UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC.,
Petitioner,

v.

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

IPR2022-00579
Patent No. 10,874,677

PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 10,874,677

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I. INTRODUCTION

Pursuant to the provisions of 35 U.S.C. § 311 and § 6 of the Leahy-Smith America Invents Act ("AIA"), and to 37 C.F.R. Part 42, Celltrion, Inc. ("Petitioner") hereby requests review of claims 1-8 of United States Patent No. 10,874,677 to Zhang et al. (hereinafter "the '677 patent," EX1001) that issued on December 29, 2020, and is assigned to Chugai Seiyaku Kabushiki Kaisa ("Chugai"), Genentech, Inc. ("Genentech"), and Hoffman-La Roche, Inc. ("Roche"; collectively, "Patent Owner").

Had Patent Owner been fully candid with the Examiner about its own prior-art publications, the '677 patent never would have issued. The independent claims are directed to an "article of manufacture" comprising a "subcutaneous administration device" filled with "a 162 mg fixed dose of tocilizumab." But NCT00965653 ("*NCT '653*") (EX1004), a clinical trial protocol sponsored by the Patent Owner and published more than one year before the priority filing date, disclosed the use of a "subcutaneous administration device" to deliver a 162 mg fixed dose of tocilizumab to rheumatoid arthritis ("RA") patients. And WO2009/084659 (*Morichika*) (EX1110), a PCT application assigned to Patent Owner and published more than one year before the earliest filing date, disclosed a formulation of tocilizumab for use in pre-filled syringes, autoinjectors and other devices used for administering biologics subcutaneously. In fact, this was the

same formulation of tocilizumab used by Patent Owner in its own clinical trials of subcutaneous tocilizumab. There can be no reasonable dispute that *NCT '653* anticipates the independent claims, and that *Morichika* enabled those of ordinary skill to practice those claims with little or no experimentation.

The dependent claims limit the "subcutaneous administration device" to, *e.g.*, pre-filled syringes or autoinjectors, which were entirely conventional and obvious choices given their widespread use for subcutaneous biologic products. A skilled person would have been motivated to choose pre-filled syringes and autoinjectors for use with the 162 mg fixed dose of *NCT '653* because they permit a patient to easily self-administer biologics such as tocilizumab at home, which is both more convenient and less costly than having to travel to a clinic for an injection, and was known to improve patient compliance. *Kivitz* (EX1050) is one prior-art publication among many that disclosed these advantages. The person of ordinary skill in the art ("POSA") would have been confident of success in filling a pre-filled syringe or autoinjector with a 162 mg dose of tocilizumab given the recipe and guidance in *Morichika.*

In light of this anticipating and obviating prior art, Petitioner respectfully submits it has demonstrated at least a reasonable likelihood that the claims are unpatentable, and thus requests institution of *inter partes* review.

A. Brief Overview of the ’677 Patent

The ’677 patent, entitled “Subcutaneously Administered Anti-IL-6 Receptor Antibody,” issued on December 29, 2020 from U.S. Patent Application No. 16/254,105, which was filed on January 22, 2019. The earliest effective filing date that can be claimed by Patent Owner is November 8, 2010. The ’677 patent discloses “formulations and devices useful for subcutaneous administration of an anti-IL-6R antibody,” noting that tocilizumab is an anti-IL-6R antibody that had been approved for IV administration for the treatment of RA at a dose of both 4mg/kg and 8mg/kg every four weeks. EX1001, 1:38-40, 2:34-38. The ’677 patent defines one aspect of its invention as an article of manufacture comprising a “subcutaneous delivery device” and a fixed dose of an anti-IL-6R antibody, such as tocilizumab, wherein the fixed dose is, *inter alia*, 162 mg. *Id.*, 4:65-5:3. As taught by the ’677 patent:

> A “subcutaneous administration device” refers to a device, such as syringe, injection device, infusion pump, injector pen, needleless device, patch delivery system, etc, which is adapted or designed to administer a drug or pharmaceutical formulation by the subcutaneous route. In one embodiment, the device administers about 0.9 mL, 1.8 mL, or 3.6 mL of a pharmaceutical formulation.

Id., 20:7-13.

Independent claim 1 is representative, and reads as follows:

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

B. Brief Overview of the Scope and Content of the Prior Art

As explained below and in the accompanying Declarations of Dr. Maarten Boers (EX1034), Dr. Dhaval Shah (EX1032), and Dr. Paul Dalby (EX1036), the use of tocilizumab to treat patients was not new as of November 8, 2009, one year prior to the earliest priority date. Tocilizumab had already been approved in Europe and Japan as an intravenous therapy for RA, and its effectiveness when dosed at 4 mg/kg or 8 mg/kg every 4 weeks had been well established by clinical trials. *See generally* EX1034 ¶54-61; EX1032 ¶¶107-108, 112.

The 162 mg subcutaneous fixed dose of the claims also was not new. ClinicalTrials.gov had published Patent Owner's own clinical trial protocol, in which a fixed dose of 162 mg of tocilizumab was administered subcutaneously to RA patients once-weekly or once every other week. EX1034 ¶73-77; EX1004, 6.

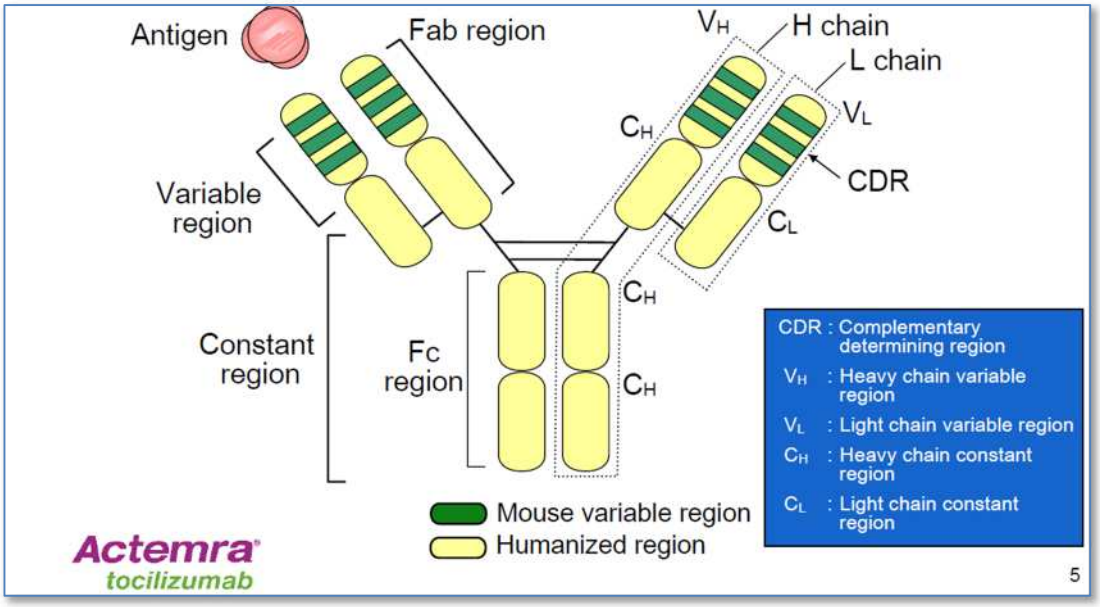
The use of pre-filled syringes and autoinjectors to permit patients to self-administer biologics like tocilizumab was also conventional, as is clear from the fact that other approved biologics had been marketed in these formats prior to November 8, 2009. Patent Owner had also published the tocilizumab formulation

it ultimately used to fill its own pre-filled syringes and autoinjectors during clinical trials that led to the approval of subcutaneous Actemra®, which provided skilled practitioners with a ready-made recipe to do the same. EX1034 ¶78-81; *see also* EX1036 ¶31-37.

1. Background: IV Tocilizumab

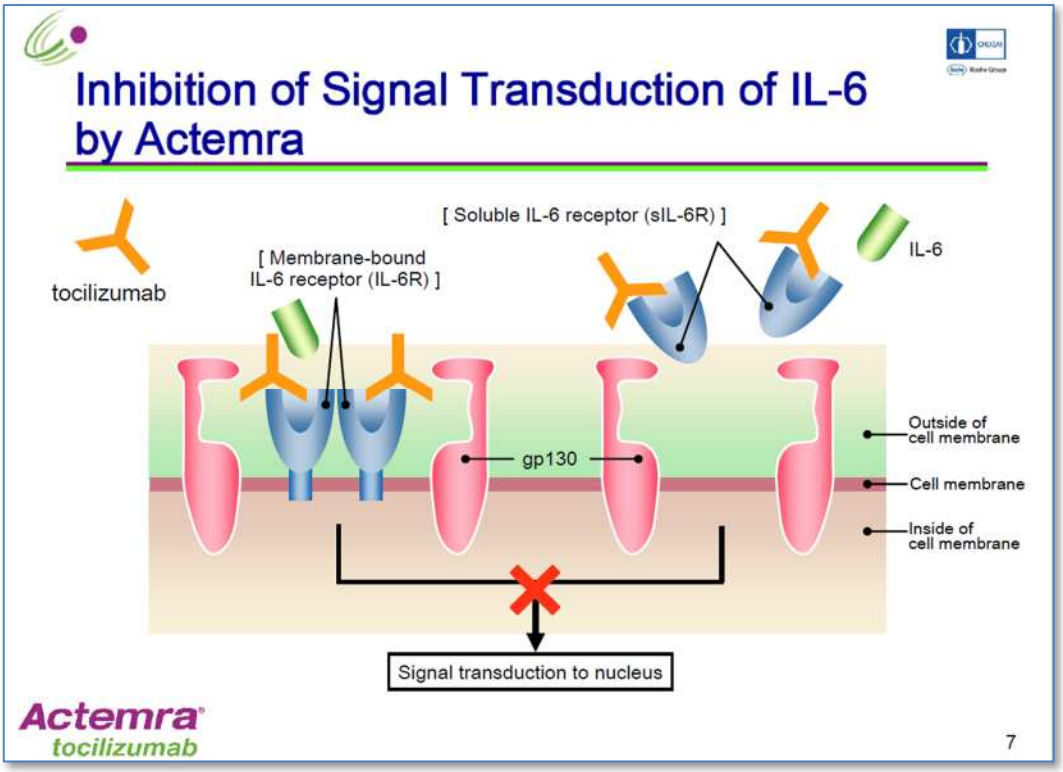
RA is a chronic, immune-mediated, systemic disease characterized by inflammation that causes pain, swelling and progressive destruction of the joints of the hands and feet. EX1034 ¶50. By the mid-1990s, methotrexate ("MTX") had become the most commonly-used disease-modifying antirheumatic drug ("DMARDs") for treating RA, yet many patients did not adequately respond to MTX alone. *Id.* ¶51; EX1037, 88; EX1038, 36. Accordingly, new drugs were sought that could be used to treat RA patients who had an inadequate response to MTX. EX1034 ¶51.

