Federal Court  Cour fédérale

Date: 20140117

Docket: T-1310-09

Citation: 2014 FC 55

Toronto, Ontario, January 17, 2014

PRESENT: The Honourable Mr. Justice Hughes

BETWEEN:

ABBVIE CORPORATION, ABBVIE DEUTSCHLAND GMBH & CO. KG AND ABBVIE BIOTECHNOLOGY LTD.

Plaintiffs (Defendants by Counterclaim)

and

JANSSEN INC.

Defendant (Plaintiff by Counterclaim)

REASONS FOR JUDGMENT AND JUDGMENT

[1] This is an action respecting the infringement and validity of a patent directed to human antibodies that bind a human cytokine known as interleukin 12 or IL-12. This binding tends to neutralize some of the effects of IL-12 and, and thus is useful in the treatment of diseases; in particular, psoriasis. Two claims of the patent are at issue. A principal ground of contention is the scope of those claims which are directed to human antibodies with particular characteristics as to

affinity and potency are too broadly drafted so as to cover more than was actually invented or could properly be claimed.

[2] For the reasons that follow, I find that the particular claims of the patent at issue are valid and infringed.

[3] As a convenience, the following index, by paragraph number, is provided:

THE PARTIES AND PRODUCT AT ISSUE

[4] For the purposes of the present trial, the Plaintiffs assert and Janssen does not contest that the Plaintiffs are related corporate entities; that AbbVie Deutschland GmbH & Co. KG is a German entity, which owns the patent at issue; that it is the patentee; that AbbVie Biotechnology Ltd. is a Bermuda corporation and is the exclusive licensee of the patent at issue; and that AbbVie Corporation is a Canadian corporation and is a sister corporation of AbbVie Bermuda; both of whom are persons claiming under the patentee. I will refer to these entities collectively as AbbVie, or the Plaintiffs.

[5] The Defendant Janssen Inc. is a research-based pharmaceutical company located in Toronto, Ontario. It has secured from the Minister of Health a Notice of Compliance to sell in Canada, and sells in Canada sterile injectable products containing 45 mg/0.5 mL and 90 mg/mL of a substance it calls ustekinumab for the treatment of chronic, moderate to severe plaque psoriasis in adult human patients who are candidates for phototherapy or systemic therapy. This product is sold under the name STELARA.

[6] AbbVie does not market such a product in Canada, nor has it received a Notice of Compliance to do so.

THE '281 PATENT IN GENERAL

[7] The patent at issue is Canadian Letters Patent No. 2 365 281, entitled "Human Antibodies that Bind Human IL-12 and Methods for Producing" (the '281 patent).

[8] The application for the '281 patent was filed in the Canadian Patent Office on March 24, 2000; thus, the provisions of the *Patent Act*, RSC 1985, c. P-4, applicable to patents applied for after October 1, 1989 (the "new" *Patent Act*) apply to this patent. The term of the patent will expire twenty (20) years from this filing date; that is, on March 24, 2020; unless the patent is otherwise expunged following a judgment of this Court.

[9] The application for its '281 patent claimed priority from an application, No. 60/126,603 filed in the United States on March 25, 1999. The Canadian application was laid open for public inspection (publication date) on September 28, 2000.

[10] The '281 patent was issued and granted to Abbott GmbH & Co., KG on August 4, 2009. For the purposes of this trial it is not contested that that entity transferred its interest in the '281 patent and all of its interests, rights or benefits related to this litigation, to the Plaintiff AbbVie Deutschland GmbH & Co. KG.

BACKGROUND TECHNOLOGY

[11] The '281 patent is concerned with technology that only recently has come before this Court. It deals with human antibodies, immunology, the creation of specific antibodies, and the selection of target materials in the human body that may be neutralized in order to treat certain diseases.

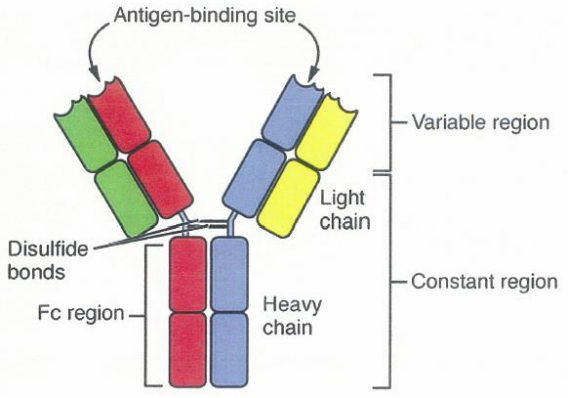
[12] I have been greatly assisted in preparation for this trial by a lecture given by Professor Jack Gauldie, provided to me by the parties jointly in the form of an hour-long DVD and accompanying booklet of diagrams. While these materials do not form part of the evidence tendered at trial, I have

marked them as Judge's Exhibits A and B in the event that they may be useful to an appellate Court. This lecture was intended to provide me with background information and some of the vocabulary necessary in understanding the evidence given at trial.

