Commissioner’s Decision # 1362
Décision du Commissaire # 1362

TOPICS: B00, F01, K11, O00
SUJETS: B00, F01, K11, O00

Application No. : 2,385,745

Demande n^{o}. : 2,385,745

IN THE CANADIAN PATENT OFFICE

DECISION OF THE COMMISSIONER OF PATENTS

Patent application number 2,385,745 having been rejected under subsection 30(3) of the *Patent Rules*, has been reviewed in accordance with paragraph 30(6)*(c)* of the *Patent Rules* by the Patent Appeal Board and the Commissioner of Patents. The recommendation of the Board and the decision of the Commissioner are as follows:

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INTRODUCTION

[1] This decision deals with a review of the rejection of patent application number 2,385,745 entitled "METHODS OF ADMINISTERING ANTI-TNF.ALPHA. ANTIBODIES" filed on 10 May 2002 by the Applicant, Abbott Laboratories (Bermuda) Ltd.

[2] A Summary of Reasons [SOR] was sent to the Patent Appeal Board [the Board] on 05 September 2012, which identified the following grounds for rejecting this application:

- certain claims are anticipated;
- all of the claims are obvious; and
- certain claims are non-statutory for being directed to methods of medical treatment.

[3] For the reasons that follow, we recommend that the application be refused.

BACKGROUND

[4] This application relates to the use of recombinant human antibodies that specifically bind to human tumor necrosis factor □ [TNF□] in the treatment of disorders in which TNF□ activity is detrimental. These antibodies have a high affinity for TNF□ and are able to neutralize TNF□ activity.

[5] TNF□ is a cytokine produced by numerous cell types, including monocytes and macrophages. TNF□ is a key regulator of inflammation and is important for the normal response to infection, but excessive production can be harmful. In particular, elevated levels of TNF□ □have been implicated in the pathophysiology of a variety of human diseases and disorders, including sepsis, infections, autoimmune diseases, transplant rejection, and intestinal disorders. This has led to the hypothesis that the treatment of these disorders may be achieved using antibodies that inhibit TNF□ activity. Indeed, therapeutic recombinant human antibodies specific for TNF□, which inhibit TNF□ activity, have been shown to be capable of controlling disease activity in rheumatoid arthritis and other inflammatory conditions.

[6] The present description relates to improved methods of treating disorders in which the administration of a neutralizing anti-TNF□ antibody is beneficial. This includes diseases and disorders in which inhibition of TNF□ activity is expected to alleviate the symptoms and/or progression of the disorder. Specifically, the Applicant is asserting that biweekly,

subcutaneous dosing provides many advantages over typical protocols for administering therapeutic antibodies which are performed intravenously on a weekly basis.

PROSECUTION HISTORY

[7] After several Office Actions, this application was rejected in a Final Action [FA] on 22 March 2011. The application was considered defective because certain claims were considered anticipated, all of the claims were considered obvious, certain claims were considered non-statutory, certain claims were considered to lack support and contain subject matter not reasonably to be inferred from the specification and drawings as originally filed and certain claims were found to lack utility over the entire scope of the claims. The lack of utility analysis was accompanied by a corresponding assertion that the specification was defective for failing to provide a sufficient disclosure with regard to the promised utility.

[8] In response to the FA, the Applicant chose to replace the claims on file with an amended claim set containing 126 claims and continued to argue in favour of the patentability of the claims.

[9] The Examiner maintained the rejection and indicated in the SOR that the Applicant had failed to overcome all of the defects identified in the FA. Notably, the SOR states that the amended claim set did overcome the grounds of lack of support, new subject matter, lack of utility and insufficient disclosure.

[10] A panel of three members of the Board was established and, during the course of our review, identified certain issues that required clarification. These observations were raised directly with the Applicant in a letter dated 20 August 2013. In particular, the Applicant was notified of the latest practice guidelines regarding medical use claims which mandate the use of purposive construction for claim analysis. The panel also requested that the Applicant distinguish between certain claims that appeared redundant in view of one another.

[11] The remaining grounds for rejection are:

- claims 102-104 contravene paragraphs 28.2(1)(*a*) and *(b*) of the Act for being anticipated;
- claims 1-126 contravene section 28.3 of the Act for being obvious; and
- claims 1-89 and 106-126 contravene section 2 of the Act for being directed to

non-statutory subject matter (methods of medical treatment).

[12] In response to the SOR and the panel's letter, the Applicant provided written submissions, serving as the basis for its presentation at an oral hearing, which was held on 25 November 2013. In its written submissions, the Applicant also requested consideration of a proposed claim set. This was presented in order to address the defects related to anticipation, obviousness, non-statutory subject matter and indefiniteness.

[13] Although this review is conducted on the basis of the claims submitted in response to the FA, as shall be seen below the proposed claim set is also considered.

THE ISSUES

[14] In view of the grounds for rejection cited by the Examiner we must address the following three questions:

(1) Are the claimed preloaded syringes anticipated?
(2) Are the claims obvious?
(3) Are certain claims non-statutory for covering a method of medical treatment?

THE CLAIMS

[15] Claims 1-126 on file contain 31 independent claims, defining the use of anti-TNF□ antibodies for inhibiting TNF□ activity in a human subject suffering from an arthritic disease or an inflammatory bowel disease, preloaded syringes containing a pharmaceutical composition comprising anti-TNF□ antibodies and kits comprising preloaded syringes comprising anti-TNF□ antibodies. The following claims are representative of the claims considered to be defective:

1. Use of an isolated human anti-TNF□ antibody, or an antigen-binding portion thereof, in the manufacture of a medicament for inhibiting human TNF□ activity in a human subject suffering from an arthritic disease or an inflammatory bowel disease wherein the medicament is adapted for subcutaneous, biweekly administration of every 13-15 days on a continuous schedule as a total body dose, wherein the total body dose is the same dose amount throughout the course of biweekly administration and the dose amount consists of about 40 mg of said human anti-TNF□ antibody, wherein said human anti-TNF□ antibody neutralizes human TNF□ cytotoxicity in a standard *in vitro* L929 assay with an IC_{50} of 1 x 10^{-9} M, comprises a light chain variable region (LCVR) comprising a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, a

CDR2 domain comprising the amino acid sequence of SEQ ID NO: 5, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 7, and comprises a heavy chain variable region (HCVR) comprising a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 6, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 8.

27. A pharmaceutical composition for inhibiting human TNF□ activity in a human subject suffering from an arthritic disease or an inflammatory bowel disease, comprising an isolated human anti-TNF□ antibody, or an antigen-binding portion thereof, and a pharmaceutically acceptable carrier, wherein the anti-TNF□ antibody, or an antigen-binding portion thereof, is adapted for subcutaneous, biweekly administration of every 13-15 days on a continuous schedule as a total body dose, wherein the total body dose is the same dose amount throughout the course of biweekly administration and the dose amount consists of about 40 mg and wherein the human anti-TNF□ antibody neutralizes human TNF□ cytotoxicity in a standard in vitro L929 assay with an IC_{50} of 1×10^{-9} M, comprises a light chain variable region (LCVR) comprising a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, a CDR2 domain comprsing the amino acid sequence of SEQ ID NO: 5, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 7, and comprises a heavy chain variable region (HCVR) comprising a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 6, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 8.

48. An isolated human anti-TNF□ antibody, or an antigen-binding portion thereof, for use in inhibiting human TNF□ activity in a human subject suffering from an arthritic disease or an inflammatory bowel disease, in accordance with a continuous schedule comprising biweekly dosing of every 13-15 days, wherein the human anti-TNF□ antibody, or an antigen-binding portion thereof, is adapted for subcutaneous administration as a total body dose, wherein the total body dose is the same dose amount throughout the course of biweekly dosing and the dose amount consists of about 40 mg, and wherein said human anti-TNF□ antibody neutralizes human TNF□ cytotoxicity in a standard in vitro L929 assay with an IC_{50} of 1×10^{-9} M, comprises a light chain variable region (LCVR) comprising a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, a CDR2 domain comprsing the amino acid sequence of SEQ ID NO: 5, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 7, and comprises a heavy chain variable region (HCVR) comprising a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, a CDR2 domain comprising the amino acid sequence of

SEQ ID NO: 6, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 8.

69. Use of an isolated human anti-TNF□ antibody, or an antigen-binding portion thereof, to treat an arthritic disease or an inflammatory bowel disease, wherein the anti-TNF□ antibody, or an antigen-binding portion thereof, is adapted for subcutaneous, biweekly administration of every 13-15 days on a continuous schedule as a total body dose, wherein the total body dose is the same dose amount throughout the course of biweekly administration and the dose amount consists of about 40 mg, and

wherein the human anti-TNF□ antibody neutralizes human TNF□ cytotoxicity in a standard in vitro L929 assay with an IC_{50} of 1 x 10^{-9} M, comprises a light chain variable region (LCVR) comprising a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, a CDR2 domain comprsing the amino acid sequence of SEQ ID NO: 5, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 7, and comprises a heavy chain variable region (HCVR) comprising a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, a CDR2 domain comprising the amino acid

sequence of SEQ ID NO: 6, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 8.

90. A kit comprising a preloaded syringe comprising a total body dose consisting of about 40 mg of any one of the isolated human anti-TNF□ antibody of claims 48-54, or antigen-binding portion thereof, and a pharmaceutically acceptable carrier, wherein the kit contains instructions for biweekly, subcutaneous administration of every 13-15 days on a continuous schedule for the treatment of arthritic disease or an inflammatory bowel disease.

102. A preloaded syringe containing a pharmaceutical composition of any one of claims 27-33, and wherein the preloaded syringe is adapted for subcutaneous, biweekly self-administration of the pharmaceutical composition of every 13-15 days on a continuous schedule.

