of the potential for such complications in November 2010. Ex. 2056 (*Samara Decl*.) ¶60.

The Institution Decision suggested that although the sort of testing Dr. Samara describes might be required for Phase-III trials, the POSA would not have

considered it necessary for earlier clinical trials, or first-in-human experiments. '01288 Decision at 33. Dr. Samara explains why this is not true. Ex. 2056 (*Samara Decl*.) ¶58. The PK and PD of an antibody is critical at *all* stages of the development process, and "[i]f anything, a pharmacokineticist would be more cautious, not less, when developing a dosing regimen for an early clinical trial because there would be limited, if any, safety data about the product." *Id.*. Dr. Zizic, on the other hand, treated this data-driven, empirical process like it was an algebra problem, although to his credit he backed off the point at his deposition and agreed that determining an appropriate subcutaneous dose requires clinical testing that accounts for numerous factors, including patient weight. Ex. 2066 (Zizic Tr.) at 56:18-57:12, 173:3-173:13. This Board should credit this approach, not the simplistic and implausible opinion Dr. Zizic proffered in his initial declaration.

2. *Bonilla* Does Not Support Petitioners' Proposed Multiplication Approach.

Bonilla is the only purported example Petitioners and Dr. Zizic cite as adopting their multiplication approach to dosing, pointing in particular to *Bonilla's* statement that "antibodies may be administered subcutaneously every week or every other week instead of intravenously every four weeks in an amount that 'over time is generally equivalent.'" Pet. 33-34. Although the Board tentatively

agreed, the current record establishes that the POSA would never determine a subcutaneous dosing regimen this way.

To start, Dr. Samara explains that the POSA designing an RA dosing regimen for monoclonal antibodies like tocilizumab would never rely this way on a reference that does not address monoclonal antibodies or RA at all. Instead, *Bonilla* describes use of a polyclonal immunoglobulin product called Vivaglobin® to treat primary immune deficiency. Ex. 1021 (*Bonilla*) at 4. The Institution Decision discounted this point in Patent Owners' Preliminary Response as "attorney argument", but now it is substantiated at length by expert testimony on subcutaneous antibody dosing.[10] Dr. Silverman and Dr. Samara explain that the

[10] The Board also relied on *Bonilla*'s statement that "any product suitable for IV administration with concentration of 10% or more . . . may be administered SC." '01288 Decision at 36 (citing Ex. 1021 at 17). But when this sentence is read in full, the "product" is clearly limited to the context of immunoglobulin replacement therapy—"*Only one product* is licensed specifically for SC administration in the United States (*Vivaglobin* . . .), although *any product* suitable for IV administration with concentration of 10% or more or IMIG also may be administered SC"—as more than one immunoglobulin "product" had been approved for SC administration as of *Bonilla*'s 2008 publication date.

polyclonal antibody product in *Bonilla*, directed to a different disease, makes this reference inapt.

-- The patients in *Bonilla* suffer from immuno*deficiencies* requiring replacement immunoglobin infusions to supplement immune responses. Giving patients immunoglobulin was intended to bring their immune response back up to normal levels. And in that process, there is little concern about providing too much immunoglobulin because, as Dr. Samara explains, the body has mechanisms to counter any potential overdose. Ex. 2056 (*Samara Decl*.) ¶65. In this respect, Dr. Samara notes, immunoglobulin can truly be said to have a wide therapeutic window. By contrast, RA patients prescribed tocilizumab suffer from an overactive immune system requiring immunosuppression. The POSA would therefore have to design the subcutaneous dosing regimen in a way that would not further aggravate the already overactive immune system. This is a consideration that *Bonilla* never needed to address.

-- From a pharmacokinetic standpoint, the POSA would understand that, for multiple reasons, the polyclonal antibodies administered in *Bonilla* would have different PK and PD profiles than tocilizumab. Ex. 2056 (*Samara Decl*.) ¶¶67-69. Immunoglobulin is a natural product that already exists in large quantities in the body. Its clearance and absorption process is fundamentally different from that of tocilizumab, a non-natural product. Also relevant are the difference in structure

between tocilizumab and Vivaglobin®, and the fact that Vivaglobin® consists of many different antibodies combined in the same product. Ex. 2056 (*Samara Decl.*) ¶67. In other words, the inherent variation in PK/PD across antibodies would be compounded the fact that Vivaglobin® contains many different antibodies. Ex. 2056 (*Samara Decl.*) ¶69.