Tocilizumab, also known as MRA, is marketed by Patent Owner in the U.S. under the trade name Actemra. Tocilizumab is a humanized mAb of the IgG1 *kappa* subclass that binds to the IL-6 receptor ("IL-6R"). EX1040, 3; EX1032 ¶130; EX1034 ¶52. It has two heavy chains (of the IgG1 subtype) and two light chains (of the *kappa* subtype) forming two antigen-binding sites. EX1032 ¶¶130-31; EX1034 ¶52. As shown below, the light and heavy chains both include a constant region (shown as C_H and C_L), and variable regions (shown as V_H and V_L):



EX1041, 5.

Chronic overproduction of IL-6, a "cytokine" signaling protein, and its interaction with its receptor, IL- 6R, which is expressed on cells of the immune system, causes the chronic inflammation associated with RA. EX1034 ¶53. Although originally intended as a treatment for multiple myeloma, Chugai repurposed tocilizumab for the treatment of RA based on its ability to block the action of IL-6, which was known to be involved in the pathogenesis of RA. *Id.*; EX1042, 42-43. IL-6 binds to both soluble and membrane-bound IL-6 receptors. EX1041, 8. Upon binding IL-6, these receptors signal cells of the immune system to initiate an inflammatory response. *Id.*, 7. As shown below, tocilizumab works by binding to the IL-6 receptors, which blocks the receptors from binding IL-6 and issuing the signal that initiates the damaging inflammation associated with RA:



Id., 8; EX1034 ¶53.

By November 8, 2009, several clinical trials had been completed that confirmed that tocilizumab was a safe and effective treatment for RA. EX1034 ¶¶54-58. *Maini 2006* demonstrated that tocilizumab was safe and effective for treating RA when administered intravenously at a dose of either 4 mg/kg or 8 mg/kg every four weeks in patients who had discontinued MTX. EX1040, 2817-18, 2825-26. The SAMURAI study, published in 2007, showed that 8 mg/kg intravenous "tocilizumab monotherapy in patients with active RA significantly inhibited the progression of structural joint damage compared with conventional DMARDs therapy." EX1026, 1166. The LITHE study, published in 2008, demonstrated that both 4 mg/kg and 8 mg/kg tocilizumab administered

intravenously every four weeks "significantly inhibited the progression of structural joint damage." EX1028, 1; EX1029, 516. The RADIATE study, published in 2008, showed that both 8 mg/kg and 4 mg/kg tocilizumab every four weeks, in combination with MTX, was effective in RA in patients who had inadequately responded to TNF antagonists. EX1034 ¶56; EX1043, 1518-19.

Tocilizumab for IV administration was approved in Japan in 2008, and in Europe in January 2009, for the treatment of RA in patients who had never been treated with DMARDs such as MTX or TNF antagonists, or who had had an inadequate response to MTX (or other DMARDs) or TNF antagonists. EX1024, 2-4; EX1044, 124; EX1006[1], 30. On January 8, 2010, the U.S. Food and Drug Administration ("FDA") approved IV tocilizumab for the treatment of RA. EX1045, 1; EX1046, 2, 25; EX1001, 2:34-38 ("TCZ 8 mg/kg IV has been approved in over 70 countries for use in RA, including Japan and Europe. In the United States, TCZ IV (4 mg/kg and 8 mg/kg) has been approved in RA patients who have had an inadequate response to anti-TNF agents."). FDA has also approved a subcutaneous formulation of Actemra for the treatment of RA as a monotherapy or in combination with MTX or other DMARDs in adult patients "with moderately to severely active rheumatoid arthritis who have had an

[1] Citations to this exhibit are to the stamped page numbers.

inadequate response to one or more [DMARDs]." EX1116, 1. This subcutaneous formulation contains a fixed dose of 162 mg of tocilizumab in a pre-filled syringe or autoinjector and is administered weekly or every other week. *Id.*, 1, 45-65.

2. Background: Subcutaneous Tocilizumab

While pursuing approval of IV tocilizumab, Patent Owner started development of a subcutaneous ("SC") version of the product. *See* EX1001, Table 1. It was well known in the prior art that SC administration provides significant commercial and therapeutic benefits over IV administration. EX1034 ¶62-64.

SC administration of drugs and biologics, which a patient can perform at home using a pre-filled syringe or autoinjector, is generally faster, more convenient and less expensive than IV administration, which must be performed in a hospital or clinic by trained medical professionals. *Id.*; EX1048, 787-88; EX1049, 265-66. This convenience is not merely a time or cost saver, but also contributes to better patient outcomes because a patient is more likely to adhere to a full course of the prescribed treatment. As one commentator noted, there are "several advantages [over IV dosing] that promote adherence to therapy":

> These agents are portable, allowing patients to self-administer the drug in the setting they choose, rather than mandating a clinic or hospital setting. Similarly, these agents can be administered at the patient's convenience rather than requiring an appointment for

> treatment. Finally, self-administered medications may reduce costs for patients and providers (e.g., travel-related costs and office visit-related costs) compared with the costs of intravenous medications.

EX1050, 110. This added convenience is particularly important to patients who suffer from a chronic disease like RA, since otherwise those patients must repeatedly travel to a clinic for the rest of their lives. The same holds true for chronic disease sufferers with poor venous access who struggle with a lifetime of repeated IV infusions. *See* EX1049, 265; *see also* EX1048, 779 (SC therapies important for patients with "primary immune deficiency diseases (PIDD) and poor tolerance of intramuscular (IM) injections or the newly developed IV preparations").

Beyond compliance, SC administration can contribute to better patient outcomes by maintaining a more consistent blood plasma level of the drug or biologic. Because they can be self-administered, SC therapies may be administered more frequently and in lower doses than IV versions. Lower, more frequent dosing prevents mean peak concentrations from spiking and producing side effects, and mean trough concentrations from dropping below the threshold of efficacy and allowing breakthrough disease. EX1048, 787-88; EX1049, 266; EX1034 ¶62.

Moreover, a *fixed* SC dose was generally considered preferable for antibodies over "mg/kg" dosing that had to be adjusted for each patient based on body weight, since fixed dosing provides "better compliance, less risk of medical errors, and cost-effectiveness." EX1052, 1012, 1023; EX1034 ¶64.

Because of their myriad advantages, there were at least four fixed-dose, SC biologics approved by FDA as of 2009, including two antibodies: Humira® (adalimumab), and Simponi® (golimumab). Humira® (adalimumab), was approved by the FDA in 2002 for the treatment of RA at a subcutaneous fixed dose of 40 mg every other week. EX1034¶66-67; EX1055, 7, 14, 16; EX1056, 5; EX1006, 21. And Simponi® (golimumab), was approved by the FDA in April 2009 for the treatment of RA, among other indications, at a subcutaneous fixed dose of 50 mg monthly. EX1058, 1; EX1059, 422; EX1015, 1, 4. The other approved biologics were Enbrel® (etanercept), approved by FDA in 1998 for treatment of RA with a subcutaneous fixed dose of 25 mg twice weekly and Cimzia® (certolizumab pegol), approved by the FDA in 2008 for treatment of Crohn's disease at a subcutaneous fixed dose of 400 mg weekly, and for RA in 2009 at 400 mg subcutaneously initially, followed by 200 mg every other week. EX1053, 441; EX1054, 141; EX1057, 3127-28; EX1111, 1.

3. Petitioner's Prior Art

The prior art Petitioner relies upon to challenge the claims in this petition is briefly described below.

a. NCT '653 (EX1004)

NCT '653 (EX1004) is a clinical trial protocol, entitled "A Study of Subcutaneously Administered Tocilizumab in Patients With Rheumatoid Arthritis." It was posted to ClinicalTrials.gov in August 2009 and thus is prior art under pre-AIA § 102(b). *NCT '653* was listed on an Information Disclosure Statement (IDS), but was not relied upon or cited by the examiner during prosecution of the '677 patent.

The "Brief Summary" section of *NCT '653* describes the clinical trial as follows: "This open-label randomized 2 arm study will investigate the pharmacokinetics, pharmacodynamics, efficacy and safety of subcutaneously administered tocilizumab in patients with rheumatoid arthritis who have shown an inadequate response to methotrexate. Patients will be randomized to receive tocilizumab 162 mg sc [subcutaneously] either weekly or every other week, in combination with methotrexate, for 12 weeks. Assessments will be made at regular intervals during treatment and on the 3 weeks of follow-up. Target sample size is <50 individuals." *Id.*, 6.

The "Arms and Interventions" section of *NCT '653* (*Id.*, 7) describes the 162 mg sc weekly and 162 mg sc every-other-week dosage regimens as follows:

▼ **Arms and Interventions**

Arms	Assigned Interventions
Experimental: 1	Drug: tocilizumab 162 mg sc weekly (QW)for 12 weeks Drug: methotrexate 7.5 - 25 mg weekly (oral or parenteral) Drug: folic acid >/= 5 mg po weekly
Active Comparator: 2	Drug: tocilizumab 162 mg sc every other week (Q2W) for 11 weeks Drug: methotrexate 7.5 - 25 mg weekly (oral or parenteral) Drug: folic acid >/= 5 mg po weekly

b. Morichika (EX1110)

WO2009/084659 ("*Morichika*") (EX1110) is a PCT application assigned to Chugai and Roche that was published on July 9, 2009, and is thus prior art under pre-AIA 35 U.S.C. §102(b). *Morichika* was not before the examiner during prosecution, nor did Fresenius cite it in IPR2021-01336 (the '1336 petition), challenging claims 1-8 of the '267 patent. It is entitled "Solution preparation containing antibody at high concentration," and discloses a high-concentration formulation of tocilizumab (referred to as "MRA" in the reference). *See generally id*. The specification of *Morichika* explains that "the formulation according to the present invention is especially suited for subcutaneous injection, (EX1110, [0053];

see also EX1115[2], 308, [0053]), and that the formulation most preferably contains the following ingredients:

a. "150 to 200 mg/mL" antibody (EX1110, [0015]; *see also* EX1115, 287, [0015)

b. "the arginine concentration is 100 to 300 mM, and the amount of methionine is 10 to 50 mM" (EX1110, [0035]; *see also* EX1115, 304, [0035])

c. "[a] histidine buffer is particularly preferred" and most preferably at a concentration of "10-20 mM" (EX1110, [0036] , *see also* EX1115, 304-305, [0036])

[2] EX1115 is a copy of portions of the prosecution history for U.S. Application No. 12/810,938, the U.S. national-phase counterpart to the *Morichika* application. Roche and Chugai submitted an English-language translation of the specification to the U.S. Patent & Trademark Office as part of this application. EX1115, 285-321. Petitioner has included citations to both Petitioner's certified translation of the original *Morichika* reference as well as the specification for U.S. Application No. 12/810,938, which is relied upon by Patent Owner. These translations include minor differences in word choice.

d. "most preferred" surfactants are polysorbates 20 and 80, and Pluronic F-68 (Poloxamer 188) and most preferably at a concentration of "0.005-3%." (EX1110, [0040]-[0041]; *see also* EX1115, 306, [0040]-[0041]).