[16] During the course of our review the panel noted that independent claims 1, 27, 48 and 69 appear to all be directed to second medical uses of similar scope. For example, claim 1 appears in the form of a “Swiss-type” medical use claim; claim 27 appears in the form of a “composition for use” claim; claim 48 appears in the form of an “antibody for use” claim; and claim 69 appears as a direct use claim. However, each of these claims is related in that they reference an isolated human anti-TNF□ antibody for “inhibiting human TNF□ activity in a human subject suffering from an arthritic disease or inflammatory bowel disease” and a dosage regimen specifying subcutaneous, biweekly administration of a dose

amount of about 40 mg. We also noted that a similar relationship appears in the following claim groups: claims 2, 28, 49 and 70; claims 3, 29, 50 and 71; claims 4, 30, 51 and 72 claims 5, 31, 52 and 73; claims 6, 32, 53 and 74; claims 7, 33, 54 and 75; claims 8 and 34; claims 9 and 55; claims 10, 35, 56; claims 11, 36, 57; claims 12, 37, 58; claims 13, 38, 59; claims 14, 39, 60; claims 15, 40, 61 and 76; claims 17 and 87; claims 19 and 88; claims 41, 62 and 77; claims 42, 63 and 78; claims 43, 64 and 79; claims 44, 65 and 80; claims 45, 66 and 81; claims 46, 67 and 82; claims 47, 68 and 83; claims 84, 117 and 122; claims 85, 119 and 124; claims 86, 118 and 123; claims 116 and 121; claims 120, 125 and 126.

PURPOSIVE CONSTRUCTION

[17] Purposive construction must be done before considering the issues of validity or infringement. During purposive construction, the elements of the claimed invention are identified as either essential or non-essential: *Free World Trust v Electro Santé Inc*, 2000 SCC 66 [*Free World Trust*]. In order for an element to be considered "non-essential", "it must be shown either (i) that on a purposive construction of the words of the claim it was clearly *not* intended to be essential, or (ii) that at the date of publication of the patent, the skilled addressees would have appreciated that a particular element could be substituted without affecting the working of the invention" (*Free World Trust* at para. 55).

[18] Further, a purposive construction of the claims requires that they be interpreted in light of the whole of the disclosure, including the specification: *Whirlpool Corp. v Camco Inc.*, 2000 SCC 67. It is also expected that one should recognize "that a patentable invention is an inventive solution to a practical problem" and "that an invention must be disclosed (and ultimately claimed) so as to provide the person skilled in the art with an operable solution": Office Patent Notice published 08 March 2013 entitled "*Practice Guidance Following the Amazon FCA Decision*" and its accompanying memo, PN 2013-02.

The person skilled in the art and their relevant common general knowledge

[19] During the course of our review, the panel reviewed the statements in the FA pertaining to the person of skill in the art [POSITA] and the common general knowledge [CGK]. Although these definitions were provided in the context of an obviousness analysis they are applicable to all analyses. In a letter dated 21 August 2013, the panel noted that the Applicant had not provided any reasons to refute the Examiner's characterization of the POSITA and the CGK and invited the Applicant to address these points in writing and/or

at the hearing. In written submissions provided on 04 November 2013, the Applicant indicated that although it was not necessary to take a position on the nature of the skilled person, the Examiner's characterization of the level of experience and knowledge of the skilled person was in dispute.

[20] The FA states that: "[t]he person skilled in the art is a skilled clinical immunologist with significant experience in clinical trial management and extensive knowledge in fundamental immunology."

[21] As indicated above, the Applicant did not agree with this characterization of the level of experience and knowledge of the skilled person. The Applicant felt that by describing the skilled person as having "significant experience " and "extensive general knowledge" the level of competence and knowledge of this person had been elevated to a standard that is well above the "ordinary " level permitted by law, citing *Beloit Canada Ltd. v Valmet Oy* (1986), 8 C.P.R. (3d) 289 page 294 [*Beloit*].

[22] Despite the Applicant's disagreement with the Examiner's more stringent characterization of the level of the skill of the person skilled in the art, the Applicant asked its experts to approach the prior art references set out in the FA using this characterization, but with the view that such person is unimaginative.

[23] We note that, although the Applicant did not agree with the level and experience that the Examiner attributed to the POSITA it did not dispute the Examiner's characterization of the POSITA as a skilled clinical immunologist. We consider this definition to be consistent with the background of the description which provides reasonable guidance as to the person(s) to whom the patent application is directed. As indicated above (para. [6]), the present application relates to improved methods of treating disorders in which the administration of a neutralizing anti-TNF□ antibody is beneficial. On this basis the Examiner's characterization of the person skilled in the art as a skilled clinical immunologist is reasonable. We also agree with the Applicant, consistent with the teachings of *Beloit*, that said person is unimaginative.

[24] Although the Examiner has defined the level of experience and general knowledge of the skilled person as "significant" and "extensive," respectively, we note that these characterizations are qualified by the CGK as defined in the FA. Accordingly, we will address these qualifiers in the context of the relevant common general knowledge the POSITA would be expected to have.

[25] Specifically, the FA characterizes the CGK of that person: "[t]he person skilled in the art is aware that the dosing requirements of a given medication are routinely assessed in clinical trials. The person skilled in the art is aware of the advantages and benefits of conducting cost-effectiveness analysis of the dosing of a given medication. The person skilled in the art is aware of the advantages and disadvantages of the different routes of administration or self-administration available, such as intravenous, subcutaneous, oral or topical. The person skilled in the art is aware of the advantages of fully human monoclonal antibodies over mouse or chimeric antibodies as therapeutic agents for use in human. The person skilled in the art is aware of beneficial roles played by the inflammatory cytokine TNF in normal immune response and the detrimental roles played by TNF in inflammatory diseases such as arthritic diseases and inflammatory bowel diseases. The person skilled in the art is aware of the routinely used therapeutic agent for treating arthritic diseases and inflammatory bowel diseases."

[26] This characterization of the common general knowledge is consistent with the declaration provided by Dr. Janet Pope, an expert working for the Applicant, which makes it clear that it was common general knowledge for the person skilled in the art to use properly designed clinical trials to determine a proper dosing regimen, including the dosing interval. Similar to the Examiner, Dr. Pope also acknowledged that it was common general knowledge to treat rheumatoid arthritis and other autoimmune diseases using known therapeutic agents such as the isolated human anti-TNF antibody D2E7 or methotrexate.

[27] The only point that was challenged was the Examiner's reference that it would be common general knowledge to dose a medication based on cost-effectiveness. Dr. Pope argued that this was manifestly untrue, that as a skilled clinical immunologist, the person skilled in the art would primarily be concerned with the safety and effectiveness of a drug. On this point we agree with the Applicant; the skilled person would not consider cost-effectiveness to be a factor in determining an appropriate therapeutic dosing regimen.

[28] We consider that the POSITA would possess the CGK identified by the Examiner and acknowledged by the Applicant. This determination is consistent with the background of the description which informs us that the skilled person is to be reasonably well read as to the state of the art regarding therapeutic strategies for the treatment of diseases and disorders in which elevated levels of TNF has been implicated; see *Manual of Patent Office Practice*, section 9.02.02. We also note that there is nothing in the Examiner's characterization of the CGK which would require the skilled person to have "significant

experience" in clinical trial management and "extensive knowledge" in fundamental immunology.

The problem and solution that the invention addresses

[29] Based on the description, the problem addressed by the claimed invention relates to improved methods for the treatment of TNF□ related disorders. As indicated above (para. [5]), the over production of TNF□ has been implicated in the pathophysiology of a variety of human diseases and disorders. Therapeutic strategies to inhibit or counteract TNF□ activity include the use of recombinant human antibodies that specifically bind to, and neutralize, human TNF□. Unlike typical protocols which call for administering therapeutic antibodies intravenously on a weekly basis, the present invention relates to a subcutaneous, self-administered, biweekly dosing regimen as a solution.

[30] Specifically, the description discloses that biweekly dosing has many advantages over weekly dosing including, but not limited to, a lower number of total injections, decreased number of injection site reactions (e.g., local pain and swelling), increased patient compliance (i.e., due to less frequent injections), and less cost to the patient as well as the health care provider. Subcutaneous dosing is advantageous because the patient may self-administer a therapeutic substance, e.g., a human TNF□ antibody, which is convenient for both the patient and the health care provider.

Claim 1, purposively construed

[31] The language of claim 1 is consistent with the phrasing of "Swiss-type" medical use claims. This format originated in the Swiss Federal Intellectual Property Office to enable protection for a second or subsequent medical use of a known compound or composition. In this instance, claim 1 defines the use of an isolated anti-TNF□ antibody, or antigen-binding portion thereof, in the manufacture of a medicament, wherein the manufactured medicament is intended for inhibiting human TNF□ activity in a human subject suffering from an arthritic disease or inflammatory bowel disease. A literal interpretation may suggest that the use in claim 1 of an anti-TNF□ antibody is simply for the manufacture of a medicament. Indeed, the claim further defines the medicament as being "adapted for subcutaneous, biweekly administration of every 13-15 days on a continuous schedule as a total body dose." However, a purposive construction of the claim does not support such an interpretation because, as indicated earlier (para. [29]), the present invention relates to improved methods for the treatment of TNF□ related disorders that feature a

subcutaneous, biweekly dosing regimen. Moreover, a literal interpretation would be inconsistent with the Applicant's submission at the hearing that, in its view, "when construing a use claim versus a Swiss-type use claim they are all the same and we shouldn't be drawing semantic hairline distinctions."

[32] Further, nowhere in the description are the medicaments characterized as being "adapted for subcutaneous, biweekly administration." A review of the prosecution history indicates that this expression was introduced into the claims in an amendment dated 16 January 2008 citing Example 3 of the description for support. Example 3 discloses the biweekly, subcutaneous administration of an anti-TNF□ antibody. During the course of our review, the panel invited the Applicant to clarify the nature of the claimed adaptation, and in particular, whether or not the anti-TNF□ antibody or medicament containing said antibody required any adaptation to make it suitable for subcutaneous, biweekly administration. At the hearing, the Applicant acknowledged that every other week administration is not intrinsic to the product and that there is no attribute of the antibody or the medicament that requires you to administer it every other week—it can be administered every other day or every other year. Instead, the Applicant indicated that reference to the adaptation was a claiming convenience, which in accordance with the context, is meant to reflect a use limitation.