Even were the POSA to consider *Bonilla* relevant, the reference does not actually teach the multiplication Dr. Zizic claims. To the contrary, *Bonilla* discloses that in the referenced study of subcutaneous Vivaglobin®, the experimental protocol "called for dose adjustment of the SC product to give a time-averaged area under the curve that was equivalent to what had been obtained previously with IVIG." Ex. 1021 (*Bonilla*) at 17. The study itself states that the protocol in question was designed "based on the results of a pharmacokinetic study carried out in a subset of 24 patients." Ex. 1017 (*Ochs 2006*) at 2. Thus, as Dr. Samara observes, a pharmacokineticist reading *Bonilla* would take away the lesson that determining a subcutaneous dosing regimen requires careful experimentation. Ex. 2056 (*Samara Decl.*) ¶70.

Nor does *Bonilla* support the proposition that one can determine what dose to give subcutaneously solely by reference to an approved intravenous dose of the same drug. To the contrary, *Bonilla* teaches that "immunoglobulin administration via the subcutaneous route is fundamentally different from IV administration." Ex.

1021 at 15. And, as of the priority date, only a few pharmacokinetic studies of subcutaneous immunoglobulins had been conducted and "the bioavailability of SCIG [subcutaneous immunoglobulins] had not been determined precisely." *Id.* at 17. At his deposition Dr. Zizic conceded each of these points. Ex 2066 (Zizic Tr.) at 204:11-205:20.

Finally, unlike the *fixed* dosage recited in the claims, the study cited in *Bonilla* teaches that the subcutaneous doses administered were "individually adjusted based on each subject's IgG levels," on a mg/kg basis. Ex. 1017 (*Ochs 2006*) at 2-3. A custom-tailored, weight-based dosing is the antithesis of the inventors' discovery that tocilizumab could be administered subcutaneously as a fixed dosage of 162 mg. Ex. 2056 (*Samara Decl.*) ¶¶70-71.

3. Petitioners' Conversion Relies on Incorrect and Arbitrary Assumptions

Petitioners also assume, incorrectly, that the POSA would have known all the necessary inputs to their simple-math approach.

a. Bioavailability

Converting from intravenous to subcutaneous dosing requires the POSA to account for differences in intravenous and subcutaneous absorption rates. Dr. Zizic, who concedes the point, argues once again that this is simple math because it was known that tocilizumab had a subcutaneous bioavailability of 72%. Ex. 1002 (*Zizic Decl.*) ¶152. But that figure comes from a single study, "in *monkeys*," Ex.

1019 (*EMA Assessment Report*) at 18 (emphasis added). Dr. Samara, who has the expertise Dr. Zizic concedes he lacks, explains why the POSA would never use animal bioavailability data as proxy for human bioavailability, given the well-known fact that monoclonal antibodies exhibit substantial interspecies variation in subcutaneous bioavailability. Ex. 2056 (*Samara Decl.*) ¶75. "For many monoclonal antibodies," Dr. Samara explains, "'it is not possible to make a correlation between the bioavailability values of the animal species tested and human.'" *Id.* (quoting Ex. 2029 (*Viola 2018*) at 8). Ex. 2056 (*Samara Decl.*) ¶¶76-77. The assumption Dr. Zizic made and the Board tentatively credited is one the POSA would never make.

Dr. Zizic also conceded that the EMA Assessment Report says nothing that a POSA could rely upon to assess the validity of the study for use in calculating the appropriate dose for subcutaneous tocilizumab in humans, even if the monkey-human comparison were otherwise apt. *See* Ex. 2066 (*Zizic Tr.*) at 164:19-165:9. The EMA reports that monkeys were given only *one 5 kg/mg dose* of the drug. It says nothing else. It does not disclose (i) the number of monkeys tested; (ii) the monkeys' average weight; (iii) where on the body the monkeys were dosed; (iv) how long after dosing the monkeys were tested; or (v) the bioavailability at a 4 mg/kg or 8 mg/kg dose—all factors that can affect bioavailability, particular for a drug like tocilizumab with a non-linear PK profile. Ex. 2066 (Zizic Tr.) at 161:18-

163:17; Ex. 2056 (*Samara Decl*.) ¶34 These are all data points the POSA would need if she were otherwise inclined to rely on bioavailability in monkeys.