The specification discloses examples of formulations of tocilizumab that were tested for stability. Formulation A8 in Table 1-1, which also appears as A26 in Table 3-1, was shown to be among the most stable (*see* EX1110, Table 1-3 and [0062]-[0070]; *see also* EX1115, 309-312, Table 1-3 and [0062]-[0070]), indicating low percentages of dimer ("Dimer (%")) and low-molecular weight degradation products (LMW (%)) after accelerated (40º C) and room-temperature (25º C) storage; *see also* EX1110, [0068] and [0086] and EX1115, 311 [0068], 318 [0086], noting that these results "suggest[] that the combination of arginine and methionine has a synergistic effect on the inhibition of dimer formation."). Formulation A8/A26 contains essentially the same ingredients as the clinical trial formulations of SC Actemra in Table 2 of the '677 patent specification:

a. 180 mg/mL tocilizumab
b. 100 mM arginine
c. 30 mM methionine
d. 0.5 mg/mL Polysorbate 80
e. 20 mM histidine buffer

f. pH 6.0

The A8/A26 formulation differs from the Table 2 formulation only in that it contains a slightly higher amount of Polysorbate 80: 0.5 mg/mL versus 0.2 mg/mL.

The specification acknowledges that antibodies can be concentrated via lyophilization and reconstitution into a smaller volume, but that the formulations of the patent are more efficiently manufactured because they avoid this reconstitution step:

> A highly concentrated antibody-containing preparation is provided that does not require reconstitution by lyophilization and does not require redissolution. The highly concentrated antibody-containing preparation of the present invention can be stably stored in solution for a long period of time and can be manufactured without a lyophilization step in the manufacturing process, thus addition of a sugar or the like as a cryoprotectant agent is not necessary.

EX1110, [0010]; *see also* EX1115, 296, [0010].

The U.S. national-phase counterpart to the *Morichika* application issued as U.S. Patent 8,568,720 (EX1112; "the '720 patent"). In this patent, Chugai and Roche claimed a "stable" formulation of tocilizumab ("MRA") containing the same ingredients as formulation A8/26:

> **1**. A stable liquid formulation suitable for subcutaneous administration comprising 180 mg/mL humanized anti-IL-6 receptor IgG1 antibody, 100 mM arginine, 10 to 50 mM methionine, further comprising 0.005 to 3% polysorbate 80 and 20 mM histidine buffer, said formulation having a pH of 6.
>
> **2**. The stable liquid formulation of claim **1** wherein the antibody comprises the humanized anti-IL-6 receptor IgG1 antibody MRA.

c. Kivitz (EX1050)

Kivitz was published in the journal Expert Review of Medical Devices in 2007 and is prior art under pre-AIA § 102(b). It was not before the examiner during prosecution.

Kivitz discloses that "[u]se of intravenous biological agents mandates administration by a healthcare professional in a clinical setting, whereas biological agents with a pharmacological composition that allows subcutaneous delivery can be administered at home by the patient or a caregiver." EX1050, 110. "Self-administered injectables offer several advantages over intravenous injections (i.e., portability, convenience and flexible scheduling). In particular, patients with chronic, debilitating diseases may need a self-administered medication available in an easy-to-use and convenient delivery device that minimizes pain and facilitates adherence to therapy." *Id.*, 109.

Kivitz further discloses that Humira® (adalimumab), Enbrel® (etanercept), and Kineret® (anakinra) were all available to patients in either an autoinjector pen

or pre-filled syringe for administration of a subcutaneous dose. *Id.*, 111. Although some patients preferred an autoinjector pen, "[t]o ensure the availability of options that meet the needs and preferences for all patients, both adalimumab and etanercept are still available in prefilled syringe." *Id*., 114. *Kivitz* further states that "[b]iological therapies delivered by autoinjector pens may quickly become the treatment of choice in RA and related diseases." *Id.*, 115.

C. Brief Overview of the Level of Skill in the Art

A POSA that would have typically developed subcutaneous dosage protocols and means for administering them would in fact have been a team of individuals possessing the different skill sets typically employed on such a project. That team would have included individuals skilled in the relevant area(s) of clinical medicine (e.g., rheumatologists), pharmacokineticists, formulators and project leads. These diversely-qualified individuals would have worked together as needed during development. EX1034 ¶48; EX1032, ¶27; EX1036, ¶¶25-26.

To the extent a different definition of POSA is adopted, that POSA would have had access to individuals skilled in clinical medicine, pharmacokinetics and formulation. EX1034, 49; EX1032, ¶27; EX1036, ¶27.

II. THE BOARD SHOULD DECLINE TO EXERCISE ITS DISCRETION TO DENY INSTITUTION

A. The Board Should Not Exercise Its Discretion Under Section 325(d) to Deny Institution

Patent Owner may urge the Board to deny institution because "the same or substantially the same prior art or arguments previously were presented to the Office." 35 U.S.C. § 325(d). As described below, however, this petition presents new arguments and art not before the Office, either during prosecution of the '677 patent or in the '1336 petition challenging the '677 patent filed by Fresenius Kabi USA, LLC and Fresenius Kabi Swissbiosim GmbH on August 18, 2021.

In determining whether to exercise its discretion to deny institution under § 325(d), the Board applies a two-part framework. *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6, 8 (Feb. 13, 2020), (precedential). The first part assesses "whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office." *Id.*, 8. "[I]f either condition of [the] first part of the framework is satisfied," the second part assesses "whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of [the] challenged claims." *Id.* The following factors help inform whether the first part of the framework is satisfied: "(a) the similarities and material differences between the asserted art and the prior art

involved during examination; (b) the cumulative nature of the asserted art and the prior art evaluated during examination; (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection; (d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art; (e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and (f) the extent to which additional evidence and facts presented in the petition warrant reconsideration of the prior art or arguments." *Id.*, 9-10; *see also Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8, 17-18 (Dec. 15, 2017) (precedential).

As discussed below, this petition presents art and arguments that are materially different than those presented to the Office during prosecution of the '677 patent and by Fresenius in the '1336 petition. Thus, the first part of the Board's two-part framework is not satisfied, and the second part need not be reached. The Board should decline to exercise its discretion under § 325(d).

During prosecution, the examiner cited *Ohta 2010* (EX1066) against the claims. EX1068, 181. In response, applicant filed a declaration under 37 C.F.R. §131 to antedate *Ohta 2010* as prior art. *Id.*, 257-273. The examiner found that the declaration was sufficient to remove *Ohta 2010* as a reference, and issued a

notice of allowability. *Id.*, 335-337, 340-341. The examiner did not cite any of *NCT '653*, *Morichika*, or *Kivitz* in any of the rejections.

This petition presents two grounds, the first relying primarily on *NCT '653*, and the second relying on a combination of *NCT '653*, *Morichika*, and *Kivitz*. Thus, factors (a), (b), and (c) favor institution. Except for *NCT '653*, none of the references relied upon were before the examiner. And while *NCT '653* was cited in an IDS as one of about 150 references, it was never cited by the examiner or used to reject the claims. *Id.*, 179-182, 236.

Factors (d) and (f) also favor institution, as there is no overlap between the arguments made during prosecution and this petition. The '1336 petition fails to cite *Morichika*. And while the '1336 petition relies on *NCT '653*, it relies on a different version than is relied upon in this petition. In addition, this petition is accompanied by the expert declarations of Drs. Shah, Boers, and Dalby, as well as Mr. Lassman. In particular, the declarations of Drs. Boers, Dalby and Shah present facts and analysis that were not presented during either prosecution or the '1336 petition. Finally, as this petition presents new art, declarations, and argument that were not before the examiner, and as the examiner failed to substantively apply *NCT '653*, factor (e) also supports institution.

B. The Board Should Not Exercise Its Discretion under Section 314(a) to Deny Institution[3]

Patent Owner may also urge the Board to exercise its discretion under § 314(a) to deny institution because this is the second petition filed requesting IPR of claims 1-8 of the '677 patent. When evaluating whether to deny institution of a "follow-on" petition, the Board generally looks to seven factors: (1) whether the same petitioner previously filed a petition directed to the same claims of the same patent; (2) whether at the time of filing of the first petition the petitioner knew of the prior art asserted in the second petition or should have known of it; (3) whether at the time of filing of the second petition the petitioner already received the patent owner's preliminary response to the first petition or received the Board's decision on whether to institute review in the first petition; (4) the length of time that elapsed between the time the petitioner learned of the prior art asserted in the second petition and the filing of the second petition; (5) whether the petitioner

[3] To the extent Patent Owner argues that the Board should exercise its discretion under *Fintiv* given future parallel district court proceedings, the *Fintiv* factors relate to whether a co-pending district court proceeding will finish before or close to the date the PTAB issues its final written decision. *See Apple v. Fintiv*, IPR2020-00019, Paper 11 (PTAB Mar. 20, 2020) (precedential). *Fintiv* is thus not applicable here.

provides adequate explanation for the time elapsed between the filings of multiple petitions directed to the same claims of the same patent; (6) the finite resources of the Board; and (7) the requirement under 35 U.S.C. § 316(a)(11) to issue a final determination not later than one year after the date on which the Director notices institution of review. *Gen. Plastic Indus. Co., Ltd. v. Canon Kabushiki Kaisha*, IPR2016-01357, Paper 19, 9-10 (Sept. 6, 2017) (precedential). As explained below, the *General Plastic* factors weigh heavily in favor of institution of the petition.

Factors (1) and (2) favor institution. This is the first petition filed by Celltrion against the '677 patent, and Celltrion was not a real-party-in-interest in the '1336 petition. And although both the '1336 petition and the instant petition rely on *NCT '653*, this petition relies on a different version of the reference, and adds the declarations of Drs. Shah, Boer, and Dalby, and Mr. Lassman. Notably, the '1336 petition fails to cite *Morichika*, which discloses tocilizumab formulations for subcutaneous administration. In addition, the declaration of Dr. Dalby presents opinions concerning *Morichika*, and Dr. Shah presents pharmacokinetic modeling, that were not presented in the'1336 petition.

Factors (3), (4), and (5) also favor institution. Celltrion had no say in the timing of the filing of the '1336 petition. And although this petition was filed after the patent owner preliminary response ("POPR"), the differences in the evidence

and arguments, such as *Morichika*, the Dalby declaration, and the Shah declaration, for which much of the data was generated before patent owner filed its POPR, demonstrate that the POPR in the '1336 IPR was not used as a roadmap. *See* EX1032 ¶188, Appendix B. This petition is also being filed before the issuance of an institution decision in the '1336 IPR.

Finally, factors (6) and (7) favor institution. Given the differences between the '1336 petition and the instant petition, the Board will not be using its resources to consider duplicative arguments. And there is no reason that Celltrion is aware of that would prevent the Board from meeting its one-year statutory requirement to issue a final written decision after institution.

III. GROUNDS FOR STANDING

Petitioner certifies that, under 37 C.F.R. § 42.104(a), the '677 patent is available for *inter partes* review, and Petitioner is not barred or estopped from requesting *inter partes* review of the '677 patent on the grounds identified.

IV. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8

Real Party-in-Interest (37 C.F.R. § 42.8(b)(1)): Petitioner identifies the following real parties-in-interest: Celltrion, Inc.; Celltrion Healthcare Co. Ltd.; and Celltrion Healthcare U.S.A., Inc.