[33] In view of the above, we construe claim 1 to mean the use of an anti-TNF□ antibody for inhibiting human TNF□ activity in a human subject suffering from an arthritic disease or inflammatory bowel disease.

[34] Therefore, claim 1 is construed to have the following essential elements:

(i) the use of an isolated human anti-TNF□ antibody, or an antigen binding portion thereof, wherein said human anti-TNF□ antibody neutralizes human TNF□ cytotoxicity in a standard *in vitro* L929 assay with an IC_{50} of 1×10^{-9} M, comprises a light chain variable region (LCVR) comprising a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 5, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 7, and comprises a heavy chain variable region (HCVR) comprising a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 6, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 8

(ii) to inhibit human TNF□ activity in a human subject suffering from an arthritic disease or inflammatory bowel disease

(iii) for subcutaneous administration
(iv) for biweekly administration of every 13-15 days on a continuous schedule
(v) wherein the dose amount is about 40 mg.

Other independent claims

[35] The remaining independent claims define alternative embodiments of the invention and have been purposively construed below.

Claims 16 and 18

[36] Independent claims 16 and 18 are "Swiss-type" medical use claims similar to claim 1, except these claims place further limitations on the anti-TNF□ antibody and the disease. In claim 16, the anti-TNF□ antibody is defined as D2E7 and the disease is restricted to arthritic disease. In claim 18, the anti-TNF□ antibody is defined as D2E7 and the disease is restricted to inflammatory bowel disease.

Claim 27

[37] The language of independent claim 27 is consistent with a "composition for use" claim and is considered an alternative format for claiming the use of a compound or composition. Specifically, claim 27 defines a pharmaceutical composition for inhibiting human TNF□ activity in a human subject suffering from an arthritic disease or inflammatory bowel disease, comprising an isolated human anti-TNF□ antibody, or an antigen binding portion thereof, and a pharmaceutically acceptable carrier. Similar to claim 1, this claim further defines the anti-TNF□ antibody as being "adapted for subcutaneous, biweekly administration of every 13-15 days on a continuous schedule as a total body dose." Consistent with our purposive construction of claim 1, we find that this expression does not limit the antibody *per se* but rather characterizes how and when the antibody is to be used. Therefore, claim 27 is construed to have the same essential elements as claim 1.

Claim 48

[38] Independent claim 48 is an "antibody for use" claim which defines an isolated human anti-TNF□ antibody, or an antigen binding portion thereof, for use in inhibiting human TNF□ activity in a human subject suffering from an arthritic disease or inflammatory bowel disease. Similar to claims 1 and 27, this claim further defines the anti-TNF□ antibody as being "adapted for subcutaneous, biweekly administration of every 13-15 days on a

continuous schedule as a total body dose." Consistent with our purposive construction of claims 1 and 27, we find that this expression does not limit the antibody *per se* but rather characterizes how and when the antibody is to be used. Therefore, claim 48 is construed to have the same essential elements as claims 1 and 27.

Claim 69

[39] Independent claim 69 is a "direct use" claim which claims the use of an isolated human anti-TNF□ antibody, or an antigen binding portion thereof, to treat an arthritic disease or inflammatory bowel disease. Similar to claims 27 and 48, this claim further defines the anti-TNF□ antibody as being "adapted for subcutaneous, biweekly administration of every 13-15 days on a continuous schedule as a total body dose." Consistent with our purposive construction of claims 27 and 48 we find that this expression is not intended to limit the antibody *per se* but rather characterizes how and when the antibody is to be used.

[40] Although claim 69 relates to the use of the antibody to "treat an arthritic disease or inflammatory bowel disease" we see no practical distinction over the use as defined in claims 1, 27 and 48 of "inhibiting human TNF□ activity in a human subject suffering from an arthritic disease or inflammatory bowel disease" as inhibiting human TNF□ activity merely defines the mechanism of action by which the anti-TNF□ antibody is expected to alleviate the symptoms and/or progression of the disorder i.e. treat an arthritic disease or inflammatory bowel disease. Therefore, claim 69 is construed to have the same essential elements as claims 1, 27 and 48.

Claims 84-89, claims 106-111 and claims 121-126

[41] Independent claims 84-89, 106-111 and 121-126 are direct use claims similar to claim 69, except these claims place further limitations on the anti-TNF□ antibody and the disease. In claims 84-86 and 121-126, the anti-TNF□ antibody is defined as having a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 2 and the disease is restricted to either rheumatoid arthritis (claims 84 and 122), Crohn's disease (claims 85 and 124), rheumatoid spondylitis (claims 86 and 123), an arthritic disease (claim 121) or ulcerative colitis (claims 125 and 126). In claims 87-89, the anti-TNF□ antibody is defined as D2E7 and the disease is restricted to either rheumatoid arthritis (claim 87), Crohn's disease (claim 88) or rheumatoid spondylitis (claim 89).

[42] In claims 106-111, the anti-TNF□ antibody is defined as having a light chain variable region

(LCVR) comprising a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 5, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 7, and comprises a heavy chain variable region (HCVR) comprising a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 6, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 8 and the disease is restricted to either rheumatoid arthritis (claim 106), rheumatoid spondylitis (claim 107), osteoarthritis (claim 108), gouty arthritis (claim 109), Crohn's disease (claim 110) or ulcerative colitis (claim 111).

Claim 90

[43] Independent claim 90 is a kit claim comprising a preloaded syringe comprising a total body dose of about 40 mg of any one of the isolated human anti-TNF□ antibodies of claims 48-54, or antigen binding portion thereof, and a pharmaceutically acceptable carrier. During prosecution, the meaning of the term "preloaded syringe" was a point of dispute between the Examiner and the Applicant. In the FA, the Examiner maintained that subcutaneous administration inherently requires a preloaded syringe. The Examiner further explained in the SOR that the POSITA understands that a syringe must be loaded before being used (i.e., preloaded). In its submissions to the panel the Applicant argued that "preloaded syringe" is a term of art—it means there is no need for a physician or patient to reconstitute or draw up a dose from a vial—it arrives from the manufacturer ready-for-use. This definition was supported by the two experts who provided declarations on behalf of the Applicant. We agree with the Applicant that "preloaded syringe" is a term of art which the skilled person would understand is meant to exclude syringes that are filled just prior to administration by the patient, a caregiver or health care professional.

[44] The kit is further defined as containing instructions for biweekly, subcutaneous administration every 13-15 days of the human anti-TNF□ antibody on a continuous schedule for the treatment of an arthritic disease or inflammatory bowel disease. Although the Applicant construed the use limitations outlined in the instructions to be essential, we do not agree. As the instructions themselves have purely intellectual significance and do not materially affect the functioning of the other contents of the kit their inclusion is not considered essential.

[45] However, as indicated below (para. [49]), the Applicant clarified that the preloaded syringe has an intrinsic route of administration limitation as not every preloaded syringe can be used subcutaneously.

[46] Therefore, claim 90 has been construed to define a kit having the following essential elements:

(i) a preloaded syringe for subcutaneous administration
(ii) comprising a total body dose consisting of about 40 mg
(iii) comprising any one of the isolated human anti-TNF□ antibody of claims 48-54, or antigen binding portion thereof, wherein the human anti-TNF□ antibody neutralizes human TNF□ cytotoxicity in a standard *in vitro* L929 assay with an IC_{50} of 1 x 10^{-9}M, comprises a light chain variable region (LCVR) comprising a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 5, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 7, and comprises a heavy chain variable region (HCVR) comprising a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 6, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 8.

Claim 102

[47] Independent claim 102 is a product claim characterized as comprising a pharmaceutical composition of any one of claims 27-33 in a preloaded syringe. There are no explicit limitations in this claim that the preloaded syringe is for a particular medical use, i.e., "for the treatment of an arthritic disease or inflammatory bowel disease."

[48] However, the preloaded syringe is further characterized as being "adapted for subcutaneous, biweekly self-administration of the pharmaceutical composition of every 13-15 days on a continuous schedule." During the course of our review, the panel invited the Applicant to clarify the nature of the claimed adaptation to the preloaded syringe. In its submissions at the hearing, the Applicant construed the claim to the preloaded syringe as a product claim with a use limitation and a route of administration limitation.

[49] With respect to the route of administration the Applicant indicated that this limitation was intrinsic to the preloaded syringe as not every preloaded syringe can be used subcutaneously. We agree with the Applicant that in this case the route of administration is an intrinsic feature of the preloaded syringe. However, we do not agree that the use limitation of a biweekly dosing interval is an essential element. Similar to our reasoning in respect of the instructions contained in the kit claim, this particular use limitation has not

been shown to have a material effect on the structure or contents of the preloaded syringe. Indeed, the Applicant has already acknowledged that every other week administration is not intrinsic to the product—it can be administered every other day or every other year [para. 32].

[50] Therefore, the reference to biweekly administration does not limit the scope of the syringe in any way and claim 102 has been construed to define a preloaded syringe, for subcutaneous administration, comprising a pharmaceutical composition of any one of claims 27-33. It follows that claim 102 is construed to have the following essential elements:

(i) a preloaded syringe for subcutaneous administration
(ii) comprising an isolated human anti-TNF□ antibody, or antigen binding portion thereof wherein said human anti-TNF□ antibody neutralizes human TNF□ cytotoxicity in a standard *in vitro* L929 assay with an IC_{50} of 1 x 10^{-9} M, comprises a light chain variable region (LCVR) comprising a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 5, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 7, and comprises a heavy chain variable region (HCVR) comprising a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 6, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 8
(iii) wherein the dose amount of the anti-TNF□ antibody, or antigen binding portion thereof consists of about 40 mg.