b. Average Weight

Another error in Dr. Zizic's arithmetic exercise is his assumption that the "typical" patient weighs 70 kg. Ex. 1002 (*Zizic Decl.*) ¶133. The prior art reported a range of different average weight figures. *See* Ex. 1022 (*Wang 2009*) at 16-17 and Figure 8 (reporting results of experiment assuming 75 kg and 90 kg median body weights); Ex. 2031 at 10 (*FDA Guidance for Industry*) (assuming an average 60 kg body weight). Dr. Samara explains why the POSA would not simply pick one of these weight figures as a starting point. Ex. 2056 (*Samara Decl*.) ¶79. In the PK field, "close" is not good enough. Rather, the POSA would insist on precision. As Dr. Zizic conceded, if the POSA chose weight-based dosing, she would need to test different weights likely to occur across the population (including for example across nationalities and genders) before arriving at a fixed-weight dosing regimen, *id*. at 170:10-14. And even if average weights were deemed relevant when designing a subcutaneous dosing regimen—and as Dr. Samara explains, they would not be—the POSA would determine the average for the specific patient population being treated by the drug in question. Dr. Zizic never performs this analysis, nor does he point to any source confirming that 70 kg is the typical weight of an RA patient. Indeed, Dr. Zizic conceded during his

deposition that he did not even look for any prior art confirming the average weight of RA patients. Ex. 2066 (Zizic Tr.) 166:14-18.

Dr. Zizic's erroneous assumption is significant because, as Dr. Samara explains, assuming a different average weight would produce a different range of potential subcutaneous doses. For example, if the POSA had assumed the same 90 kg median body weight used in *Wang*, the range of potential subcutaneous dosages using Petitioners' calculation approach would be between 180 to 250 mg, well *above* the 162 mg amount claimed in the '264 Patent. *See* Ex. 2056 (*Samara Decl*.) ¶78. The logical conclusion is that Dr. Zizic selected 70 kg as an average weight through hindsight, with the goal of reverse-engineering the claimed invention.

c. Starting Dose

Given the hindsight-driven nature of Dr. Zizic's analysis, it is not surprising that his opinion depends on another jerry-rigged, and unstated, assumption about which IV dosage the POSA would start from. According to Dr. Zizic, the POSA would use the 4 mg/kg IV dose as the basis for determining the every-other-week subcutaneous dose, but would have used the 8 mg/kg IV dose to determine the every-week subcutaneous dose. Dr. Zizic never explains why the POSA would have limited their selection of starting dose in this manner. But the explanation is apparent: As Dr. Samara shows, if Dr. Zizic had used a different but completely

logical starting point, his calculated subcutaneous dosing ranges would have failed to capture the claimed 162 mg dose. Ex. 2056 (*Samara Decl.*) ¶81. Here again, Dr. Zizic has simply worked backward from the invention to manufacture an obviousness argument.[11]

d. Other Biologics

Finally, Dr. Zizic attempts to support his opinions by invoking other biologics approved for subcutaneous administration prior to November 2010. But as Dr. Samara explains, these drugs—etanercept, certolizumab, adalimumab, and golimumab—all have linear PK profiles, that is, as the dose administered increases, so too does the amount of drug in the patient's body.[12] Tocilizumab,

---

[11] 70 kg x (4 mg/kg every four weeks) = 280 mg every four weeks, or 70 mg every week. 70 kg x (8 mg/kg every four weeks) = 560 mg every four weeks, or 280 mg every two weeks. Adjusting 280 mg to account for differences in bioavailability between intravenous and subcutaneous dosing using Petitioners' assumed 72% bioavailability results in an upper limit of 389 mg (280/0.72 = 389).

[12] Petitioners imply that Enbrel® (etanercept) and Cimzia® (certolizumab pegol) also are monoclonal antibody therapies. '01288 Pet. 12-13. This is not true. The former is an Fc fusion protein and the latter an antibody fragment conjugated to polyethylene glycol, *see* Ex. 1082 at 3; Ex. 1024 at 4-5. These structural and

however, has a non-linear PK profile, meaning the connection between dose and response is far less predictable. Ex. 2056 (*Samara Decl*.) ¶83. Dr. Samara explains that, given this difference, creating a subcutaneous dosing regimen for tocilizumab would be significantly more difficult than for the antibodies Dr. Zizic cites. Ex. 2056 (*Samara Decl*.) ¶84. At his deposition, Dr. Zizic conceded that tocilizumab's non-linear PK profile makes its bioavailability less predictable, Ex. 2066 (Zizic Tr.) at 11:15-12:6, and that he did not take this difference into account when making his comparisons, *id*. at 14:1-20. Indeed, he did not compare the pharmacokinetics of the drugs at all, because those "would be quite different." *See id*. 14:21-15:3.