[13] Many of the workings of the human immune system have been known for over a century; much is becoming known; and yet more is still unknown. For over a hundred years, it has been known that if a foreign substance such as protein found on a bacteria or virus (often referred to as an antigen) is introduced into the human body, the body will react by creating antibodies that will attach themselves to that antigen and neutralize it. It has also been known that a protein found in the system of another animal, such as a mouse, if introduced into the human system will be recognized as a foreign antigen and provoke an unwanted response by the human body.

[14] Antibodies, being part of the adaptive immune system, are highly regulated. Upon discovery of a foreign body (antigen), the immune system responds by producing a large number of antibodies directed at the identified antigen in an attempt to clear the body of the antigen. The regulation of antibody production and immune system response is controlled by signalling proteins called cytokines. Cytokines function is to mediate and regulate the immune reactions in the body. Among the various identified cytokines are a type called interleukins, of which there are many. As of March 1999, several interleukins had been identified, including Interleukin-12, usually referred to as IL-12. IL-12 was known to have some sort of role in dealing with immunity. In the context of the present case, IL-12 is targeted by antibodies constructed by the human body, and thus can be considered as an antigen; that is, something that may be bound by or neutralized by the antibody.

[15] Antibodies, in particular monoclonal antibodies, are often depicted in the form of a Y structure. They can be shown as:



[16] The central Y structure is called the heavy chain, and the structures on the sides of the upper branches of the Y are called light chains. At the tip of the upper branches of the heavy and light chains are sections that are called variable regions. These variable regions bind the antibody to the antigen at sites on the exterior surface of the antigen, which sites are called epitopes. There may be a number of such sites on the exterior of an antigen that provide suitable epitopes for binding. The binding serves as a signal for immune cells to destroy or neutralize the antigen. Binding is not permanent; an antibody may bind and release many times, depending on the affinity or, what I will call the stickiness of the antibody.

[17] While antibodies are naturally created in the human body, it has been desirable to create modified versions for study and ultimate therapeutic use in the human body. In about the middle of the last century, antibodies were developed using mice. These types of antibodies are referred to as murine antibodies. The human body recognized those antibodies as foreign proteins (non-human); and, therefore, usually rejects them. Genetic engineering ensued to make these antibodies less

mouse-like and more human. These were called humanized antibodies. The human body, by and large, still recognizes humanized antibodies as foreign.

[18] The quest was on to create "fully human" antibodies. The result was the emergence of at least two techniques. One was phage display. A "library" of pieces of genetic material forming parts of the light and heavy chains of the antibody was created, and from these pieces scientists assembled a variety of antibodies made up of human parts only. The antibody "library" can be used to select a specific antibody which binds to an antigen in question. These antibodies, once constructed, could be readily multiplied.

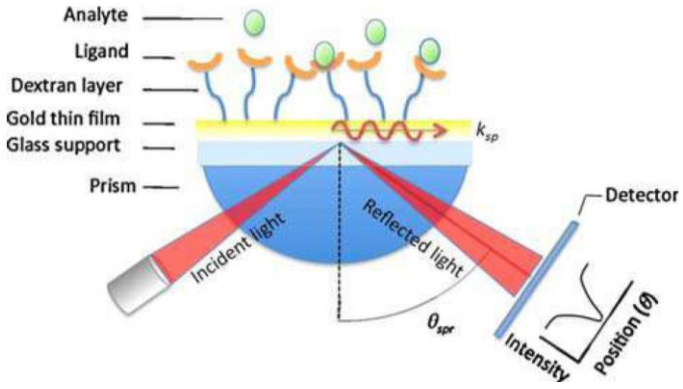
[19] Another technique was to modify mice to express human antibodies. The technique uses a two-step process. Initially, the mouse immune system is destroyed so that the mice could no longer produce antibodies or an immune response. Such a mouse is sometimes called a knockout mouse or transgenic mouse. Subsequently, the immune-deficient mice are genetically modified and cloned to contain human antibody genes. The mice, when presented with an antigen, would produce human antibodies to that specific antigen. Those antibodies can be taken from the mouse and multiplied.