Claims 116-120

[51] Independent claims 116-120 are "antibody for use" claims similar to claim 48, except these claims place further limitations on the anti-TNF□ antibody and the disease. In each of these claims the anti-TNF□ antibody is defined as having a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 2 and the disease is restricted to either an arthritic disease (claim 116), rheumatoid arthritis (claim 117), rheumatoid spondylitis (claim 118), Crohn's disease (claim 119) or ulcerative colitis (claim 120).

Dependent claims

[52] The dependent claims add features such as the presence of an additional therapeutic agent,

additional limitations to the anti-TNF□ antibody and specific arthritic or inflammatory bowel diseases. The prosecution history reveals no disagreement between the Applicant or Examiner as to the meaning or understanding of these claims.

Claim redundancy

[53] As indicated earlier, the panel noted that multiple claims setting out second medical uses of similar scope appear in the claim set on file. The Applicant did not specifically address this concern in the context of the claims on file as its written submissions to the panel included a proposed set of claims. However, at the hearing the Applicant acknowledged that all of the elements of the claims that are critical elements are the same.

[54] To aid in our analysis, the preambles for claims 1, 27, 48 and 69 are reproduced below:

> 1. Use of an isolated human anti-TNF□ antibody, or an antigen-binding portion thereof, in the manufacture of a medicament for inhibiting human TNF□ activity in a human subject suffering from an arthritic disease or an inflammatory bowel disease ...
>
> 27. A pharmaceutical composition for inhibiting human TNF□ activity in a human subject suffering from an arthritic disease or an inflammatory bowel disease ...
>
> 48. An isolated human anti-TNF□ antibody, or an antigen-binding portion thereof, for use in inhibiting human TNF□ activity in a human subject suffering from an arthritic disease or an inflammatory bowel disease ...
>
> 69. Use of an isolated human anti-TNF□ antibody, or an antigen-binding portion thereof, to treat an arthritic disease or an inflammatory bowel disease ...

[55] Although the preambles of these claims are not identical, we have already established in our purposive construction that these claims are alternative formats that define the same subject matter. Specifically, the body of the claims define the particular means to be applied to achieve the inhibition of TNF□ activity in a human subject suffering from an arthritic disease or an inflammatory bowel disease. Given that each of these claims define identical means we see no practical distinction in their scope as each of these use claims achieves the same result. If there is a difference in scope, based on the specification as a whole, it is not apparent. Therefore, claims 1, 27, 48 and 69 are considered to be redundant in view of one another and can be analyzed collectively. Similar claim groupings can be made between

the following claims: claims 2, 28, 49 and 70; claims 3, 29, 50 and 71; claims 4, 30, 51 and 72 claims 5, 31, 52 and 73; claims 6, 32, 53 and 74; claims 7, 33, 54 and 75; claims 8 and 34; claims 9 and 55; claims 10, 35, 56; claims 11, 36, 57; claims 12, 37, 58; claims 13, 38, 59; claims 14, 39, 60; claims 15, 40, 61 and 76; claims 17 and 87; claims 19 and 88; claims 41, 62 and 77; claims 42, 63 and 78; claims 43, 64 and 79; claims 44, 65 and 80; claims 45, 66 and 81; claims 46, 67 and 82; claims 47, 68 and 83; claims 84, 117 and 122; claims 85, 119 and 124; claims 86, 118 and 123; claims 116 and 121; claims 120, 125 and 126.

[56] Further, the lack of clarity in the difference in scope of the claims leads to avoidable ambiguity. It follows that the lack of clear differentiation between claims 1, 27, 48 and 69 makes these claims indefinite and therefore non-compliant with subsection 27(4) of the *Patent Act*. Similarly, the lack of clear differentiation between claims 2, 28, 49 and 70; claims 3, 29, 50 and 71; claims 4, 30, 51 and 72 claims 5, 31, 52 and 73; claims 6, 32, 53 and 74; claims 7, 33, 54 and 75; claims 8 and 34; claims 9 and 55; claims 10, 35, 56; claims 11, 36, 57; claims 12, 37, 58; claims 13, 38, 59; claims 14, 39, 60; claims 15, 40, 61 and 76; claims 17 and 87; claims 19 and 88; claims 41, 62 and 77; claims 42, 63 and 78; claims 43, 64 and 79; claims 44, 65 and 80; claims 45, 66 and 81; claims 46, 67 and 82; claims 47, 68 and 83; claims 84, 117 and 122; claims 85, 119 and 124; claims 86, 118 and 123; claims 116 and 121; and, claims 120, 125 and 126; respectively, makes these claims non-compliant with subsection 27(4) of the *Patent Act*.

[57] Moreover, the multiple independent claims which have been identified as having all the same features are also considered defective for not complying with subsection 87(1) of the *Patent Rules*.

[58] However, as shall be seen below, given our conclusions regarding the patentability of the claims, we do not need to further consider these defects.

ISSUE 1: ARE THE CLAIMED PRELOADED SYRINGES ANTICIPATED?

Legal Framework

[59] The statutory provision relevant for assessing anticipation is subsection 28.2(1) of the *Patent Act*. That subsection provides, in part:

> The subject-matter defined by a claim in an application for a patent in Canada (the "pending application") must not have been disclosed
>
> (*a*) more than one year before the filing date by the applicant, or by a person who obtained knowledge, directly or indirectly, from the applicant, in such

> a manner that the subject-matter became available to the public in Canada or elsewhere;
> (*b*) before the claim date by a person not mentioned in paragraph (*a*) in such a manner that the subject-matter became available to the public in Canada or elsewhere.

[60] In *Free World Trust* (at para. 25) the Supreme Court made clear that if a single prior art publication discloses all of the essential elements of the claimed invention in an enabling manner, there is anticipation.

[61] In *Apotex Inc. v Sanofi-Synthelabo Canada Inc.*, 2008 SCC 61 [*Sanofi*], the Supreme Court further clarified the test for anticipation by explicitly endorsing a two-step approach in which the requirements of "prior disclosure" and "enablement" should be considered separately.

[62] In order to meet the disclosure requirement for anticipation, there must be disclosure of subject matter which, if performed, would necessarily result in infringement of the claim(s). The person skilled in the art is taken as trying to understand what the author of the disclosure meant; trial and error experimentation is not permitted when considering the disclosure test. If the disclosure test is satisfied, it is necessary to then consider enablement.

[63] At the enablement stage, the question is whether the skilled person would be able to work the invention. Trial and error experiments are permitted at this stage, so long as they do not involve an inventive step or undue burden.

The Examiner's position

[64] In the FA and SOR, the Examiner maintained that the claimed preloaded syringes were anticipated by two prior art studies which disclosed the subcutaneous administration of a human anti-TNF□ antibody, D2E7, to patients suffering from rheumatoid arthritis: see Kempeni, Annals of the Rheumatic Diseases 1999: 58, Supplemental I70-I72 and Rau, Zeitschrift für Rheumatologie 1999: 58, Supplemental S51.

[65] Although no syringe is specifically disclosed in either Kempeni or Rau, the Examiner further observed that subcutaneous administration inevitably requires a preloaded syringe. As indicated above (para. [43]), the Examiner construed the term "preloaded syringe" to encompass a syringe that is loaded before being used. The Examiner also argued that "a

syringe is inherently adapted for self-administration."

[66] With respect to a dose amount of 40 mg, this dose is encompassed by the teachings of Rau which discloses a phase 2 clinical study in which patients received 20, 40 or 80 mg of D2E7 weekly subcutaneously. Similarly, a dose amount of 40 mg is also encompassed by the teachings of Kempeni which discloses administration of any dose from 0.5 mg/kg to 10 mg/kg, a range that necessarily includes 40 mg/80 kg (80 kg being the average weight for the average human subject).

The Applicant's position

[67] As indicated above (para. [43]), the Applicant has argued that "preloaded syringe" is a term of art and would not be understood by the skilled addressee to include syringes that are filled just prior to administration by the patient, a caregiver or health care professional. Given this construction of the phrase "preloaded syringe," the Applicant maintained their position that a preloaded syringe adapted for subcutaneous self-administration is not disclosed by either reference.

[68] Specifically, the Applicant argued that subcutaneous administration as referred to in Kempeni and Rau would have been understood by the person skilled in the art, given the format in which the investigational agent was then distributed, to mean that the person administering the dose first reconstituted the lyophilized drug, then drew the drug up into an (empty) syringe. This is not a "preloaded syringe" as that term is understood by those skilled in the art.

[69] In response to the FA the Applicant also argued that, in respect to a fixed dose of about 40 mg of the recited antibody, Kempeni discloses a body weight-based dosing regimen that teaches away from the presently claimed fixed dose. The Applicant also pointed out that there was no evidence that at least one patient that was treated with weekly, subcutaneous injections of 0.5 mg/kg of D2E7 actually had a body weight of 80 kg or that the patient population being treated had an average body weight of about 80 kg.

[70] Concerning the phase 2 study described in Rau, in which some patients were administered 40 mg of D2E7 subcutaneously on a weekly basis, the Applicant argued that there is not enough evidence to necessarily reach the conclusion that a preloaded syringe having about 40 mg of antibody was used. Instead, the Applicant posited that, at least in theory, a large capacity syringe that can hold 200 mg (or more) of antibody could be used to facilitate

successive injections of 40 mg of drug to a group of patients, with only needle tip changes in between injections.

[71] Finally, the Applicant has argued that an uninventive skilled person would not read the prior art references and understand that any syringe that is preloaded in the course of the teachings of the references could be adapted for self-administration. In particular, the references teach none of the factors that need to be considered with a preloaded syringe for self-administration, "such as ensuring that the syringe is properly loaded with the appropriate amount of the composition, ensuring that the composition appears as it should or requires further agitation, determining what to do with air bubbles, determining how and when to store the preloaded syringe."