4. Petitioners' Multiplication Approach Is Especially Implausible With Respect to Claims 4 and 5.

Claims 4 and 5 recite application of the inventors' method of treatment in two particular groups of patients: those who are "TNF-inhibitor-inadequate responder[s]," and those who are "methotrexate (MTX) naïve or ha[ve] discontinued MTX." Ex. 1001 ('264 Patent) at 59. Petitioners insist that Grounds 1 and 3 in the '01542 proceeding that the POSA reading *NCT00965653* would

---

functional differences curtail the aggregation and immunogenicity concerns associated with highly concentrated *antibody* formulations.

have been motivated to use the claimed method of treatment in these patient populations based on *Emery* and *Maini*. Neither reference supports that argument.

Emery and *Maini* disclose using IV tocilizumab administered on a weight-adjusted basis. As Dr. Silverman explains, subcutaneous dosing regimens like the one *NCT00965653* proposes to test were considered riskier than the IV regimens utilized in *Emery* and *Maini*, because the high concentrations required for subcutaneous administration and the injection beneath the skin were both factors thought to increase the risk of an immunogenic reaction, tissue damage, and formation of neutralizing anti-drug antibodies. Ex. 2044 (*Braun 1997*) at 3, 6); *see also* Ex. 1087 (*Lobo 2004*) at 9; Ex. 2047 (*Ponce 2005*) at 2 (highly concentrated proteins can result in protein aggregation, which "ha[d] been associated with increased immunogenicity for a number of decades"); Ex. 2045 (*Stas 2010*) at 5 ("Aggregate and immune-complex formation are major drivers of an immune response and hence immunogenicity.").

Dr. Silverman explains that immunogenicity would have been an especially important concern for the POSA developing a method of treating RA using tocilizumab—an antibody for which there was no published safety data when administered subcutaneously. As of the priority date, "immunogenicity [was] not well understood, and the immunogenicity of a therapeutic protein [could] not be reliably predicted." Ex. 1087 (*Lobo 2004*) at 9. "Humanized antibodies" like

tocilizumab were developed to avoid the severe immunogenic reactions that could be triggered by chimeric antibodies. However, humanized antibodies were still known to potentially cause significant immunogenicity levels. Tocilizumab, like other humanized antibodies, had been reported to induce "anti-tocilizumab antibodies" in certain patients, sometimes causing "hypersensitivity reactions leading to withdrawal." Ex. 1015 (*Smolen 2008*) at 9. When used in "inflammatory and autoimmune disease" like RA, these antibodies were typically more immunogenic than when used in other indications like cancer. Ex. 2045 (*Stas 2010*) at 4, 8.

A patient's inadequate response to TNF-α inhibitors and MTX would further complicate the analysis given these patients' poor overall prognosis, long disease duration, previously failed multiple RA therapies, and propensity to serious infections and comorbidities. *Emery* notes that RA patients' refractory to TNFα inhibitors (TNF-IR) often have a "long disease duration" (averaging 11-12 years) and may "switch[] between anti-TNF treatments" due to inadequate response—in some cases, to three or more TNFα inhibitors. Ex. 1014 at 3, Table 1. Likewise, in *Maini*'s clinical study, patients had previously received at least "1-3 different DMARDs" (some "more than 5 different DMARDs"), and "[f]ifty patients had received TNF inhibitors (infliximab or etanercept) prior to study enrollment." Ex. 1025 (*Maini*) at 6. As Dr. Silverman explains, these patients' inadequate response

to RA biologics, and the attendant difficulty in treating them, was known to be due in part to immunogenic reactions. Ex. 2055 (Silverman Decl.) ¶ 78-85.

To minimize immunogenicity risks, 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." Ex. 2044 (*Braun 1997*) at 6 (emphases added)). *NCT00965653* proposes the exact opposite. The POSA would understand it to advocate subcutaneous dosing, more frequently (weekly or every other week instead of monthly), and at a high concentration for all patients. For this reason, Dr. Silverman opines, the POSA would not have been motivated to administer *NCT00965653*'s subcutaneous dosing regimen to the TNF-IR and MTX-IR patients in *Emery* and *Maini*.