[20] Different antibodies can be created by either means; which would, selectively, attach themselves to certain areas, called epitopes, on the surface of certain antigens that are found in the human body.

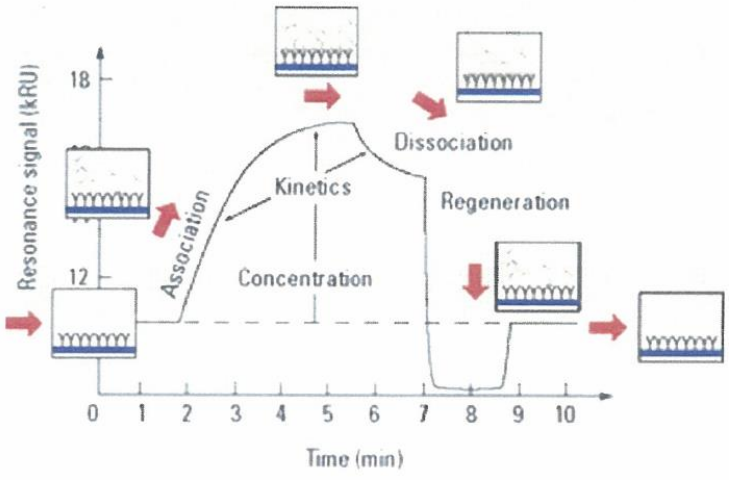
[21] The degree of antibody-antigen attachment and release referred to as "on" and "off", sometimes called affinity and I call stickiness, can be measured by passing a thin stream of the

antibody over the antigen (or vice-versa) in the presence of refracted light. The refraction of the light is measured; which relates to the attachment/release of the antibody and antigen. This is a way of measuring and categorizing the particular antibody. The '281 patent refers to a particular device used for this purpose, called a BIAcore. The results are expressed in terms such as k_{off} rate constant of 1×10^{-4} s^{-1} as found in the claims at issue.

[22] I reproduce a simplified diagram of the BIAcore technique:



[23] Typical of a graph as produced by the machine is as follows:



[24] Another measurement can be taken to analyze the ability of the antibody to inhibit the functional activity of the antigen; a property called potency. The functional inhibition of the antigen is measured through PHA Blast Proliferation assay (PHA assay). Human PHA Blast Proliferation Assay measures the antibodies ability to block antigen binding to its associated cell receptor, the binding which induces the proliferation of PHA stimulated human blast cells. In terms of the technology at issue, various dilutions of the antibody are washed over plates containing the IL-12 induced proliferating human blast cells. As proliferation is induced by the interaction of IL-12 and the blast cell receptor, any decrease in cell proliferation correlates to the ability of the antibody to inhibit the activity of IL-12. The results are measured in terms of the antibody concentration, the $IC_{50,}$ necessary to diminish the proliferation of the blast cells by 50%. PHA assay is analysed with results measured in terms of an IC_{50} such as 1×10^{-9}M as claimed in the patent.

[25] With respect to the k_{off} property, i.e. stickiness, the stickier the antibody to the antigen, the better. Stickiness is expressed in terms of 10^{-x} where x is an exponential number expressing a descending degree of magnitude; the larger the x number is, the stickier the antibody. Thus, 10^{-4} is stickier than 10^{-2}.

[26] Similarly, when referring to the PHA assay, which is a measure of the potency of the antibody, the property is again measured in descending degrees of magnitude, 10^{-x} where x is a number. The less of a given quantity of antibody to inhibit an antigen, the better. A more potent antibody requires less of it to inhibit fifty percent (expressed as IC_{50}) of an antigen. An antibody having an IC_{50} of 10^{-9} is more potent than one having an IC_{50} of 10^{-7}.

[27] With respect to the claims at issue, the properties of the antibody are expressed in terms of stickiness and potency.

[28] Turning to a different aspect, life forms are comprised of building blocks known as amino acids, of which there are over twenty known acids. These acids are often referred to by a three-letter short form or a capital letter; thus, glycine is often written as gly or a letter G, and so forth for the other amino acids. These acids are strung together in different orders and lengths to form substances such as proteins and peptides (essentially short proteins). As these chains become longer and more complex, they fold, sometimes because of the individual amino acid interaction within the protein and specific hydrophobicity of each amino acid. The folding of the amino acid chains results in the formation of globular structures emerging as shapes such as the "Y" shape of the resultant antibodies at issue here.