Related Matters (37 C.F.R. § 42.8(b)(2)):

Petitioner notes that it also filed IPR2022-00578 against related U.S. Patent

8,580,264 on the same day as the filing of this petition. Petitioner also notes that petitioners Fresenius Kabi USA, LLC and Fresenius Kabi Swissbiosim GmbH, filed IPR2021-01336 challenging the '677 patent on August 18, 2021, as well as IPR2021-01288 and IPR2021-01542, challenging the related '264 patent.

Lead and Back-Up Counsel (37 C.F.R. § 42.8(b)(3))

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Service Information – 37 C.F.R. § 42.8(b)(4):

Petitioner hereby consents to electronic service. Please direct all correspondence to lead and back-up counsel at the contact information below. A power of attorney accompanies this petition.

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V. STATEMENT OF THE PRECISE RELIEF REQUESTED FOR EACH CLAIM CHALLENGED

Petitioner requests review of claims 1-8 of the '677 patent under 35 U.S.C. § 311 and AIA § 6. The grounds for relief are expressly limited to a determination that each of claims 1-8 of the '677 patent be canceled as unpatentable as follows:

Ground	Claims	Description
1	1 and 5	Anticipated under § 102(b) by *NCT '653* (EX1004)
2	1-8	Obvious under § 103 over the combination of *NCT '653*, *Morichika* (EX1110) and *Kivitz* (EX1050)

VI. CLAIM CONSTRUCTION

Claim terms are generally given their ordinary and customary meaning as would be understood by a POSA. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005) (*en banc*); s*ee also* 37 C.F.R. § 42.100(b).[4] A few terms that

[4] Without taking a position on whether the claims are sufficiently definite, even when the metes and bounds of a claim are indefinite, the Board nevertheless can

warrant discussion are identified and discussed below.

A. "fixed dose" (claims 1 and 5)

The term "fixed dose" is defined in the '677 patent as "a dosage of a drug, such as an anti-IL-6R antibody which is administered without regard to the patient's weight or body surface area (BSE), i.e., it is not administered as either a mg/kg or mg/m^2 dose." EX1001, 15:15-18.

B. "delivers to a patient" (claims 1 and 5)

Independent claims 1 and 5 are drawn to an article of manufacture comprising a subcutaneous administration device and a fixed dose of 162 mg of the anti-IL-6R antibody, tocilizumab. The statement in the claim that the article of manufacture delivers to a patient the 162 mg fixed dose is merely a statement of intended use and not a patentable limitation as it fails to add any additional structural limitations beyond that of the subcutaneous administration device and the fixed dose of antibody. *E.g.*, *In re Schreiber,* 128 F.3d 1473, 1477 (Fed. Cir.

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determine whether embodiments plainly within the scope of the claim would have been obvious. *Ex parte Tanksley*, 26 U.S.P.Q.2d (BNA) 1384, 1387 (B.P.A.I. 1991) (embodiment within scope despite indefiniteness); *Ex parte Sussman*, 8 U.S.P.Q.2d (BNA) 1443, 1445 n.a1 (B.P.A.I. 1988) (affirming obviousness despite indefinite claim format).

1997) (a "structure [that] will be used to dispense popcorn does not have patentable weight if the structure is already known, regardless of whether it has ever been used in any way in connection with popcorn.").

C. "subcutaneous administration device" (claim 3)

The term "subcutaneous administration device" is defined in the specification as "a device, such as syringe, injection device, infusion pump, injector pen, needleless device, patch delivery system, etc., which is adapted or designed to administer a drug or pharmaceutical formulation by the subcutaneous route." EX1001, 20:7-11.

VII. DETAILED EXPLANATION OF GROUNDS FOR UNPATENTABILITY

A. Ground 1: Claims 1 and 5 are Anticipated By *NCT '653*

1. *NCT '653* Was Publicly Available Prior to November 2009

NCT '653 is a printed publication that was available on ClinicalTrials.gov prior to November 2009, which makes it prior art under § 102(b). EX1035 ¶¶12-33, 50; EX1034 ¶¶73-77.

To the extent that patent owner attempts to argue it is not prior art as required by 35 U.S.C. § 312, Petitioner notes that the very purpose of ClinicalTrials.gov is to make such trials as widely and promptly available to the public as possible. *See* EX1035 ¶¶13-19, 23. The FDA Modernization Act of

1997 required that the National Institutes of Health ("NIH") establish a database of information on clinical trials conducted in the United States on drugs for serious or life-threatening diseases and conditions, and NIH's National Library of Medicine launched ClinicalTrials.gov in February 2000 to give the public better access to information on clinical studies. EX1035 ¶¶13, 14. The database was intended to provide "patients, families and members of the public ***easy access to information***." EX1079, 1 (emphasis added). The FDA Amendments Act of 2007 later expanded the database by requiring sponsors of clinical trials to disclose additional information, enabling electronic searching, and imposing a fine for failure to submit information within 21 days of first patient enrollment. EX1035 ¶¶15-16.

The ClinicalTrials.gov database provides key publication dates for each study submitted. According to the NIH, the "First Posted" date is "[t]he date on which the study record was first available on ClinicalTrials.gov." EX1064, 8. The study record for *NCT '653* was "First Posted" on August 25, 2009. EX1004, 1. That is sufficient to demonstrate that the posting was publicly available by August 2009.[5] EX1035 ¶32; *see also Grunenthal GmbH v. Antecip Bioventures II, LLC.*,

[5] Chugai, one of the patent owners, sponsored the *NCT '653* clinical study and therefore likely has additional documentary evidence that the study was publicly available on ClinicalTrials.gov before November 2009. To the extent Chugai

PGR2019-00003, Paper No. 22, 17-18 (PTAB May 5, 2020) (finding a protocol available on ClinicalTrials.gov to have been publicly available as of its "first posted" date and therefore a "prior art printed publication").

2. *NCT '653* Discloses Every Element of Claims 1 and 5

a. "[a]n article of manufacture comprising a subcutaneous administration device" (claims 1 and 5)

NCT '653 describes an "open label randomized 2 arm study" to "investigate the pharmacokinetics, pharmacodynamics, efficacy and safety of **subcutaneously administered** tocilizumab in patients with rheumatoid arthritis." EX1004, 6 (emphasis added). "Patients will be randomized to receive tocilizumab 162 mg **sc [subcutaneously]** either weekly or every other week." *Id*. *NCT '653* does not describe the specific device (*e.g.,* a syringe or an autoinjector) used in the study; however, a POSA would have understood that a "subcutaneous administration

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alleges that *NCT '653* is not prior art, or that Petitioner has not carried its burden to establish *NCT '653* as prior art, Petitioner intends to seek "routine discovery" and/or "additional discovery" from Chugai that is inconsistent with that position. *See* PTAB Trial Practice Guide (Nov. 2019) at 23-24 (providing for "routine discovery" on "relevant information that is inconsistent with a position advanced during the proceeding" and "additional discovery … in the interests of justice").

device" was necessary to administer the tocilizumab subcutaneously. EX1034, ¶204. This implicit disclosure is sufficient for anticipation. *See In re Baxter Travenol Labs*, 952 F.2d 388, 390-391 (Fed. Cir. 1991) (finding anticipation where "one skilled in the art would have known that Becker was referring to a DEHP-plasticized bag and a Teflon® secondary bag" despite "no express reference to DEHP in the Becker document").

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

NCT '653 discloses that "**[p]atients will** be randomized to **receive tocilizumab 162 mg sc** either weekly or every other week, in combination with methotrexate, for 12 weeks". EX1004, 6 (emphasis added). The 162 mg dose was "fixed," *i.e.*, it did not vary from patient to patient regardless of body weight or body surface area. *Id.* A POSA would have understood that the "subcutaneous administration device" used in the study contained and delivered a 162 mg fixed dose of tocilizumab to the patient. EX1034 ¶205. *NCT '653* thus discloses this limitation.

c. "which contains and delivers to a patient a 162 mg fixed dose of an anti-IL-6R antibody, wherein the anti-IL-6R antibody comprises the light chain and heavy chain amino acid sequences of SEQ ID NOs. 1 and 2, respectively" (claim 5)

NCT '653 states that "[p]atients will be randomized to receive **tocilizumab** 162 mg sc either weekly or every other week, in combination with methotrexate, for 12 weeks." EX1004, 6. Tocilizumab is an anti-IL-6R antibody. EX1001, 5:29-30 ("The invention also concerns subcutaneously administering an anti-IL-6R antibody (e.g. tocilizumab)."). Tocilizumab is comprised of the light chain and heavy chain amino acid sequences of SEQ ID. Nos. 1 and 2, respectively. This is clear from the following evidence, which includes Chugai's and the '677 patent inventors' own admissions:

- The '677 patent specification confirms that tocilizumab comprises the claimed amino acid sequences: "FIGS. 7A and 7B depict the amino acid sequences of the ***light chain*** (FIG. 7A: ***SEQID NO: 1***) and ***heavy chain*** (FIG. 7B: ***SEQID NO:2***) of ***Tocilizumab***." EX1001, 7:12-16 (emphasis added).
- During prosecution of the '677 patent, the Examiner understood that tocilizumab comprises the claimed sequences, rejecting claims directed to SEQ ID Nos. 1 and 2 as anticipated by *Ohta 2010* (EX1066), which

discloses tocilizumab, stating that the "amino acid sequence characteristics would be inherent in the antibody of the prior art." EX1068, 181.

- During prosecution, the named inventors of the '677 patent confirmed that tocilizumab comprises the claimed sequences. The inventors submitted an inventor declaration to the Examiner to antedate *Ohta 2010*, admitting therein that tocilizumab has the claimed sequence: "MRA227 was a phase I/Il clinical study of the anti-IL-6R antibody '***tocilizumab'*** also called 'MRA' ***which we understand comprises the light chain and heavy chain amino acid sequences as in Figs. 7A-B*** of the above application." EX1068, 257-258 (emphasis added)[6]; *see also* EX1115, 91 (Patent Owner admitting during the prosecution of the '720 patent that "a skilled person would understand that humanized anti-IL-6 receptor antibody MRA is clearly a synonym for Tocilizumab.").
- In a Request for Patent Extension, Chugai acknowledged and relied on the fact that tocilizumab has the claimed amino acid sequences. *See* EX1067, 2; EX1032 ¶¶175-182.

[6] The named inventors made the same admission during prosecution of U.S. Patent No. 8,580,264, which shares the same specification as the '677 patent. EX1065 1025-1026.

- As explained by Dr. Shah, tocilizumab has the claimed amino acid sequences for the heavy and light chains. EX1032 ¶¶151-87.

Thus, the tocilizumab administered in *NCT '653* is the same as the claimed "anti-IL-6R antibody…compris[ing] the light chain and heavy chain amino acid sequences of SEQ ID Nos. 1 and 2, respectively." EX1034 ¶206.