Even if motivated to try the claimed methods, moreover, the POSA would have had no reasonable expectation of success in "treating rheumatoid arthritis" in the claimed patient populations. Petitioners' argument to the contrary rests on their misguided construction of "treating" as "administering" and their contention that the preamble is not limiting. Pet. 18-20. As explained *supra*, a proper construction of these claims requires a reasonable expectation of *effectively* treating RA.

5. Claim 12 Is Not Obvious Even Under Petitioners' Multiplication Approach To Dosing.

Even if Petitioners' hindsight-driven "equivalen[cy]" arguments were correct as a general matter, Petitioners fail to establish that the POSA using that approach would have been motivated to invent, or a reasonable expectation of achieving, the methods in claim 12. That claim contain additional limitations requiring "inhibiting progression of structural joint damage" in an RA patient by administering 162 mg subcutaneous tocilizumab "every two weeks," "wherein structural joint damage at week 24 or week 48 is found to be inhibited." Ex. 1001 ('264 Patent) at 60.

NCT00965653 alone would not motivate the POSA to create or use this method. That reference does not disclose measuring any parameters necessary for assessing progression of structural joint damage (e.g., TSS, ES, and/or JSN), and instead, proposes evaluating "pharmacokinetics," "pharmacodynamic[s]," "safety," and "efficacy according to ACR and DAS-EULAR parameters" for at most 15 weeks. Ex. 1028 at 3-4.

Recognizing this hole in their obviousness case, Petitioners combine *NCT00965653* with *Nishimoto*. But *Nishimoto* does not supply the missing motivation. As Dr. Silverman explains, *Nishimoto* does not teach or suggests subcutaneous administration of tocilizumab, let alone at the claimed fixed dosage or frequency. Instead, *Nishimoto* reports inhibiting progression of structural joint damage by administering "tocilizumab monotherapy at *8 mg/kg* intravenously

every 4 weeks" (Ex. 1089 at 1). Under Petitioners' (erroneous) logic, this amount corresponds to the higher subcutaneous dosage of 162 mg *every week*. Pet. 3. Nowhere does *Nishimoto* disclose or even suggest that a *lower* 4 mg/kg IV dose—the IV dosage Dr. Zizic contends is equivalent to 162 mg subcutaneous every two weeks—would also be effective for inhibiting progression of structural joint damage at week 28 or 48. In fact, as Dr. Silverman notes, *Nishimoto* suggests even the 8 mg/kg dose could be insufficient; *Nishimoto* proposes that research investigate whether "combination with MTX would provide greater benefit." Ex. 1089 at 5. According to Petitioners' own logic, *NCT00965653* and *Nishimoto* would at most have motivated the POSA to administer 162 mg of subcutaneous tocilizumab *every week*, not every other week as recited in Claim 12.

Nor was there a reasonable expectation of success. Dr. Zizic cites *Kremer* (Ex. 1093), to argue that the POSA would have expected success with the lower 4 mg/kg dosage because it was known to inhibit progression of structural joint damage "to a similar extent as 8 mg/kg by week 52." Ex. 1002 at ¶187; Pet. 48. But Petitioners do not include *Kremer* in their proposed obviousness combination in Ground 7, so they cannot rely on it to supply any teachings missing from the two references they do cite (*NCT00965653* and *Nishimoto*). *See Sirona Dental Sys. GmbH v. Institut Straumann AG*, 892 F.3d 1349, 1356 (Fed. Cir. 2018).

Kremer does not help Petitioners anyway. As Dr. Silverman explains, when the entirety of *Kremer*'s data is considered, it would have pointed the POSA to the 8 mg/kg monthly IV dose, not the 4 mg/kg dose, in designing a subcutaneous dosing regimen. Specifically, *Kremer* explains that "treatment goals" for RA have "shifted towards achieving remission" and reports "significantly higher" remission rates with only the 8 mg/kg monthly IV dose. Ex. 1014 (*Kremer 2008*) at 7.

This reference also only discloses assessments of structural joint damage at baseline and week 52, not week 24 or 48 as recited in claim 12. Dr. Zizic acknowledges this omission but contends "there is no reason" not to expect inhibition of structural joint damage at week 48 "simply because it was only evaluated at week 52 in *Kremer*." Ex. 1002 at ¶187. But Dr. Zizic cites nothing to support this assertion. And it is contradicted by the testimony of Dr. Silverman, who explains that clinical improvements like inhibition of joint damage do not necessarily occur linearly. The POSA would therefore understand that results achieved after a year of treatment with tocilizumab would not automatically be present at earlier stages.