Analysis under the *Sanofi* Two-Step Approach

Disclosure

[72] We agree with the Examiner that the person skilled in the art would understand that a syringe must be loaded before being used (i.e., preloaded), however, we also agree with the Applicant that this is not the construction that a person skilled in the art would attribute to a "preloaded syringe." We have already determined (at para. [43]) that "preloaded syringe" is a term of art—it means there is no need for a physician or patient to reconstitute or draw up a dose from a vial—it arrives from the manufacturer ready-for-use. By definition, it is meant to exclude syringes that are filled just prior to administration by the patient, a caregiver or health care professional.

[73] As indicated above, in order to meet the disclosure requirement for anticipation, the prior art must disclose subject matter which, if performed, would necessarily result in something within the claims. In this context, what must be considered is whether the skilled person would understand that the presently claimed syringe which is ready-for-use, without the need to reconstitute the antibody or draw up the dose from a vial into an empty syringe, can be distinguished from the syringe that is disclosed by either Kempeni or Rau.

[74] As indicated by the Examiner, both Kempeni and Rau teach subcutaneous administration, which inevitably requires a syringe be loaded prior to use. We have already established in our analysis of claim 102 that characterizing the preloaded syringe as being "adapted for subcutaneous, biweekly self-administration of the pharmaceutical composition of every 13-15 days on a continuous schedule" is meant to reflect a use limitation and a route of

administration limitation. The adaptation is not meant to imply that any structural modifications have been made to the syringe. Therefore, the presently claimed preloaded syringe *per se* cannot be distinguished from a syringe that would be used for subcutaneous administration as taught by either Kempeni or Rau.

[75] Similarly, with respect to the contents of the syringe, there is no evidence that the pharmaceutical compositions contained in the presently claimed preloaded syringes can be distinguished from the subcutaneous doses of D2E7 antibody as disclosed in either Kempeni or Rau. Indeed, the description broadly refers to pharmaceutical compositions formulated in a manner suitable for the intended mode of administration and therapeutic application. As there is no mention of any specific formulation requirements associated with a preloaded syringe for subcutaneous administration, the contents of the syringe cannot be distinguished from the subcutaneous doses of D2E7 antibody used in either Kempeni or Rau.

[76] The Applicant has also argued that Kempeni discloses a body weight-based dosing regimen that teaches away from the presently claimed fixed dose and there was no evidence that 40 mg of D2E7 was actually used to treat any patient. However, Kempeni teaches weekly 0.5 mg/kg subcutaneous injections of D2E7. Therefore, the person skilled in the art in following the teachings of Kempeni would necessarily be led to dose an 80 kg patient using a syringe loaded with the claimed dose amount of 40 mg. The fact that the dose amount was calculated based on body weight is irrelevant as how the dose amount is calculated is outside the scope of the claim.

[77] Concerning the disclosure of Rau, we agree with the Examiner that the person skilled in the art would understand that the syringe contains a single dose of 40 mg of D2E7. We find the Applicant's suggestion that the syringe could be a large capacity syringe to be used to facilitate successive injections of 40 mg of drugs to a group of patients, with only needle tip changes in between injections, is improbable given patient safety concerns. On a fair and balanced reading of Rau the POSITA would expect that single-dose syringes were used to facilitate the subcutaneous administration of D2E7.

[78] Although the Applicant has also argued that the references teach none of the factors that need to be considered with a preloaded syringe for self-administration, these factors are outside the scope of the claimed preloaded syringe. Moreover, the Applicant's own description, which is clearly directed to syringes for self-administration, is silent on the consideration of the factors identified by the Applicant at para. [71]. Even so, the person

skilled in the art would recognize these factors are necessary considerations for the successful administration of subcutaneous injections, regardless of whether the administration is to be performed by a medical professional or self administered by the patient.

[79] In view of the above, the person skilled in the art would consider that the syringe used in either Kempeni or Rau, i.e. a syringe for subcutaneous administration that is inevitably loaded for use, cannot be distinguished from the presently claimed syringes.

Enablement

[80] Both Kempeni and Rau disclose the use of subcutaneous administration to deliver the D2E7 antibody to patients suffering from rheumatoid arthritis. Therefore, we find that each of these references provides sufficient information to enable the skilled person to preload a syringe with a dose amount of D2E7 antibody that falls within the scope of the claims.

Conclusions

[81] We find that claims 102-104 are anticipated by Kempeni and Rau, each taken independently, which contain all of the essential features of the claimed preloaded syringes.

Purposive construction of proposed claim 1

[82] As indicated above, we consider claims 102-104 to preloaded syringes to be anticipated therefore we will assess whether the proposed claim set submitted 04 November 2013 overcomes this defect. A concordance table provided by the Applicant indicates that proposed claims 1-12 correspond to claims 102-104 on file.

[83] Proposed claims 1-12 contain 1 independent claim which is reproduced below:

1. A preloaded syringe comprising a syringe, 40 mg of an isolated human anti-TNF□ antibody wherein said antibody

(a) comprises a light chain variable region (LCVR) comprising a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 5, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 7; and

(b) comprises a heavy chain variable region (HCVR) comprising a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, a CDR2 domain

comprising the amino acid sequence of SEQ ID NO: 6, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 8;

and at least one pharmaceutically acceptable carrier, for treating an arthritic disease or an inflammatory bowel disease in a human subject, said preloaded syringe being (i) adapted for subcutaneous administration of its contents to the human subject in need thereof and (ii) for use on a continuous schedule having an every other week dosing interval of 14 days.

[84] Both claim 102 on file and proposed claim 1 are directed to preloaded syringes. However, unlike claim 102 on file, proposed claim 1 contains an explicit limitation that the preloaded syringe is for a particular medical use, i.e., "for the treatment of an arthritic disease or inflammatory bowel disease." Therefore, we consider that proposed claim 1 defines a "product for use." In this case, the use is further defined by a specific dosing schedule.

[85] Consistent with our purposive construction of the medical use claims on file, we consider that the essential elements of proposed claim 1 include:

(i) a preloaded syringe for subcutaneous administration
(ii) comprising a fixed dose of 40 mg
(iii) for the treatment of an arthritic disease or inflammatory bowel disease
(iv) for use on a continuous schedule having an every other week dosing interval of 14 days.

Disclosure

[86] We have already established that both Kempeni and Rau disclose a syringe for subcutaneous administration that cannot be distinguished from the preloaded syringe of the claims on file. However, as proposed claim 1 is in the form of a "product for use" we must now consider whether the featured use limitations are also disclosed by either Kempeni or Rau. Both of these references are directed to the use of D2E7 for the treatment of rheumatoid arthritis. However, in Kempeni the subcutaneous administration of the D2E7 antibody was limited to weekly injections of 0.5 mg/kg or single injections of 1 mg/kg. Similarly, Rau discloses subcutaneous administration of 40 mg of D2E7 given on a weekly dosing schedule. Therefore, neither of the cited references disclose the added feature that the preloaded syringe is for use on a continuous schedule having an every other week dosing interval of 14 days.

Enablement

[87] As the disclosure requirement has not been satisfied it is unnecessary to consider enablement.

Conclusions

[88] Proposed claim 1 is not anticipated by either Kempeni or Rau and could form the basis for amendments to claim 102 on file if proposed claim 1 is found to otherwise comply with the *Patent Act* and *Patent Rules*.

ISSUE 2: ARE THE CLAIMS OBVIOUS?

Legal Framework

[89] Section 28.3 of the *Patent Act* sets out the information that may be considered in assessing whether a claim is obvious:

> The subject-matter defined by a claim in an application for a patent in Canada must be subject-matter that would not have been obvious on the claim date to a person skilled in the art or science to which it pertains, having regard to
> (a) information disclosed more than one year before the filing date by the applicant, or by a person who obtained knowledge, directly or indirectly, from the applicant in such a manner that the information became available to the public in Canada or elsewhere; and
> (b) information disclosed before the claim date by a person not mentioned in paragraph (a) in such a manner that the information became available to the public in Canada or elsewhere.

[90] A four step approach for assessing obviousness is set out in *Sanofi*, as follows:

(1) (a) Identify the notional "person skilled in the art";
(b) Identify the relevant common general knowledge of that person;

(2) Identify the inventive concept of the claim in question or if that cannot readily be done, construe it;

(3) Identify what, if any, differences exist between the matter cited as forming part of the "state of the art" and the inventive concept of the claim or the claim as construed;

(4) Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?

Analysis under the *Sanofi* Four-Step Approach

Step 1: Identify the notional "person skilled in the art" and the relevant common general knowledge of that person

[91] These have been discussed above at paras. [20-28].

Step 2: Identify the inventive concept of the claim in question or if that cannot readily be done, construe it

[92] The FA and SOR maintained that the inventive concept, which is common to all claims with the notable exception of certain claims to preloaded syringes, is the use of a human anti-TNF□ antibody for inhibiting human TNF□ activity in a human subject suffering from an arthritic disease or an inflammatory bowel disease wherein the human anti-TNF□ antibody is adapted for subcutaneous, biweekly administration on a continuous schedule as a total body dose, wherein the total body dose is the same dose amount throughout the course of treatment and the dose amount consists of 40 mg. With respect to the remaining claims, the inventive concept is a preloaded syringe containing a human anti-TNF□ antibody and wherein the preloaded syringe is adapted for subcutaneous administration on a continuous schedule.

[93] In contrast, the Applicant has argued in its submissions to the panel that there is one inventive concept common to all of the claims, namely: subcutaneous dosing of 40 mg of the human anti-TNF□ antibody D2E7 according to a continuous schedule with an every other week interval in the range of 13-15 days. This characterization of the inventive concept was held to apply to all claims whether dealing with the use claims, Swiss-type use claims, preloaded syringe claims or the kit. It is noted that this definition of the inventive concept is consistent with the Examiner's understanding of the inventive concept of the medical use claims.