3. *NCT '653* is enabled

A POSA would have been able to make a "subcutaneous administration device" containing the 162 mg fixed dose of tocilizumab in *NCT '653* using nothing more than routine skill. When a claimed invention is fully disclosed in one prior art reference, an additional prior art reference may be relied on to show that the primary reference has an enabling disclosure. *See In re Samour*, 571 F.2d 559, 562-63 (CCPA 1978); *In re Donohue*, 766 F.2d 531, 533-34 (Fed. Cir. 1985). As explained in the declaration of Professor Paul Dalby, a POSA who wanted to practice *NCT '653* could have made a 162 mg dose of tocilizumab suitable for SC injection by following the instructions and copying the recipe for the A8/A26 formulation of tocilizumab disclosed by Patent Owner in *Morichika*, which was published on July 9, 2009, more than a year before the earliest possible effective filing date of the '677 patent. EX1036 ¶¶31-37; EX1034 ¶207. The A8/A26 formulation contains 162 mg of antibody in 0.9 mL, which is small enough to be accommodated within a single pre-filled syringe, autoinjector, or other suitable

administration device. EX1036 ¶37. *Morichika* states that the formulation is "especially suited for subcutaneous injection." EX1110, [0053]; *see also* EX1115, 308, [0053].

4. Efficacy is not a limitation of claims 1 and 5

As discussed above, independent claims 1 and 5 are drawn to articles of manufacture and do not require that the 162 mg fixed dose be efficacious, and the claim language that it "deliver" the dose to the "patient" receiving the treatment is merely a statement of intended use. EX1034 ¶207.

But even if the claims are construed to require efficacy, *NCT '653* discloses a 162 mg fixed dose of tocilizumab delivered via a "subcutaneous delivery device" that is efficacious. EX1034 ¶208. Patent Owner cannot dispute this. Patent Owner obtained FDA approval for its subcutaneous version of Actemra, which employs a "subcutaneous delivery device" filled with this same fixed dose. EX1034 ¶209; EX1116, 1, 47-65. It does not matter whether a skilled artisan would have appreciated this efficacy or not. The claimed administration and the administration in *NCT '653* are the same. To the extent one produces at least some efficacy in some patients, so must the other. *See, e.g.*, *In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990) ("It is a general rule that merely discovering and claiming a new benefit of an *old* process cannot render the process again patentable."); *In re Papesch*, 315 F.2d 381, 391 (1963) ("a compound and all of its

properties are inseparable; they are one and the same thing."); *King Pharms., Inc. v. Eon Labs., Inc.*, 616 F.3d 1267, 1275-76 (Fed. Cir. 2010) (to anticipate, the prior art need only meet the claimed limitation to the extent the patented method does.).

B. Ground 2: Claims 1-8 Are Obvious Over the Combination of *NCT '653*, *Morichika* and *Kivitz*

As discussed above, *NCT '653* discloses all the limitations of claims 1 and 5. But if the Board finds that claims 1 and 5 are not anticipated by *NCT '653* because that reference does not expressly describe a particular kind of "subcutaneous administration device," then those claims, as well as dependent claims 2-4 and 6-8, are nevertheless invalid for obviousness. EX1034 ¶210.

1. All of the elements of claims 1-8 are disclosed in the combination of *NCT '653*, *Morichika* and *Kivitz*

Claims 1 and 5 require only a subcutaneous administration device, without specifying what that device is. Dependent claims 2-4 and 6-8 limit claims 1 and 5 to embodiments that employ specific "subcutaneous administration devices." The narrowest claims are limited to "a syringe, including a pre-filled syringe" (claims 3 and 7), and "an autoinjector" (claims 4 and 8).

As explained, *NCT '653* teaches the subcutaneous delivery of 162 mg of tocilizumab to patients. EX1004, 6. Although a POSA would understand that a device, such a syringe, needs to be used to administer the SC tocilizumab

(EX1034 ¶204), *NCT '653* does not expressly describe the device to be used. But both pre-filled syringes and autoinjectors were conventional devices that had been used to deliver antibodies and other biologics subcutaneously to RA patients, and indeed were already in *commercial* use as of 2009. For example, *Kivitz*, published in 2007 and prior art under pre-AIA § 102(b), describes the subcutaneous delivery of fixed doses of adalimumab (Humira®), etanercept (Enbrel®) and anakinra (Kineret®) via autoinjector and pre-filled syringes to RA patients. EX1034 ¶213, EX1050, 111.

As also explained, *Morichika* taught how to formulate tocilizumab so that it, too, could be delivered to RA patients via an autoinjector or pre-filled syringe. *See supra* Section VII.A.4. *Morichika* discloses a tocilizumab formulation that is "especially suitable" for SC administration, such as through injection. EX1034 ¶212, 214; EX1110, [0053].

It would have been obvious to a POSA to use the tocilizumab formulation of *Morichika* in the pre-filled syringe or autoinjector of *Kivitz* to arrive at the claimed article of manufacture, *i.e.,* a device comprising the 162mg dose of tocilizumab of *NCT '653* in a subcutaneous administration device such as a prefilled syringe or an autoinjector. EX1034 ¶¶215, 227. For the reasons described below, the POSA would have been motivated to make

this combination and would have had a reasonable expectation of success of arriving at the clamed article of manufacture.

2. A POSA would have been motivated to use a pre-filled syringe or autoinjector to deliver the 162 mg fixed dose of tocilizumab in *NCT '653*

The motivation for combining the fixed-dose subcutaneous regimen in *NCT '653* with the pre-filled syringes and autoinjectors of *Kivitz* and the formulation of *Morichika* is clear from the prior art.

As *Kivitz* explains, RA is a chronic disease in which long-term efficacy depends on patients adhering to their prescribed dosage regimen. EX1050, 110. This dosage regimen can persist for a lifetime. EX1048, 786-87. Intravenous medications for RA usually require a patient to visit a clinic for each dose, so that a trained medical professional can administer the IV infusion. EX1050, 110. The inconvenience of this travel, especially for elderly patients or those with debilitating disease, may affect patient adherence. *Id*., 114. Patients with a fear of the IV procedure or who have poor venous access may also have difficulty adhering to their prescribed dosage regimen. *Id*., 110; *see also* EX1049, 265; *see also* EX1034, ¶¶62-65, 216.

In contrast, patients can self-administer pre-filled syringes and autoinjectors at home whenever convenient. EX1050, 110. The devices are easy to use and minimize both the pain and duration of injection. *Id*. For those

with a fear of needles, autoinjectors are constructed so as to prevent the needle from being visible. *Id*. The cost of at-home, self-administration can also be lower than intravenous delivery since no clinic or medical professional needs to be involved. EX1050, 110. All of these advantages may increase patient adherence. *Id*., 110, 114; *see also* EX1034, ¶¶62-65, 115, 216.

Fixed subcutaneous dosing was also known to have therapeutic benefits over intravenous dosing. EX1034 ¶64. Fixed dosing avoids the calculations needed for body-weight dosing (e.g., calculating mg/kg), which must be done for each dose and can sometimes lead to dosing errors. *Id*., ¶64. Subcutaneous doses are also generally smaller and administered more frequently than intravenous doses. *Id*. ¶64. Smaller, more frequent doses tend to avoid the large peaks and troughs in mean blood plasma concentration often seen with intravenous delivery. *Id.* ¶64. Large peaks can cause adverse side effects from too much drug in the system, and troughs can permit breakthrough disease from having too little drug in the system. *Id*. ¶216.

Given the known advantages of subcutaneous administration of antibodies via pre-filled syringes and autoinjectors, and the particular advantages of those devices when delivering treatments to RA patients, the publication of a new subcutaneous dosage regimen for RA in *NCT '653* would have immediately

motivated a POSA to combine that regimen with the devices in *Kivitz*. EX1034, ¶¶216-21.

This motivation would have been further fueled by the SAMURAI, LITHE and RADIATE studies, which had already demonstrated that 4 mg/kg and 8 mg/kg of IV tocilizumab are effective at treating RA, and by the approval of Actemra in Europe and Japan as a safe and effective treatment for RA. EX1034, ¶¶216-21.

Chugai and Roche would have stoked this motivation further still with their disclosures that subcutaneous administration of tocilizumab was preferred, and that a subcutaneous version of Actemra was in the works. EX1034 ¶219. For example, in February 2009, Chugai announced that a subcutaneous version of Actemra was in Phase II development. EX1034 ¶69; EX1071, 4. Similarly, in June 2009, Roche announced that a "Subcutaneous dose form" of Actemra® was "in development," and that Actemra had "[c]ontinued strong efficacy data" and had "[d]emonstrated long-term safety with increasing efficacy over time." EX1034 ¶69; EX1072, slide 12. Chugai also noted publicly that tocilizumab was preferably administered subcutaneously. EX1030, 4 (tocilizumab's "preferred form of administration in chronic autoimmune diseases is thought to be subcutaneous formulation").

In light of this flurry of news about subcutaneous Actemra®, a POSA would have been very interested in the 162 mg fixed dose regimen of *NCT '653*, and

would have been motivated to deliver that regimen to RA patients in a convenient, known format, which included the pre-filled syringes and autoinjectors mentioned in *Kivitz*. EX1034 ¶219.

Finally, Chugai and Roche's publication of a stable formulation of tocilizumab suitable for use in an autoinjector or pre-filled syringe in *Morichika* would have increased interest in *NCT '653* and encouraged the use of one of those devices to deliver the fixed dose to RA patients. The availability of a ready-made recipe for the formulation would have saved the POSA time and expense. EX1034 ¶221.

3. A POSA Would Have Reasonably Expected to Succeed In Making The "Subcutaneous Administration Device" of the Claims

A POSA would have had a reasonable expectation of success in presenting 162 mg of tocilizumab in an autoinjector or pre-filled syringe. EX1034 ¶¶222-26. As explained with respect to enablement, a POSA would have been able to follow Patent Owner's own teachings in *Morichika* to create a concentrated formulation of tocilizumab that would fit into an autoinjector or pre-filled syringe. *See supra* Section VII.A.3 above. Indeed, *Morichika* later entered national stage in the U.S. and issued as a U.S. patent prior to the filing date of the '677 patent, with claims to a "stable" formulation of tocilizumab "suitable for subcutaneous administration." EX1034 ¶68; *see* EX1112; s*ee also* EX1115, 96 (Chugai and Roche noting during

the prosecution of the '720 patent, which is the § 371 application of *Morichika*, "The present application concerns the development of a high concentration anti-IL-6R antibody liquid formulation that is stable and suitable for subcutaneous (SQ) administration to human patients. This is an important medical breakthrough for patients who can now administer the anti-IL-6R antibody in an outpatient setting.").

As explained, the claims do not require that the "article of manufacture" be efficacious for a particular disease. No disease is mentioned in the claims and importing a specific disease as a limitation into the claims would be improper. *See Acceleration Bay, LLC v. Activision Blizzard Inc.*, 908 F.3d 765, 771 (Fed. Cir. 2018) (affirming Board decision not to read limitation into claim where the specification did not "contain the sort of precise and clear language that would warrant" doing so). This is particularly true given that the specification mentions ***over 100 different diseases*** as "examples of IL-6-mediated disorders to be treated herein." EX1001, 13:27-60. Therefore, no reasonable expectation of efficacy is required in order for the claims to be obvious.