C. *Ohta 2010* Does Not Anticipate the Challenged Claims.

1. *Ohta 2010* Is Not § 102(a) Prior Art.

Ground 3 of the '01288 proceeding and Ground 5 of the '01542 proceeding both rely on *Ohta 2010*, a reference that the Examiner determined during

prosecution was not § 102(a) prior art. Although the Board in its Institution Decisions did not decide the prior art status of *Ohta 2010*, it noted that the evidence Patent Owners submitted to remove *Ohta 2010* as prior art "tends to support its argument that *Ohta 2010* is not prior art." '01288 Decision at 40-41. That unchallenged evidence continues to establish that the subcutaneous dosing regimen disclosed in this reference came from the inventors of the '264 patent, and was invented by them prior to *Ohta*'s purported September 2010 publication date.

A reference is not prior art under 35 U.S.C. § 102(a) "unless it is describing the work of another." *In re Katz*, 687 F.2d 450, 454 (C.C.P.A. 1982). An inventor's "own work is not prior art . . . even though it has been disclosed to the public in a manner or form which would otherwise fall under [§] 102(a)." *Id.*

A reference also is not prior art under 35 U.S.C. § 102(a) if the patentee shows either (1) prior actual reduction to practice of the claimed invention, or (2) prior conception of the claimed invention and diligence to an actual or constructive reduction to practice through the filing of a patent application. *FreeBit AS v. Bose Corp.*, IPR2017-01307, Paper 8, at 20 (P.T.A.B. Nov. 14, 2017); *see also In re Steed*, 802 F.3d 1311, 1316 (Fed. Cir. 2015). To demonstrate an actual reduction to practice, the inventors must have: (1) constructed an embodiment or performed a process that met all the limitations of the claim and (2) determined that the invention would work for its intended purpose. *In re Steed*, 802 F.3d at 1318.

Here, the record is conclusive that the allegedly anticipatory matter in *Ohta 2010*—its disclosure of subcutaneously administering a 162 mg fixed dose of tocilizumab every week or every other week to RA patients—was invented by Mr. Terao, a co-author of *Ohta 2010* and co-inventor of the '264 patent, in collaboration with another '264 patent co-inventor, Dr. Amy Zhang. The record further establishes that Mr. Terao and Dr. Zhang made their invention prior to October 2010. These facts are established by declarations from Mr. Terao (Ex, 2005; Ex. 2051), Dr. Zhang (Ex. 2007), and two corroborating witnesses, Ms. Eriko Tarumi (Ex. 2052) and Mr. Masayuki Nishiyama (Ex. 2006). These declarations are supported by internal Chugai documents detailing the scope and timing of the inventors' work. Ex. 2001, 2002, 2003, 2004.

This evidence, which Patent Owners summarized in their Preliminary Responses, establishes (i) that none of the non-inventor co-authors of *Ohta 2010* made an inventive contribution to the disclosed subcutaneous dosing regimen, and (ii) that Mr. Terao's and Dr. Zhang's inventions were conceived of and reduced to practice before the publication of *Ohta 2010*. *Ohta 2010* is therefore removed as prior art to all that challenged claims, and Petitioners' grounds relying on *Ohta 2010* fail.

2. *Ohta 2010* Does Not Enable the Claimed Subcutaneous Dosing Regimen.

Ohta 2010 neither discloses nor otherwise provides any guidance on how to make the 162 mg fixed dose subcutaneous tocilizumab formulation necessary to practice the claimed methods. Ex. 2057 (*Little Decl.*) ¶50. Therefore, like *NCT00965653*, even were it prior art, *Ohta 2010* it does not enable the claimed invention and therefore cannot anticipate it. *See supra*.

D. *Ohta 2010* Does Not Render Any of the Challenged Claims Obvious.

Petitioners' obviousness arguments in Ground 4 of the '01288 proceeding, and Grounds 2, 4, and 6 of the '01542 proceeding, also depend on *Ohta 2010*, and likewise fail. The most serious problem is that *Ohta 2010* is not prior art. *See supra*. But even if it were, *Ohta 2010*, whether in combination with *Emery*, *Maini*, or *Nishimoto*, would not have provided the POSA with a reasonable expectation of success in creating the claimed dosing regimen because none of these references enables the creation of a subcutaneous formulation of tocilizumab. *See supra*.