[94] Although the Applicant argued that this characterization of the inventive concept was held to apply to all the claims, we do not agree. In the present case, the use limitation of dosing on an every other week interval cannot form part of the inventive concept of claims formulated as product claims *stricto sensu*. Indeed, this interpretation is consistent with the Applicant's

acknowledgement that every other week administration is not intrinsic to the product—it can be administered every other day or every other year [paras. 32 and 49]. We note that this interpretation is also consistent with our purposive construction of the claims to preloaded syringes and kits comprising preloaded syringes. It follows that the inventive concept of the product claims is limited to a preloaded syringe for subcutaneous dosing of 40 mg of the human anti-TNF□ antibody D2E7.

[95] In the present case, the inventive concepts of the medical use claims and product claims align with the essential elements of the claims as construed. Therefore, for the purposes of the analyses that follow the inventive concepts of the medical use claims and product claims will be presented in terms of the essential elements.

[96] For representative medical use claims 1, 27, 48 and 69, the inventive concept includes the following essential elements:

(i) an isolated human anti-TNF□ antibody, or an antigen binding portion thereof, wherein said human anti-TNF□ antibody neutralizes human TNF□ cytotoxicity in a standard *in vitro* L929 assay with an IC_{50} of 1 x 10^{-9} M, comprises a light chain variable region (LCVR) comprising a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 5, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 7, and comprises a heavy chain variable region (HCVR) comprising a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 6, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 8

(iii) for subcutaneous administration

(iv) for biweekly administration on a continuous schedule

(v) wherein the dose amount is about 40 mg.

[97] The remaining medical use claims add features such as the presence of an additional therapeutic agent or place further limitations on the anti-TNF□ antibody and specific arthritic or inflammatory bowel diseases.

[98] With respect to representative product claims 90 and 102, the inventive concept includes the following essential elements:

(i) a preloaded syringe for subcutaneous administration

(ii) comprising a total body dose consisting of about 40 mg

(iii) comprising any one of the isolated human anti-TNF□ antibody of claims 48-54,

or antigen binding portion thereof, wherein the human anti-TNF□ antibody neutralizes human TNF□ cytotoxicity in a standard *in vitro* L929 assay with an IC_{50} of 1 x 10^{-9}M, comprises a light chain variable region (LCVR) comprising a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 5, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 7, and comprises a heavy chain variable region (HCVR) comprising a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 6, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 8.

[99] The remaining product claims add features such as the presence of an additional therapeutic agent or place further limitations on the anti-TNF□ antibody.

Step 3: Identify what, if any, differences exist between the matter cited as forming part of the "state of the art" and the inventive concept of the claim or the claim as construed

[100] In the present case, the main disagreement between the Examiner and the Applicant lies in step 3 of the *Sanofi* framework. Specifically, the Examiner considers that there is no difference between the claimed subject matter and the references cited as state of the art. In contrast, the Applicant submits that neither Kempeni nor Rau, either alone or in combination, provide one of ordinary skill in the art sufficient information to reliably predict the efficacy of an isolated human anti-TNF□ antibody for treating arthritic disease, according to a biweekly, subcutaneous regimen using a total body dose of about 40 mg of the antibody, as presently recited in the claims.

[101] Although the Examiner cited additional references which disclose the use of human anti-TNF□ antibodies, alone or in combination with at least one additional therapeutic agent, for the treatment of disorders in which TNF□ activity is detrimental including arthritic and inflammatory bowel diseases, the Applicant considered these references to be irrelevant. We have already established that the information provided by these disclosures was part of the CGK (see paras. [24-28]).

[102] As the Applicant does not distinguish between D2E7 and any other isolated human anti-TNF□ antibodies, we will not consider the isolated human anti-TNF□ antibodies defined by structure (CDRs) and function as a difference. Notably, the independent claims refer to human anti-TNF□ antibodies that are broadly defined in terms of the known

structural and functional characteristics of D2E7. Specifically, the antibodies are structurally characterized as comprising the CDR domains of D2E7 and functionally characterized as having the same inhibitory activity as D2E7.

[103] Likewise, the Applicant does not distinguish between rheumatoid arthritis and the other autoimmune diseases featured in the claims, therefore we will not consider the specific arthritic or inflammatory bowel diseases as differences. Finally, for similar reasons, we will also not consider the presence of an additional therapeutic agent as a difference. Moreover, the Applicant did not consider the other isolated human anti-TNF□ antibodies, autoimmune diseases or therapeutic agents featured in the claims to be differences over the state of the art.

[104] Therefore, with respect to medical use claims 1, 27, 48, 69, 84-89, 106-111 and 116-120 (and claims dependent thereon), what remains in dispute is whether the following elements of the inventive concept are differences over the matter cited as state of the art: (iii) for subcutaneous administration, (iv) for biweekly administration on a continuous schedule, and (v) wherein the dose amount is about 40 mg.

[105] In order to determine whether any of these features of the inventive concept are differences over the state of the art, we agree with the Applicant that only the references of Kempeni and Rau need be considered.

[106] With respect to product claims 90 and 102, in view of our analysis under anticipation, there are no differences in the inventive concept of these claims over the matter cited as state of the art. As indicated above, we have already established that Kempeni and Rau, each taken independently, contain all of the essential features of claims 102-104 to preloaded syringes. Given that claims 90 and 102 have been construed to have the same essential elements, this determination is also applicable to kit claims comprising preloaded syringes. Although some of the dependent claims feature the presence of an additional therapeutic agent or place further limitations on the anti-TNF□ antibody, as indicated above, the Applicant considered these features to be part of the common general knowledge of the person skilled in the art and not as differences over the state of the art.

Kempeni and the differences therefrom

[107] Kempeni discloses preliminary clinical data evaluating the efficacy and safety of using the fully human anti-TNF□ monoclonal antibody D2E7 to treat patients with rheumatoid

arthritis. Specifically disclosed are the results of three clinical trials in which patients were treated with single, multiple or weekly, intravenous or subcutaneous injections of D2E7 alone or in combination with methotrexate. All studies featured a body weight-based dosing regimen in which the dose amount given to patients ranged from 0.5 to 10 mg/kg.

[108] The first clinical trial was designed to evaluate the tolerability of increasing doses of D2E7. These studies also determined that the estimated mean terminal half life of D2E7 was 11.6 to 13.7 days and that sustained therapeutic effects and some continuing improvement was realized after multiple infusions of D2E7. Indeed, response rates of more than 80% were achieved with a mean dosing interval of 2.5 weeks. Although there is no indication which treatment group the 80% response rate refers to, what is clear from this study is the fact that the therapeutic index for D2E7 includes a range of 0.5 to 10 mg/kg and that biweekly, intravenous infusions provide a therapeutic benefit. Although a biweekly dosing interval is taught, the dose amount was calculated based on the weight of the patient and the mode of administration was intravenous.

[109] The next study was designed to evaluate the efficacy of weekly, subcutaneous dosing at 0.5 mg/kg. Similar to the first study, the dose of D2E7 was increased to 1 mg/kg for non-responders or those losing their responder status. Based on the success of this trial, the investigators concluded that subcutaneous self administration is a promising approach for D2E7 delivery. Although the mode of administration was changed from intravenous to subcutaneous, the dose amount was still calculated based on the weight of the patient. Further, the dosing interval was changed from biweekly to weekly administration.

[110] Finally, the third clinical trial demonstrated that the use of single intravenous or subcutaneous injections of 1 mg/kg of D2E7 in combination with methotrexate, in patients whose stable dose of methotrexate was insufficient to control symptoms, was sufficient to achieve a reduction in disease activity. Although subcutaneous injections are taught, these were given as a single dose that was calculated based on the body weight of the patient.

[111] Although each of the clinical trials disclosed teaches one of the elements present in the inventive concept of the medical use claims, none of the trials teach a dosing regimen that contains all of the elements of the inventive concept. The closest comparison to be made is with the study that evaluated weekly, 0.5 mg/kg subcutaneous injections of D2E7.

[112] On this basis, we find that the following elements of the inventive concept of medical use claims 1, 27, 48, 69, 84-89, 106-111 and 116-120 (and claims dependent thereon) are

differences over the teachings of Kempeni: (iv) for biweekly administration on a continuous schedule, and (v) wherein the dose amount is about 40 mg.

Rau and the differences therefrom

[113] Rau discloses the results of a phase 1 study demonstrating that intravenous administration of D2E7 in single doses of 0.5 to 10 mg/kg every two weeks over a period of 1 ½ years led to an impressive, statistically significant and prolonged reduction of disease activity for all doses greater than 1 (up to 3) mg/kg. Although a biweekly dosing interval is taught, the dose amount was calculated based on the weight of the patient and the mode of administration was intravenous.

[114] Also disclosed are the results of a phase 2 study which evaluated the effect of 20, 40 or 80 mg of D2E7 administered weekly, subcutaneously. Although the mode of administration was changed from intravenous to subcutaneous, and a fixed dose amount was administered, the dosing interval was also changed from biweekly to weekly administration.

[115] Finally, the third study disclosed that in patients whose stable dose of methotrexate was insufficient to control symptoms, the use of single dose of 1 mg of D2E7 given intravenously or a single subcutaneous injection of 1 mg/kg of D2E7 in combination with methotrexate, was sufficient to achieve a reduction in disease activity. Although subcutaneous injections are taught, these were given as a single dose that was calculated based on the body weight of the patient.

[116] Each of the clinical trials disclosed teaches at least one of the elements present in the inventive concept of the medical use claims, however, none of the trials teach a dosing regimen that contains all of the elements of the inventive concept. The closest comparison to be made is with the study that evaluated weekly, subcutaneous injections of a 40 mg fixed dose of D2E7.

[117] On this basis, we find that the following element of the inventive concept of medical use claims 1, 27, 48, 69, 84-89, 106-111 and 116-120 (and claims dependent thereon) is the only difference over the teachings of Rau: (iv) for biweekly administration on a continuous schedule.