Should the Board disagree, however, a POSA would have had a reasonable expectation from the prior art that a 162 mg SC fixed dose of tocilizumab, when delivered to an RA patient subcutaneously in a pre-filled syringe or autoinjector, would have efficacy against RA in at least some patients. The claims do not

specify a dosing frequency, degree of efficacy, or disease. Any total dose of tocilizumab, given at any frequency, that produces any efficacy against any disease, would read on such a claim. A skilled artisan would have understood that 162 mg of tocilizumab delivered subcutaneously at a sufficient frequency will have at least some efficacy in at least some patients against RA. EX1034 ¶224.

For example, as discussed by Dr. Boers, tocilizumab dosed 8mg/kg IV had been approved in Japan and Europe for treating RA, and there were an abundance of clinical trial results showing that both 4mg/kg and 8mg/kg IV doses were efficacious in RA patents. *Id.* ¶¶55-56, 61, 224. Specifically, the SAMURAI, LITHE and RADIATE studies showed that 4 mg/kg and 8 mg/kg of IV tocilizumab were effective at treating RA, and Actemra® had been approved in Europe and Japan as a safe and effective treatment for RA. *Id.* ¶224. The skilled artisan would have understood that 162 mg of tocilizumab can be delivered subcutaneously at some total dose and frequency to approximate these effective IV doses. *Id.*

A POSA also would have expected that tocilizumab would be effective when administered via the subcutaneous route, in addition to the IV route. Chugai and Roche represented in *Morichika* that their high-concentration formulation of tocilizumab would be effective intravenously *or subcutaneously*, *id.* ¶78; EX1110, [0053], and Chugai represented that subcutaneous administration was "preferred"

for tocilizumab. EX1034 ¶¶219, 221, 225; *see also* EX1071, 4; EX1072, slide 12, EX1030, 4. These representations would have further supported the conclusion that a skilled artisan would have viewed the 162 mg SC dose of tocilizumab in *NCT '653* as being efficacious.

Further, as Dr. Shah explains in his declaration, a POSA would have been able to employ routine pharmacokinetic modeling to predict whether the 162 mg fixed dose in *NCT '653* would have at least some efficacy against RA. EX1032 ¶¶82, 119, 123. A POSA would have understood from the prior art that maintaining a mean blood plasma level of tocilizumab at or above 1 μg/ml would be effective against RA. EX1032 ¶104-109; 114; EX1034 ¶59. For example, *Nishimoto 2008* (EX1008) reported that 1 μg/mL was the minimum effective concentration ("MEC") at which tocilizumab would effectively block the activity of IL-6. EX1008, 3961-63. The Japanese Ministry of Health's Report on Deliberation Results for Actemra (EX1024) also stated that 1 μg/mL was "the minimum effective blood concentration of MRA [tocilizumab]." EX1024, 22-23.

With this MEC in hand, the POSA could have generated a routine pharmacokinetic model to assess whether 162 mg of tocilizumab would produce mean blood plasma levels at or above the MEC. EX1034 ¶¶70-72, 179, 226; EX1032 ¶¶115-123. By 2009, such models had become an essential and routine part of drug product development, and they were in wide use for precisely this sort

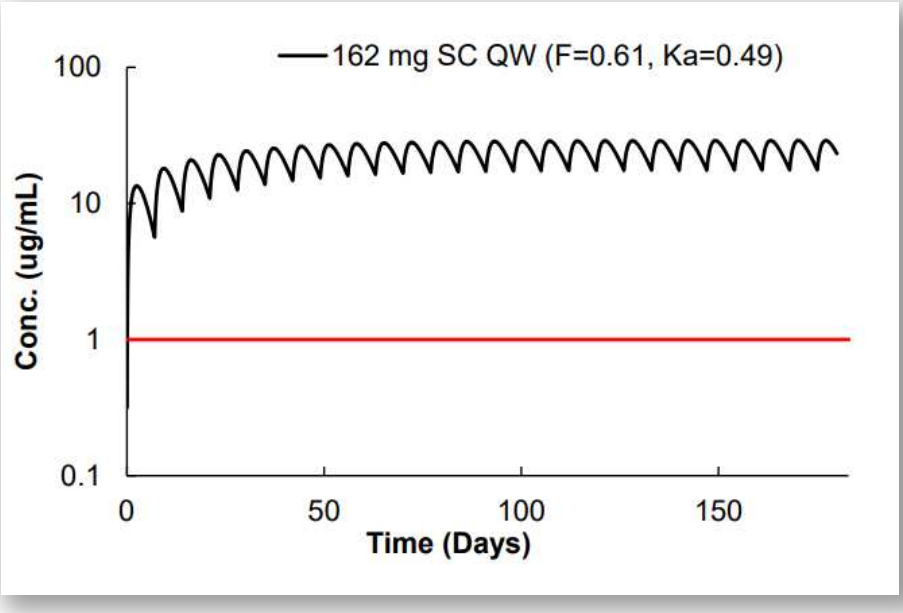
of analysis. EX1034 ¶¶70-72. The POSA would have chosen a two-compartment PK model for tocilizumab, guided in part by the two-compartment model in *Ng 2005* for efalizumab, which is an IgG1-*kappa* subtype antibody structurally similar to tocilizumab, and the two-compartment model for tocilizumab that Roche included in the *FDA Review* and *EMA Report*, which it submitted to the FDA and EMA in support of the regulatory approval of Actemra. *Id.* ¶¶104, 179; EX1032 ¶¶ 80-82, 85; EX1007, 1091-92 and Fig 1A; EX1010[7], 110-124; EX1006, 41.

All of the pharmacokinetic parameters for tocilizumab needed to produce a reasonably predictive two-compartment model were available in, or could have been estimated from, the prior art. EX1032 ¶¶84-85. Most of the parameters are expressly set forth in Table 3 of the *FDA Review*. EX1032 ¶90-91; EX1010. Even if this chart were not available, a POSA would have found essentially the same parameters in the *EMA Report* and *Chernajovsky 2008* (or been able to extract those parameters from the data in these references). EX1032 ¶¶87-89, 100-103; EX1009, 154-55 and Fig. 3; EX1006, 41-42. The two parameters not disclosed in the prior art are bioavailability (F) and rate of absorption (K_a). But the prior art reports F and K_a values for structurally-similar antibodies. EX1032 ¶¶92-98. At least six such antibodies had been formulated into subcutaneous therapeutics, and

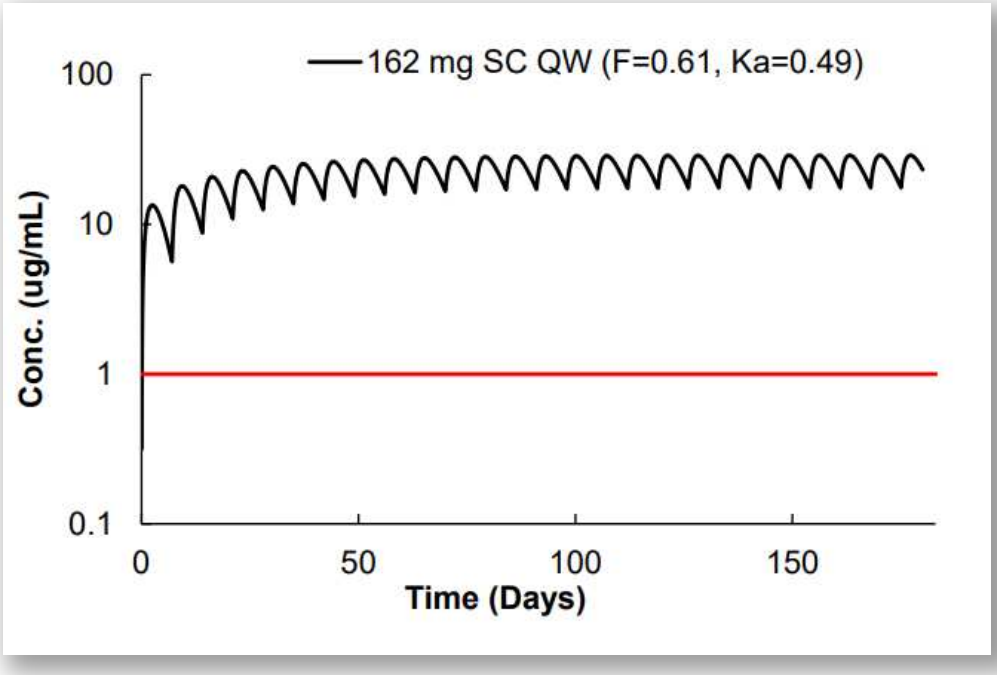
[7] Citations to this exhibit are to the stamped page numbers.

F and K_a values for them had been published in the prior art. *Id.* A POSA would have expected tocilizumab to be roughly similar and used the average of these values. *Id.* ¶98.

As Dr. Shah demonstrates in his declaration, a routine two-compartment model, when programmed with the prior-art pharmacokinetic parameters for tocilizumab found in the *FDA Review*, predicts that a 162 mg subcutaneous dose of tocilizumab, when administered weekly, will produce and maintain a mean blood plasma concentration well above the 1 µg/ml MEC for tocilizumab at steady state:



EX1032 ¶117, Fig 14. Essentially the same result is obtained when using the pharmacokinetic parameters obtained from *EMA Report* and *Chernajovsky 2008:*



EX1032 ¶115, Fig 12. From these modeling results, a POSA would have had at least a reasonable expectation that an autoinjector filled with a 162 mg dose of tocilizumab, when used by an RA patient once a week, would have at least some efficacy. *Id.* ¶119; EX1034, ¶226.

Further, a POSA would have assumed from the fact that Patent Owner had sponsored *NCT '653*, its public statements about subcutaneous tocilizumab being "in development," and Chugai's statement that subcutaneous tocilizumab was the "preferred form," that Roche had done PK/PD modeling and other analyses to confirm that the 162 mg dose in *NCT '653* administered, *e.g.,* once weekly, would demonstrate at least some efficacy in at least some patients. EX1034 ¶¶225-226. In fact, the POSA would have known from documents like *EMA Report* that

Roche had done PK/PD modeling of tocilizumab and had made predictions of efficacy based on it. EX1034 ¶226; EX1032 ¶80. A POSA would reasonably have expected that Roche would not have invested the time and money, nor gambled on the welfare of the patients enrolled in the study, without at least a reasonable expectation that the dosage amount in *NCT '653* would show some efficacy in some patients, regardless of whether the trial ultimately met its secondary outcome goals. EX1034 ¶¶155, 225-226.

VIII. SECONDARY CONSIDERATIONS

Petitioner is not aware of any relevant secondary considerations that have a nexus to, or are commensurate in scope with, any of the challenged claims. EX1034 ¶228. Moreover, to the extent the claims are anticipated by *NCT '653*, "secondary considerations are not an element of a claim of anticipation." *Cohesive Techs. Inc. v. Waters Corp.*, 543 F.3d 1351, 1364 (Fed. Cir. 2008).

IX. CONCLUSION

For the reasons set forth above, claims 1-8 of the '677 patent are unpatentable. Petitioner therefore requests that an *inter partes* review of these claims be instituted.