E. Petitioners' Other Obviousness Combinations Fail.

Petitioners argue that combining *Bonilla* and *Wang 2009* with *Emery* ('01542 Ground 8), *Maini* ('01288 Ground 5, '01542 Ground 9), and *Maini* and *Nishimoto* ('01542 Ground 10) renders claims 4, 5, and 12 obvious. But these proposed combinations also fail to raise a reasonable likelihood that the challenged

claims are invalid. Ex. 2055 (*Silverman Decl*.) ¶¶96-97; Ex. 2057 (*Little Decl*.) ¶¶ 54-55.

Emery, *Maini*, and *Nishimoto* each disclose the use of intravenous, weight-based dosing for tocilizumab. To show a reasonable expectation of success in Grounds 8, 9, and 10, Petitioners argue again that the POSA would have performed a weight-times-IV-dosage calculation *Bonilla* never actually teaches and *Wang* does not support. That argument is meritless for the reasons discussed above, *see supra*.

Petitioners also never credibly explain how their invented weight-times-IV-dosage approach would have led to the precise (162 mg) subcutaneous dosage claimed. They admit that their own calculations produce a range of fixed doses from 140 mg to 195 mg. Pet. 53. In fact, the range of potential dosing options is far broader than Petitioners posit. Multiple studies had shown that IV tocilizumab was safe and effective when dosed from 4 mg/kg to 8 mg/kg every four weeks. Using Petitioners' own rule of thumb—that subcutaneous dosages could be derived by multiplying intravenous dosages by bodyweight—the potential subcutaneous dosage could range from as little as 70 mg to as much as 389 mg, depending on

whether dosing occurs weekly or every other week.[13] As explained above, *see supra*, there is no reason why the POSA would have limited herself in this manner.

Although the Institution Decision acknowledged Petitioners' calculations produce a broad range of potential doses, '01288 Decision at 38, the Board concluded that there was a presumption of obviousness because the claimed 162 mg dose fell within that range. *Id.* Patent Owners respectfully submit this conclusion misapprehends the case law. The Federal Circuit has repeatedly held that a prima facie case of obviousness only exists "when the ranges of a claimed composition overlap the ranges *disclosed* in the prior art." *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003) (emphasis added). Under this standard, the prior art must actually disclose the range purportedly rendering the claims obvious. *See Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013) (noting that burden of production shifts to patentee "where there is a range *disclosed* in the prior art, and the claimed invention falls within that range") (emphasis added);

[13] 70 kg x (4 mg/kg every four weeks) = 280 mg every four weeks, or 70 mg every week. 70 kg x (8 mg/kg every four weeks) = 560 mg every four weeks, or 280 mg every two weeks. Adjusting 280 mg to account for differences in bioavailability between intravenous and subcutaneous dosing using Petitioners' assumed 72% bioavailability results in an upper limit of 389 mg (280/0.72 = 389).

Ormco Corp. v. Align Tech., Inc., 463 F.3d 1299, 1311 (Fed. Cir. 2006) ("Where a claimed range overlaps with a range *disclosed* in the prior art, there is a presumption of obviousness.") (emphasis added).

Here, Petitioners never point to an actual, express disclosure of an overlapping range in the prior. Rather, Petitioners contend—incorrectly—that an overlapping range "can be derived or calculated from the disclosures of the prior art." *ModernaTx, Inc. v. Arbutus Biopharma Corp.*, 18 F.4th 1364, 1373 (Fed. Cir. 2021). The Federal Circuit "ha[s] never before applied the presumption of obviousness for overlapping ranges in a case in which the prior art does not contain an express disclosure of a range." *Id.*; *see also Moderna Therapeutics, Inc. v. Arbutus Biopharma Corp.*, No. IPR2019-00554, 2020 WL 4237232, at *12 (P.T.A.B. July 23, 2020) ("[T]he Federal Circuit has only applied the presumption where the overlapping range is expressly disclosed, not where an overlap might be assumed based on other motivating factors."). The Board should not break new ground with this case.

Even if the presumption of obviousness applied, Patent Owners have rebutted it. As discussed above, *supra*, and in the declaration of Dr. Little, the prior art taught that there was a concentration limit of 100 mg/ml for subcutaneously administered antibodies. The prior art thus taught away from the claimed invention, which requires a concentration well above the threshold the

POSA would have thought achievable. Rather than attempt to create an ultra-high concentration formulation, the POSA would have at most been motivated to experiment with the lower end of Petitioners' supposed range (beginning at 70 mg).