Summary of differences

[118] We find that the combined state of the art does not disclose the following element of the inventive concept of medical use claims 1, 27, 48, 69, 84-89, 106-111 and 116-120 (and claims dependent thereon):

- Neither Kempeni or Rau disclose:
  (iv) for biweekly administration on a continuous schedule.

Step 4: Do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?

[119] We agree with the Applicant, that the feature of a biweekly dosing interval in the inventive concept of medical use claims 1, 27, 48, 69, 84-89, 106-111 and 116-120 (and claims dependent thereon) is an inventive difference over the disclosures of Kempeni and Rau, taken together or independently, in view of the common general knowledge.

[120] With respect to Kempeni, a biweekly dosing interval was a feature of the first clinical trial disclosed. Further, data from this first clinical trial established that the mean terminal half life of D2E7 was 11.6 to 13.7 days. Arguably, the effectiveness of a mean dosing interval of 2.5 weeks could be attributed to the estimated half life of D2E7. Indeed, the Examiner relies on this association as suggesting that a biweekly dosing frequency will be effective. In response, the Applicant argued that the suggestion that a dosing frequency can be reliably predicted using the half-life of an antibody is incorrect and cited multiple examples where the half life of a therapeutic antibody did not correlate to administration frequency. Based on the definition of the CGK of the POSITA [paras. 24-28], we agree with the Applicant that the half life of a therapeutic antibody would not be the only factor used to determine dosing frequency.

[121] Indeed, this conclusion appears to be supported by the subsequent clinical trial which evaluated the efficacy of weekly, subcutaneous dosing at 0.5 mg/kg. Given that in subsequent trials subcutaneous administration of D2E7 was done on a weekly basis, we consider that these teachings would actually dissuade the person skilled in the art from choosing a biweekly dosing interval.

[122] Similarly, Rau discloses a phase 1 study featuring a biweekly dosing interval. In this study biweekly, intravenous administration of D2E7 in single doses of 0.5 to 10 mg/kg were given over a period of two years. Although doses as low as 0.5 mg/kg were given to patients, the authors only report that the administration of doses greater than 1 (up to 3) mg/kg led to an

impressive, statistically significant and prolonged reduction of disease activity. The person skilled in the art would consider that biweekly dosing in the range of 0.5 to 1 mg/kg may not be effective as no results are given for this range.

[123] This conclusion appears to be supported by the subsequent phase 2 study which evaluated the efficacy of weekly, subcutaneous fixed doses of 20, 40 or 80 mg of D2E7. Given that in subsequent trials subcutaneous administration of D2E7 was done on a weekly basis, we consider that these teachings would actually dissuade the person skilled in the art from choosing a biweekly dosing interval.

[124] Further, similar to the phase 1 study, the authors only report that meaningful efficacy was observed with fixed doses of 40 mg and 80 mg of D2E7. On this basis, the Applicant argued that the skilled person would consider that weekly dosing at the lowest dose of 20 mg was not effective and would not have had a reasonable expectation that biweekly dosing at 40 mg would work.

[125] The Applicant also pointed out that even though the subcutaneous, weekly administration of 40 mg and 80 mg doses were shown to provide therapeutic results above an arbitrary threshold response, since Rau does not disclose what the actual data were, there would have been no way for a skilled person to select between these two doses. Moreover, in the absence of any suggestion that a fixed dose of 40 mg was as effective as an 80 mg dose, the skilled person would not consider cutting the dosing frequency by one half.

[126] We also note, that if one assumes that the average weight of a human subject is 80 kg then, fixed dose amounts of 40 and 80 mg of D2E7 correspond to weight based dosing at 0.5 and 1 mg/kg, respectively. As indicated above (para. [122]), based on the phase 1 study disclosed by Rau, the person skilled in the art would infer that biweekly dosing in this range may not be effective as no data is reported for this range.

[127] In view of the above, the person skilled in the art would not consider the presently claimed biweekly dosing interval to be obvious in view of the teachings of either Kempeni or Rau, taken together or independently.

Proposed claims 1-26

[128] As indicated above, there were no differences in the inventive concept of the claims to preloaded syringes and kits comprising preloaded syringes over the teachings of either Kempeni or Rau (para. [106]). A concordance table provided by the Applicant indicates that proposed claims 1-12 correspond to claims 102-104 on file and proposed claims 13-26

correspond to claims 90-101 on file.

[129] In our anticipation analysis, we performed a purposive construction of proposed claim 1 and determined the feature that the preloaded syringe "for use on a continuous schedule having an every other week dosing interval of 14 days" is an essential element (para. [85]). It follows that proposed claim 1 is inventive over the teachings of either Kempeni or Rau, taken together or independently.

[130] We now need to assess whether proposed claims 13-26, to kits comprising preloaded syringes, also overcome the obviousness defect.

Purposive construction of proposed claim 13

[131] Proposed claims 13-26 contain 1 independent claim which is reproduced below:

13. A kit comprising a unit dosage form containing 40 mg of an isolated human anti-TNF antibody wherein said antibody

(a) comprises a light chain variable region (LCVR) comprising a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 5, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 7; and

(b) comprises a heavy chain variable region (HCVR) comprising a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 6, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 8;

and at least one pharmaceutically acceptable carrier, for treating an arthritic disease or an inflammatory bowel disease in a human subject, associated with instructions for subcutaneous administration of the contents of said unit dosage form according to a continuous schedule having an every other week dosing interval of 14 days.

[132] Both claim 90 on file and proposed claim 13 are directed to kits. However, unlike claim 90 on file, proposed claim 13 also contains an explicit use limitation that the kit comprises a unit dosage form for a particular medical use i.e., "for the treatment of an arthritic disease or inflammatory bowel disease in a human subject." Therefore, we consider that proposed claim 13 defines a "kit for use." In this case, the use is further defined in "associated written instructions." Notably, the biweekly dosing interval is recorded in these written instructions. Consistent with our purposive construction of claim 90 on file, the instructions are not considered essential as they have no material effect on the other contents

of the kit. Therefore, proposed claim 13 is construed to have the following essential elements:

(i) a unit dosage form
(ii) containing 40 mg
(iii) of an isolated human anti-TNF antibody
(iv) for treating an arthritic disease or an inflammatory bowel disease in a human subject.

[133] As we have already established that all of these features are known, it follows that proposed claim 13 is not inventive. With respect to dependent claims 14-26, these claims feature the presence of an additional therapeutic agent or place further limitations on the anti-TNF antibody. However, as indicated above, the Applicant considered these features to be part of the common general knowledge of the person skilled in the art and not as differences over the state of the art.

Conclusions

[134] We find that medical use claims 1, 27, 48, 69, 84-89, 106-111 and 116-120 (and claims dependent thereon) would not have been obvious to the person skilled in the art in view of Kempeni or Rau, alone or in combination, together with the common general knowledge.

[135] In contrast, claims 90 and 102 (and claims dependent thereon), to preloaded syringes and kits comprising preloaded syringes, would have been obvious to the person skilled in the art in view of Kempeni or Rau, each taken independently.

[136] With respect to claim 90 (and claims dependent thereon), to kits comprising preloaded syringes, corresponding proposed claims 13-26 do not provide any additional, inventive features that can overcome this defect.

[137] With respect to claim 102 (and claims dependent thereon), to preloaded syringes, corresponding proposed claim 1 would not have been obvious to the person skilled in the art in view of Kempeni or Rau, alone or in combination, together with the common general knowledge and could form the basis for amendments to claim 102 on file if proposed claim 1 is found to otherwise comply with the *Patent Act* and *Patent Rules*.

ISSUE 3: ARE CERTAIN CLAIMS NON-STATUTORY FOR COVERING A METHOD OF MEDICAL

TREATMENT?

Legal Framework

[138] Section 2 of the *Patent Act* defines "invention" as:

> any new and useful art, process, machine, manufacture or composition of matter, or any new and useful improvement in any art, process, machine, manufacture or composition of matter.

[139] An Office Patent Notice, published 10 June 2013, entitled "*Examination Practice Respecting Medical Uses*" along with an accompanying Exam Memo, PN 2013-04, provide specific guidance on current Office practice and interpretation of relevant jurisprudence pertaining to medical use claims.

[140] As explained in part A) of the Exam Memo, medical use claims are generally permitted as long as they do not equate to medical or surgical methods. However, inventions preventing physicians from exercising their skill and judgment in using a known compound for an established purpose effectively cover a method of medical treatment: *Janssen Inc. et al. v Mylan Pharmaceuticals et al.,* 2010 FC 1123 [*Janssen*]. This interpretation is consistent with the "how and when" exclusion adopted by the Supreme Court in *Apotex Inc. v Wellcome Foundation Ltd.* 2002 SCC 77 [*AZT*]:

> The AZT patent does not seek to "fence in" an area of medical treatment. It seeks the right to provide AZT as a commercial offering. How and when, if at all, AZT is employed is left to the professional skill and judgment of the medical profession. [para. 50]

[141] It follows that, if it is determined after a purposive construction that a dosage regimen or dosage range is an essential element of a claim encompassing the use of a known compound in an established treatment, then the claim covers a method of medical treatment, and thus, is not compliant with section 2 of the *Patent Act*.

The Examiner's position

[142] In the FA and SOR, the Examiner argued that claims 1-89 and 106-126 cover a method of medical treatment citing *Janssen* as the authority. Specifically, the Examiner asserted that by attempting to monopolize an effective dosage regimen for the old and known

monoclonal antibodies, the claims were interfering with the ability of physicians to exercise their judgment in the administration of the antibodies.