Respectfully submitted,

Dated: February 21, 2022

/Lora M. Green /
Lora M. Green, Lead Counsel
Reg. No. 43,541

X. CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. §42.24(d), the undersigned certifies that this Petition complies with the type-volume limitation of 37 C.F.R. §42.24(a). The word count application of the word processing program used to prepare this Petition indicates that the Petition contains 9,405 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a).

Respectfully submitted,

Dated: February 21, 2022

/Lora M. Green /
Lora M. Green, Lead Counsel
Reg. No. 43,541

XI. PAYMENT OF FEES UNDER 37 C.F.R. §§ 42.15(A) AND 42.103

The required fees are submitted herewith. If any additional fees are due at any time during this proceeding, the Office is authorized to charge such fees to Deposit Account No. 23-2415.

XII. APPENDIX – LIST OF EXHIBITS

Exhibit No.	Description
1001	U.S. Patent No. 10,874,677 ("the '677 Patent")
1002	Curriculum Vitae of Dhaval K. Shah B. Pharm., M.S., Ph.D.
1003	Excerpts from Milo Gibaldi and Donald Perrier, Pharmacokinetics, 2d Ed. (2007) ("*Gibaldi 2007*")
1004	U.S. National Library of Medicine, ClinicalTrials.gov, NCT00965653, "A Study of Subcutaneously Administered Tocilizumab in Patients with Rheumatoid Arthritis" (August 21, 2009), available at https://clinicaltrials.gov/ct2/history/NCT00965653?V_1 ("*NCT '653*")
1005	Vicki Oldfield, et al., "Tocilizumab, A Review of its Use in the Management of Rheumatoid Arthritis", *Drugs* 2009: 69(5): 609-632 ("*Oldfield*")
1006	Affidavit of Duncan Hall (Internet Archive), containing *About Clinicaltrials.gov* (p.5), *About the ClinicalTrials.gov Results Database* (p.7), *ClinicalTrials.gov Protocol Data Element Definitions* (p.10), *FAQ: ClinicalTrials.gov – Submission and Review of Information* (p.19), *FDA Talk Paper* (p.21), *Assessment Report for RoActemra* (p.24) ("*EMA Report*"), *ClinicalTrials.gov Fact Sheet* (p.80), *Registering Clinical Trials With ClinicalTrials.gov* (p. 86) ("*Duncan Hall Aff.*")
1007	Chee M. Ng et al., "Pharmacokinetic-Pharmacodynamic-Efficacy Analysis of Efalizumab in Patients with Moderate to Severe Psoriasis", *Pharmaceutical Research* 22(7): 1088-1100 (July 2005) ("*Ng 2005*")
1008	Norihiro Nishimoto et al., "Mechanisms and pathological significances in increase in serum interleukin-6 (IL-6) and soluble IL-6 receptor after administration of an anti-IL-6 receptor antibody, tocilizumab, in patients with rheumatoid arthritis and Castleman disease", *Blood* 112:3959-64 (2008) ("*Nishimoto 2008*")
1009	Excerpt from Y. Chernajovsky and A. Nissim, Handbook of Experimental Pharmacology 181, "Humanized Antihuman IL-6

	Receptor Antibody, Tocilizumab" 151-60 (2008) ("*Chernajovsky 2008*")
1010	Clinical Pharmacology and Biopharmaceutics Review(s) for IV Actemra, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/125276s000ClinPharmR.pdf ("*FDA Review*")
1011	Nicolas Frey et al., "Population Pharmacokinetic Analysis of Tocilizumab in Patients With Rheumatoid Arthritis", *J. Clin. Pharmacol.* 2010;50:754-766 "(*Frey 2010*")
1012	Package Insert for HUMIRA (adalimumab), Revised January 2008, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/125057s0110lbl.pdf ("*Humira 2008 Label*")
1013	Gino Vena et al., "Drug focus: adalimumab in the treatment of moderate to severe psoriasis", *Biologics: Targets & Therapy* 2007:1(2) 93-103 ("*Vena 2007*")
1014	Package Insert for ILARIS (canakinumab), Revised June 2009, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125319s000lbl.pdf ("*Ilaris 2009 Label*")
1015	Package Insert for SIMPONI (golimumab), Revised April 2009, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125289s000lbl.pdf ("*Simponi 2009 Label*")
1016	Excerpt of Physicians' Desk Reference, 61st Edition (2000) for Xolair® (omalizumab) ("*PDR 2007 Excerpt – Xolair*")
1017	Intentionally left blank
1018	Zhenhua Xu et al., "Population Pharmacokinetics of Golimumab, an Anti-Tumor Necrosis Factor-α Human Monoclonal Antibody, in Patients With Psoriatic Arthritis", *J. Clin. Pharmacol.* 2009;49:1056-1070 ("*Xu 2009*")
1019	Yu-Nien Sun et al., "Population Pharmacokinetics of Efalizumab (Humanized Monoclonal Anti-CD11a Antibody Following Long-Term Subcutaneous Weekly Dosing in Psoriasis Subjects", *J. Clin. Pharmacol.* 2005;45:468-476 ("*Sun 2005*")
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1021	Naoto Hayashi et al., "A mechanism-based binding model for the population pharmacokinetics and pharmacodynamics of omalizumab", *Br. J. Clin. Pharmacol.* 63(5):548-561 (2006) ("*Hayashi 2006*")
1022	WM Awni et al., "Steady-state Adalimumab (HUMIRA) Pharmacokinetics (PK) Following Every Other Week (eow) Dosing of 40mg Subcutaneous (s.c.) Injection, in Rheumatoid Arthritis (RA) Patients Treated With and Without Concomitant Methotrexate (MTX)" (2004) ("*Awni 2004*")
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1024	Evaluation & Licensing Division, Pharmaceutical & Food Safety Bureau; Ministry of Health, Labour and Welfare, Report on the Deliberation Results for Tocilizumab (March 6, 2008), available at https://www.pmda.go.jp/files/000153709.pdf ("*Actemra PDMA Report*")
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1026	Norihiro Nishimoto et al., "Study of Active Controlled Monotherapy Used For Rheumatoid Arthritis, an IL-6 Inhibitor (SAMURAI): Evidence of Clinical Radiographic Benefit From an X-Ray Reader-Blinded Randomised Controlled Trial of Tocilizumab", *Ann. Rheum. Dis.* 2007;66:1162-1167 ("*Nishimoto 2007*")
1027	Norihiro Nishimoto et al., "Treatment of Rheumatoid Arthritis With Humanized Anti-Interleukin-6 Receptor Antibody", *Arthritis & Rheumatism* 50(6), 1761-1769 (June 2004) ("*Nishimoto 2004*")
1028	J.M. Kremer et al., "Tocilizumab Inhibits Joint Structural Damage in Rheumatoid Arthritis Patients With an Inadequate Response to Methotrexate: The LITHE Study," Arthritis & Rheumatism, Vol. 58, No. 12 (December 2008) ("*Kremer 2008*")
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1030	Certificate of Translation (pg. 1), Translation (pgs. 2-183) & Original (pgs. 184-364):

	PCT International Publication No. WO2009/041621 A1 ("*WO '621*")
1031	Sequence Listing for WO2009/041621 A1, available at available at https://patentscope.wipo.int/search/docs2/pct/WO2009041621/file/PphyAKMJApl6qJur_mQDG7n2NOAu9YwcdqjMGsyXX6b_bnMLPWCn_59rPesoMSl4mjvztdpx7fiDIHCOKJVdgz8J9eGByoDOWNx1v2cz1uuUeFKSU_AVoVegLcdK2DoO5KC3fpHz4mBZZBfs PdRfhg?docId=id00000007993190 ("*Sequence Listing*")
1032	Declaration of Dhaval K. Shah, B. Pharm., M.S., Ph.D. ("Shah Decl.")
1033	Intentionally Left Blank
1034	Declaration of Maarten Boers, M.D., M.Sc., Ph.D. ("Boers Decl.")
1035	Declaration of Prescott M. Lassman, Esq. ("Lassman Decl.")
1036	Declaration of Paul A. Dalby, Ph.D. ("Dalby Decl.")
1037	G. Jones et al., "Comparison of Tocilizumab Monotherapy Versus Methotrexate Monotherapy in Patients with Moderate to Severe Rheumatoid Arthritis: The AMBITION Study," *Annals of the Rheumatic Diseases* 69:88–96 (2010) ("*Jones*")
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1039	Eric L. Matteson, "Concise Review for Clinicians, Current Treatment Strategies for Rheumatoid Arthritis," *Mayo Clinic Proceedings* 75:69–74 (2000) ("*Matteson*")
1040	R. N. Maini et al., "Double-Blind Randomized Controlled Clinical Trial of the Interleukin-6 Receptor Antagonist, Tocilizumab, in European Patients with Rheumatoid Arthritis Who Had an Incomplete Response to Methotrexate," *Arthritis & Rheumatism* 54(9):2817–29 (2006) ("*Maini 2006*")
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1043	P. Emery et al., "IL-6 Receptor Inhibition with Tocilizumab Improves Treatment Outcomes in Patients with Rheumatoid Arthritis Refractor to Anti-Tumour Necrosis Factor Biologicals: Results from a 24-Week Multicenter Randomized Placebo-Controlled Trial," *Annals of the Rheumatic Diseases* 67:1516–23 (2008) ("*Emery*")
1044	Pharmaceuticals and Medicals Devices Agency of Japan, Annual Report FY 2008, available at https://www.pmda.go.jp/files/000232775.pdf ("*PMDA FY 2018 Report*")
1045	Food and Drug Administration, BLA 125276 Approval Letter for Actemra® (January 8, 2010), available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/125276s000ltr.pdf ("*BLA 125276 Approval Letter*")
1046	ACTEMRA® (tocilizumab) Prescribing Information (Revised January 2011), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125276s007s010s011lbl.pdf ("*Actemra 2011 Label*")
1047	David Macht, The History of Intravenous and Subcutaneous Administration of Drugs, *J. of Am. Med. Ass'n,* Vol. LXVI, No. 12 (March 18, 1916) ("*Macht*")
1048	Melvin Berger, "Subcutaneous Administration of IgG," *Immunology and Allergy Clinics of North America* 28:779–802 (2008) ("*Berger*")
1049	Hans D. Ochs et al., "Safety and Efficacy of Self-Administered Subcutaneous Immunoglobulin in Patients with Primary Immunodeficiency Diseases," *Journal of Clinical Immunology* 26(3):265–73 ("*Ochs*")
1050	Alan Kivitz and Oscar G. Segurado, "HUMIRA® Pen: a novel autoinjection device for subcutaneous injection of the fully human monoclonal antibody adalimumab," *Expert Rev. Med. Devices* 4(2):109–16 (2007) ("*Kivitz*")