F. The Every-Other Week Dosing Regimen Exhibits Unexpected Properties.

Real-world evidence further demonstrates the patentability of the inventors' work. As detailed in the declarations of Dr. Samara and Dr. Silverman, the prior art and fundamental PK principles would have suggested to the POSA that high concentrations of tocilizumab were necessary in order to effectively treat RA patients. Ex. 2056 (*Samara Decl.*) ¶¶85-90; Ex. 2055 (*Silverman Decl.*) ¶¶98-103 []. Specifically, the POSA would have understood the closest prior art, the *Maini 2006* and *Nishimoto 2007* references, to teach that the 8 mg/kg IV dose of tocilizumab showed superior efficacy compared to doses of 4 mg/kg and 2 mg/kg. Ex. 2056 (*Samara Decl.*) ¶¶88-89; Ex. 2055 (*Silverman Decl.*) ¶¶100-101. The POSA would have expected higher doses of tocilizumab to be necessary in subcutaneous dosing as well, given that the amount of drug patients are exposed to is limited by absorption and bioavailability, considerations not at play in IV administration. Ex. 2056 (*Samara Decl.*) ¶90; Ex. 2055 (*Silverman Decl.*) ¶102.

Surprisingly, however, the inventors of the '264 Patent discovered that for subcutaneously administered tocilizumab, effective treatment could be achieved

using 162 mg of tocilizumab administered weekly *or* every other week. This latter insight is reflected in claims 9 and 12, both of which specifically require that tocilizumab be administered every two weeks. The inventors' finding is unexpected because, as Drs. Samara and Silverman explain, under Dr. Zizic's approach, the 162 mg every-other-week regimen would provide patients with far less tocilizumab than they would receive using the 8 mg/kg IV treatment regimen. Ex. 2056 (*Samara Decl.*) ¶90; Ex. 2055 (*Silverman Decl.*) ¶102.

The unexpected nature of the improvement over the prior art is particularly notable with respect to claim 12. Ex. 2055 (*Silverman Decl.*) ¶¶102-103. As Figure 3 of the patent demonstrates, the 162 mg SC dose administered every two weeks changed patients' DAS28 score from baseline more effectively than the 8 mg/kg IV dose at 8 weeks. This effect, and the inhibition of structural joint damage disclosed and claimed in claim 12, is confirmed by post-priority publications from tocilizumab clinical trials. Ex. 1086 at 30-31; Ex. 2069(*Kivitz 2013*).

The inventors' ability to develop an efficacious, one-size-fits-all method of treating RA thus underscores the value of the invention. Considering this evidence of non-obviousness is "crucial in avoiding the trap of hindsight," *Leo Pharm. Prods., Ltd., v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013) (internal quotation omitted), a trap into which Petitioner repeatedly falls.

VII. CONCLUSION

For the reasons set forth above Patent Owner respectfully submits that the Board should confirm the patentability of all challenged claims.

May 24, 2022

/*Thomas S. Fletcher*/

Thomas S. Fletcher (Reg. No. 72,383)
Paul B. Gaffney (*pro hac vice*)
Ana C. Reyes (*pro hac vice*)
Charles L. McCloud (*pro hac vice*)
Angela X. Gao (*pro hac vice*)
WILLIAMS & CONNOLLY LLP
680 Maine Ave. SW
Washington, DC 20024
202-434-5000 (Telephone)
202-434-5029 (Facsimile)

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), the undersigned hereby certifies that a true and correct copy of the foregoing was served on May 24, 2022, by delivering a copy via electronic mail on the following counsel of record for Petitioners:

Elizabeth J. Holland (Reg. No. 47,657)
Daniel P. Margolis
ALLEN & OVERY LLP
1221 Avenue of the Americas
New York, NY 10020
Telephone: (212) 610 6300
Elizabeth.Holland@allenovery.com
Daniel.Margolis@ allenovery.com

May 24, 2022

/Thomas S. Fletcher/
Thomas S. Fletcher (Reg. No. 72,383)

CERTIFICATE OF WORD COUNT

Pursuant to 37 C.F.R. § 42.24(d), the undersigned hereby certifies that the foregoing Patent Owners' Response complies with the type-volume limits of 37 C.F.R. § 42.24(b) because it contains 13,933 words (as calculated by the word processing system used to prepare this document), excluding the parts of the document exempted by 37 C.F.R. § 42.24.

May 24, 2022 /*Thomas S. Fletcher*/
Thomas S. Fletcher (Reg. No. 72,383)