The Applicant's position

[143] In response to the FA, the Applicant argued that the claims of the present application are completely different than those considered in *Janssen*. The interference that underlies *Janssen* is interference by way of fencing off territory within which the physician or surgeon exercises skill. In *Janssen*, the claims were directed to an optimal dosage schedule for the drug galantamine. Specifically, the claims featured a gradual increase in the drug being administered over predefined time periods to reduce the frequency and severity of patient side effects to the drug. In contrast, the claims in the present case are directed to a fixed dose of 40 mg—not a large dose range requiring the exercise of judgment and intervention of a medical practitioner. There is no need for the physician to consider body weight, prior history, tolerability to drugs, and patient reaction to adjust the dose—all factors considered by court in the *Janssen* case.

[144] In their submissions to the panel, the Applicant argued that the state of the law in Canada concerning medical use claims is that claims that incorporate fixed dosages or fixed dosing intervals, do not claim the exercise of professional skill and are patentable subject matter. On the other hand, claims that incorporate dosage ranges or dosage interval ranges or variable titrations, are not patentable subject matter because they literally claim the choice and therefore the exercise of professional skill.

[145] In support of their position, the Applicant pointed to several Federal Court decisions that interpreted the *AZT* decision and held that patent claims that incorporated as part or the whole of the inventive concept a fixed dosage and a fixed dosing interval (that is to say, a fixed regimen) were found to not cover the exercise of professional skill and judgment: *Merck & Co. v. Apotex Inc.* 2005 FC 755 [*Merck*[1]]; *Merck & Co. v. Pharmascience Inc.* 2010 FC 510 [*Merck*[2]]; *Bayer Inc. v Cobalt Pharmaceuticals Company 2013 FC 1061* [*Bayer*].

[146] The Applicant argues that, consistent with the claims considered in *Merck*[1], *Merck*[2] and *Bayer*, which are binding on the Commissioner, the present claims also feature a fixed dose and fixed dosing interval. Given that in each of these decisions "the how and the when of the *AZT* case has already been construed as not prohibiting a claim to a dose that has an interval," the Applicant concludes that the present medical use claims are statutory.

Analysis

[147] As indicated above, there is a general distinction in the case law between claims to vendible products on the one hand, and claims related to the professional skill and judgment of the medical profession on the other hand. The former are patentable, the latter are not. The Applicant has argued that because the present claims feature a fixed dose and fixed dosing interval they exclude the exercise of medical professional skill or judgment and are patentable subject matter.

[148] In particular, the Applicant has cited several Federal Court decisions in which the Courts have construed use claims which recited a fixed dose and fixed dosing interval as vendible products. We agree with the Applicant that in each of *Merck*[1], *Merck*[2] and *Bayer*, the Courts construed claims which featured a fixed dose and fixed dosing interval to be vendible products. However, the case law makes it clear that the mere presence of these two features in a claim is not always sufficient to avoid the method of medical treatment prohibition.

[149] This was first addressed in *Janssen* where the Court held that claims which cover an area for which a physician's skill or judgment is expected to be exercised constitute methods of medical treatment. Notably, one of the claims at issue was limited to a dosage regimen featuring a first dosage of 8 mg/day of galantamine for four weeks followed by a final dosage of 16 mg/day i.e. a fixed dose and fixed dosing schedule. However, the Court relied on expert evidence to establish that the titration regimen claimed could only be seen as a recommendation to physicians. Effective patient management may require on-going individualized surveillance and concomitant dosing adjustments. On this basis, the Court concluded "that a patent claim over the administration of a drug, whereby the physician, while relying on the dosage advice of the patentee, would still be expected to be alert and responsive to a patient's profile and to the patient's reaction to the compound" is an unpatentable method of medical treatment because it "covers an area for which a physician's skill or judgment is expected to be exercised."

[150] This conclusion was recently affirmed by the Federal Court of Appeal: *Novartis Pharmaceuticals Inc. v Cobalt Pharmaceuticals Company 2014 FCA 17* aff'g *Novartis Pharmaceuticals Inc. v Cobalt Pharmaceuticals Company 2013 FC 985* [*Novartis*]. In that case, one of the claims in question featured the use of 5 mg of zoledronic acid to be administered intravenously, once a year for the treatment of osteoporosis, i.e. a fixed dose and fixed dosing interval. However, the only expert witness to address the issue of method of medical treatment opined that the patent in question makes clear that the mode

and dosage will vary from patient to patient and the physician must determine, based on his skill and professional judgment, the appropriate dosage regimen to give. Based on a reading of the entire patent, the expert witness also construed the interval "about one year" to mean a range of dosing intervals between once every 6 months to once every 12 months. Further, the claims at issue also featured treatment by intermittent dosages with some claims specifying a dosage range and others specifying specific dosages and some claims claiming more frequent intervals of dosing, and others less. On this basis, the Court rationalized that the claims include that which lies within the skill of the medical practitioner and were all invalid.

[151] With respect to whether the claims cover an area in which a physician would be expected to exercise their skill or judgment, at the hearing we asked the Applicant to address statements in the description that seemed to indicate that determining the dosage for administration is expected to remain within the purview of a physician:

> [a]n exemplary, non-limiting range for a therapeutically or prophylactically effective amount of an antibody or antibody portion of the invention is 10-100mg, more preferably 20-80 mg and most preferably about 40 mg. It is to be noted that dosage values may vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that dosage ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition. (para. bridging pages 27-28).

[152] In response, the Applicant argued that unlike *Janssen* and *Novartis*, where the language was "required content in the description because they are claiming ranges," in the present description the language is not relevant to the invention as claimed, "it is not necessary, it's extraneous and it's drafting boiler plate."

[153] In this regard, we note that the description broadly refers to methods of treating any disorder in which TNF□ activity is detrimental and it is in this broad context to which the statements relate. Further, based on the exemplary data, it is clear that the most preferred embodiment of subcutaneous, biweekly administration of 40 mg of D2E7 is not only supported but was shown to have better efficacy than a fixed dose of 20 mg and comparable to a fixed dose of 80 mg. Therefore, unlike the situations in *Janssen* and *Novartis*, there is nothing in the description or claims to suggest that an appropriate dosage regimen includes a range of doses and/or range of dosing intervals from which a medical

practitioner would be required to make an selection.

[154] However, we do not agree with Applicant that the interference with the ability of physicians to exercise their skill and judgment that underlies *Janssen* is limited to claims which cover a range of doses and/or range of dosing intervals from which a medical practitioner would be required to make an selection. In *Janssen* at paras. [51]-[53], the Court also made clear that the "concern with patenting a dosage regimen is that the physician may be prevented from exercising skill and judgment in using a known compound for an established purpose absent a license from the patentee" and that "[b]y attempting to monopolize an effective titration regimen for galantamine, the '950 Patent interferes with the ability of physicians to exercise their judgment in the administration of generic versions of the drug" citing *AZT* and *Tennessee Eastman Company et al. v Commissioner of Patents* (1972), 8 CPR (2d) 202 SCC as the authorities. As outlined in *Janssen*, this concern relates to the idea that "enforcement of the '950 Patent might impose practice limitations on physicians attempting to prescribe galantamine" (our emphasis added) which falls squarely within the "how and when" exclusion set forth in *AZT*.

[155] Therefore, consistent with the reasoning in *Janssen*, which we are bound by, the granting of monopoly rights to a dosage regimen featuring biweekly, subcutaneous administration of a dose amount of 40 mg would place restrictions on "how and when" the old and known human monoclonal anti-TNF antibodies are to be administered. This would interfere with the ability of physicians to exercise their judgment in the administration of generic versions of the drug which will eventually become available, or indeed with the administration of Humira™, absent a licence for the regimen.

Proposed claims 1-12 and 27-51

[156] We have already established in our purposive construction of proposed claim 1 that it recites the same unpatentable dosage regimen featuring subcutaneous administration of a dosage of 40 mg according to a continuous schedule having an every other week dosing interval of 14 days (para. [85]).

[157] Similarly, all of proposed claims 27-51 also recite the same unpatentable dosage regimen. Therefore, although the Applicant has indicated that proposed claims 27-39 correspond to claims 1-26 on file and proposed claims 40-51 correspond to claims 69-89, 106-115 and 121-126 on file, proposed claims 27-51 do not provide any amendments that can overcome the conclusion that claims 1-26, 69-89, 106-115 and 121-126 cover a method of medical treatment.

Conclusions

[158] We find that the medical use claims 1-89 and 106-126, and proposed claims 1-12 and 27-51, effectively cover a method of medical treatment.

RECOMMENDATION OF THE BOARD

[159] In view of the above findings, we recommend that the application be refused because:

(1) Claims 102-104 are non-compliant with paragraphs 28.2(1)(*a*) and *(b*) of the *Patent Act*;
(2) Claims 90-105 are non-compliant with section 28.3 of the *Patent Act*;
(3) Claims 1-89 and 106-126 are directed to methods of medical treatment and therefore are non-compliant with section 2 of the *Patent Act*; and
(4) Claims 27-40, 48-83, 117-119 and 121-126 are non-compliant with subsection 27(4) of the *Patent Act.*

Christine Teixeira	Cara Weir	Paul Sabharwal
Member	Member	Member

DECISION OF THE COMMISSIONER

[160] I concur with the Patent Appeal Board's findings and their recommendation that the rejection of the application be upheld on the basis of the following:

(1) Claims 102-104 are non-compliant with paragraphs 28.2(1)(*a*) and *(b*) of the *Patent Act*;
(2) Claims 90-105 are non-compliant with section 28.3 of the *Patent Act*;
(3) Claims 1-89 and 106-126 are directed to methods of medical treatment and therefore are non-compliant with section 2 of the *Patent Act*; and
(4) Claims 27-40, 48-83, 117-119 and 121-126 are non-compliant with subsection 27(4) of the *Patent Act.*

[161] Accordingly, I refuse to grant a patent on this application. Under section 41 of the *Patent Act*, the Applicant has six months within which to appeal my decision to the Federal Court of Canada.

Sylvain Laporte
Commissioner of Patents

Dated at Gatineau, Quebec,
this 27th day of March, 2014