1051	Francisco A. Bonilla, "Pharmacokinetics of Immunoglobulin Administered via Intravenous or Subcutaneous Routes," *Immunology and Allergy Clinics of North America* 28:803–19 (2008) ("*Bonilla*")
1052	Diane D. Wang et al., "Fixed Dosing Versus Body Size-Based Dosing of Monoclonal Antibodies in Adult Clinical Trials," *Journal of Clinical Pharmacology* 49:1012–24 (September 2009) ("*Wang*")
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1055	Package Insert for HUMIRA (Adalimumab), Revised (December 2002) ("*2002 Humira FDA Label*")
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1057	"CIMZIA (certolizumab pegol)," *Physicians' Desk Reference* (63rd ed. 2009) ("*2009 PDR - CIMZIA*")
1058	"TNF Blocker Wins Approvals," *Internal Medicine News*, Vol. 42, No. 11 (2009) ("*TNF Blocker Wins Approvals*")
1059	Mazumdar et al., "Golimumab," *mAbs* 1(5):422–31 (September/October 2009) ("*Golimumab*")
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1065	Prosecution File History of U.S. Patent No. 8,580,264 ("'264 File History")
1066	Shuji Ohta et al., "1115 Optimal Dose Prediction by Pharmacokinetic and Biomarker Response of Subcutaneous Tocilizumab Treatment – A Phase I/II Study Evaluating the Safety, Pharmacokinetics and Clinical Response in Patients with Rheumatoid Arthritis," *Arthritis & Rheumatism* 62(10 Supplement):S467–68 (2010) ("*Ohta 2010*")
1067	Application for Patent Term Extension Under 35 U.S.C. § 156 to the PTO for U.S. Patent. No. 5,795,965 ("*Application for Patent Term Extension*")
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1069	Josef S. Smolen et al., "Effect of Interleukin-6 Receptor Inhibition with Tocilizumab in Patients with Rheumatoid Arthritis (OPTION Study): A Double-Blind, Placebo-Controlled, Randomised Trial," *Lancet* 371:987–97 (2008) ("*Smolen*")
1070	Mark C. Genovese, "Interleukin-6 Receptor Inhibition with Tocilizumab Reduces Disease Activity in Rheumatoid Arthritis with Inadequate Response to Disease-Modifying Antirheumatic Drugs," *Arthritis & Rheumatism* 58(10):2968–80 (2008) ("*Genovese*")
1071	"Overview of Development Pipeline," Chugai Pharmaceutical Co., Ltd., Tatsuro Kosaka, February 4/5, 2009, available at https://www.chugai-harm.co.jp/cont_file_dl.php?f=FILE_2_63.pdf&src=[%0],[%1]&rep=139,63 ("*Chugai 2009 Report*")
1072	Roche, "Investor Event at EULAR 2009," June 12, 2009, available at https://www.roche.com/dam/jcr:aa643d56-6ea3-47b0-9109-5f027b1c1fef/en/irp090612_eular.pdf ("*Roche 2009 Report*")
1073	Curriculum Vitae of Maarten Boers, M.D., M.Sc., Ph.D.
1074	Mike A. van Leeuwen et al., "Individual Relationship Between Progression of Radiological Damage and the Acute Phase Response in Early Rheumatoid Arthritis. Toward Development

	of a Decision Support System", *J. Rheumatology* 1997;24:1, 20-27 ("*Van Leeuwen 1997*")
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1076	Norihiro Nishimoto et al., "A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Trial of Humanized Anti-interleukin-6 (IL-6) Receptor Monoclonal Antibody (MRA) in Rheumatoid Arthritis (RA)," *Arthritis & Rheumatism*, Vol. 46, No. 9 (Supplement):S559 (2002) ("*Nishimoto Abstract*")
1077	Curriculum Vitae of Scott M. Lassman, Esq.
1078	U.S. National Library of Medicine, National Institutes of Health, ClinicalTrials.gov, *History, Policies, and Laws*, https://clinicaltrials.gov/ct2/about-site/history ("*ClinicalTrials.gov*, *History, Policies, and Laws*")
1079	Intentionally Left Blank
1080	Affidavit of Nathaniel E Frank-White (Internet Archive), including *ClinicalTrials.Gov, Basic Search* (p.5); *ClinicalTrials.Gov, Advanced Search* (p. 7); *ClinicalTrials.Gov, Help For Searching ClinicalTrials.Gov* (p.9) ("*Nathaniel E Frank White Aff.*")
1081	U.S. National Library of Medicine, National Institutes of Health, ClinicalTrials.gov, *How to Edit Your Study Record*, https://clinicaltrials.gov/ct2/manage-recs/how-edit ("*ClinicalTrials.gov, How to Edit Your Study Record*")
1082	Deborah A. Zarin et al., "Reporting 'Basic Results' in ClinicalTrials.gov", *CHEST* 136(1), 295-303 (July 2009) ("*Zarin*")
1083	U.S. National Library of Medicine, National Institutes of Health, *ClinicalTrials.gov, ClinicalTrials.gov Background*, https://www.clinicaltrials.gov/ct2/about-site/background ("*ClinicalTrials.gov Background*")
1084	Food & Drug Administration, *Drugs@FDA Homepage*, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm ("*Drugs@FDA Homepage*")
1085	Food & Drug Administration, *Drugs@FDA FAQ*, available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=faq.page ("*Drugs@FDA FAQ*")

1086	U.S. National Library of Medicine, National Institutes of Health, ClinicalTrials.gov, *Key Record Dates – NCT00965653*, https://clinicaltrials.gov/ct2/keydates/NCT00965653 ("*Key Record Dates*")
1087	U.S. National Library of Medicine, National Institutes of Health, ClinicalTrials.gov archive, *History of Changes for Study: NCT00965653*, https://clinicaltrials.gov/ct2/history/NCT00965653 ("*History of Changes*")
1088	U.S. National Library of Medicine, U.S. National Institutes of Health, ClinicalTrials.gov archive, *Changes (Merged) for Study: NCT00965653, August 21, 2009 (v1) – November 1, 2016 (v69)*, https://clinicaltrials.gov/ct2/history/ NCT00965653?A=1&B=69&C=merged#StudyPageTop ("*Comparison of August 21, 2009 Record and November 1, 2016 Record*")
1089	U.S. National Library of Medicine, National Institutes of Health, ClinicalTrials.gov archive, *Changes (Merged) for Study: NCT00965653, August 21, 2009 (v1) – August 26, 2009 (v2)*, https://clinicaltrials.gov/ct2/history/ NCT00965653?A=1&B=2&C=merged#StudyPageTop ("*Comparison of August 21, 2009 Record and August 26, 2009 Record*")
1090	U.S. National Library of Medicine, National Institutes of Health, ClinicalTrials.gov archive, *Changes (Merged) for Study: NCT00965653, August 26, 2009 (v2) – September 15, 2009 (v3)*, https://clinicaltrials.gov/ct2/history/ NCT00965653?A=2&B=3&C=merged#StudyPageTop ("*Comparison of August 26, 2009 Record and September 15, 2009 Record*")
1091	U.S. National Library of Medicine, National Institutes of Health, ClinicalTrials.gov archive, *Changes (Merged) for Study: NCT00965653, September 15, 2009 (v3) – October 15, 2009 (v4)*, https://clinicaltrials.gov/ct2/history/ NCT00965653?A=3&B=4&C=merged#StudyPageTop ("*Comparison of September 15, 2009 Record and October 15, 2009 Record*")
1092	Food & Drug Administration, *Drugs@FDA, BLA 125276 Homepage*, https://www.accessdata.fda.gov/scripts/cder /daf/index.cfm?event=overview.process&ApplNo=125276

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1095	Food & Drug Administration, *Drugs@FDA, BLA 125276 Approval Package*, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/125276s000TOC.cfm (“*BLA 125276 Approval Package*”)
1096	Actemra Summary Review, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/125276s000SumR.pdf (“*Actemra Summary Review*”)
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1098	Norihiro Nishimoto et al., “Toxicity, Pharmacokinetics, and Dose-Finding Study of Repetitive Treatment with the Humanized Anti-Interleukin 6 Receptor Antibody MRA in Rheumatoid Arthritis. Phase I/II Clinical Study,” *The Journal of Rheumatology* 30:1426–35 (2003) (“*Nishimoto 2003”*)
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1101	World Intellectual Property Office, WO2009041621, available at https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2009041621&tab=PCTDOCUMENTS (“*WIPO*”)
1102	Lawrence W. Dick et al., “Determination of the origin of the N-terminal pyro-glutamate variation in monoclonal antibodies using model peptides,” *Biotechnology & Bioengineering* 97(3):544–53 (November 10, 2006) (“*Dick*”)
1103	Dirk Chelius et al., “Formation of Pyroglutamic Acid from N-terminal glutamic acid In immunoglobulin gamma antibodies,” *Anal. Chem.* 78:2370–76 (April 1, 2006) (“*Chelius*”)

1104	Y. Diana Liu et al., "N-terminal glutamate to pyroglutamate conversion in vivo for human IgG2 antibodies," *J. of Biol. Chem.* 286(13):11211–17 (April 1, 2011) ("*Liu*")
1105	William E. Werner et al., "The removal of pyroglutamic acid from monoclonal antibodies without denaturation of the protein chains," *Anal. Biochem.* 342:120–25 (2005) ("*Werner*")
1106	Certificate of Translation (pg. 1), Translation (pgs. 2–27), & Original (pg. 28–52): PCT International Publication No. WO2005/090405 A1 ("*WO '405*")
1107	U.S. Patent No. 5,795,965 ("The '965 patent")
1108	NCATS description of tocilizumab, https://gsrs.ncats.nih.gov/ginas/app/substance/fff5a4c0-d59d-4327-b2e7-7e36e4e676e1 ("*NCATS – Tocilizumab*")
1109	Curriculum Vitae of Paul A. Dalby, Ph.D.
1110	Certificate of Translation (pg. 1-2), Translation (pgs. 3-32), & Original (pg. 33–64): PCT International Publication No. WO 2009084659A1 ("*Morichika"*)
1111	Package Insert for CIMZIA (certolizumab pegol), Revised May 2009 ("*CIMZIA 2009 Label*")
1112	U.S. Patent No. 8,568,720 ("The '720 patent")
1113	U.S. Patent No. 6,267,958 ("The '958 patent")
1114	September 17, 2013 PTO Notice of Final Determination and Requirement for Election for U.S. Pat. No. 5,795,965 ("*September 17, 2013 PTO Notice of Final Determination and Requirement for Election*")
1115	Prosecution File History of U.S. Patent No. 8,568,720 ("'720 File History")
1116	Package Insert for ACTEMRA (tocilizumab), Revised March 2021, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125276s131lbl.pdf ("*Actemra March 2021 Label*")
1117	Declaration of Yahn Lin Chu, Esq. ("Chu Decl.")

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), this is to certify that I caused to be served a true and correct copy of the foregoing Petition for Inter *Partes* Review (and accompanying Exhibits 1001-1117) by overnight courier (Federal Express or UPS), on this 21st day of February 2022, on the Patent Owner at the correspondence address of the Patent Owner as follows:

Genentech
1 DNA Way
South San Francisco, CA 94080

Respectfully submitted,

Dated: February 21, 2022

/Lora M. Green /
Lora M. Green, Lead Counsel
Reg. No. 43,541