[29] These Y-shaped antibodies are composed of amino acid chains, and those that are made by the phage display method have their amino acid structure referred to in detail in the '281 patent. The amino acid structure of the Y-shaped antibodies created by the phage display method differs from those created by the transgenic mouse method. Further, the attachment points or epitopes on the antigen to which the Y-shaped antibodies created by the phage display are attached differ from the epitopes on the antigen to which the Y-shaped antibodies created by the transgenic mouse method are attached.

THE '281 PATENT IN DETAIL

[30] The '281 patent is very large; it is called a "Jumbo Patent" by the Canadian Patent Office. It includes 169 pages of description, a vast number of pages of sequence listing, 223 claims and fourteen pages of tables and charts. At trial, I was provided with a useful table of contents, which reproduce here:

TABLE OF CONTENTS of '281 PATENT

[31] At pages 1 through 3, the patent discusses the Background of the Invention. In particular, it discusses a genetic material found in humans, a cytokine, called interleukin 12, or IL-12. It comprises two subunits; a 35 kDa (kilodalton – a measure of weight) and a 40 kDa unit linked together by a disulphide bridge referred to as the p70 subunit. Functionally, IL-12 is said to play a central role in regulating the balance between certain T cells in the body. It is acknowledged that IL-12 appears to play a role in respect of a variety of human disorders; thus, strategies to inhibit or counteract IL-12 have been designed, beginning with antibodies derived from mice (murine). Those antibodies provoke an unwanted response (HAMA) in humans. The Background concludes at page 3:

> In general, attempts to overcome the problems associated with use of fully-murine antibodies in humans, have involved genetically engineering the antibodies to be more "human-like." For example, chimeric antibodies, in which the variable regions of the antibody chains are murine-derived and the constant regions of the antibody chains are human-derived, have been prepared (Junghans, *et al.* (1990) *Cancer Res.* 50:1495-1502; Brown *et al.* (1991) *Proc. Natl. Acad. Sci.* 88:2663-2667; Kettleborough *et al.* (1991) *Protein Engineering*, 4:773-783). However, because these chimeric and humanized antibodies still retain some murine sequences, they still may elicit an unwanted immune reaction, the human anti-chimeric antibody (HACA) reaction, especially when administered for prolonged periods.

> A preferred IL-12 inhibitory agent to murine antibodies or derivatives thereof (*e.g.*, chimeric or humanized antibodies) would be an entirely human anti-IL-12 antibody, since such an agent should not elicit the HAMA reaction, even if used for prolonged periods. However, such antibodies have not been described in the art and, therefore are still needed.

[32] At page 3, over to page 34, there is provided a Summary of the Invention, which begins as follows:

> **Summary of the Invention**
>
> The present invention provides human antibodies that bind human IL-12. The invention also relates to the treatment or prevention of acute or chronic diseases or conditions whose pathology involves IL-12, using the human anti-IL-12 antibodies of the invention.

[33] The patent proceeds from page 3 to discuss various aspects of the invention. At page 15, it discusses, as another aspect, a method of inhibiting IL-12 in persons suffering from certain disorders. Psoriasis is not mentioned:

> In another aspect, the invention provides a method for inhibiting human IL-12 activity in a human subject suffering from a disorder in which IL-12 activity is detrimental, comprising administering to the human subject the antibody of the invention, *e.g.*, J695, such that human IL-12 activity in the human subject is inhibited. The disorder can be, for example, Crohn's disease, multiple sclerosis or rheumatoid arthritis.

[34] Commencing at page 35, the patent discusses a Detailed Description of the Invention. A number of terms are defined, including "antibody" (page 35) and "recombinant human antibody" (page 39):

> The term "antibody" includes an immunoglobulin molecule comprised of four polypeptide chains, two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as HCVR or VH) and a heavy chain constant region.
>
> . . .
>
> The phrase "recombinant human antibody" includes human antibodies that are prepared, expressed, created or isolated by recombinant means, such as antibodies expressed using a recombinant expression vector transfected into a host cell (described further in Section II, below), antibodies isolated from a recombinant, combinatorial human antibody library (described further in Section III, below), antibodies isolated from an animal (*e.g.*, a mouse) that is transgenic for human immunoglobulin genes (see *e.g.*, Taylor, L.D., *et al.* (1992) *Nucl. Acids Res.* 20:6287-6295) or antibodies prepared, expressed, created or isolated by any other means that involves splicing of human immunoglobulin gene sequences to other DNA sequences.
>
> . . .

[35] Commencing at page 44, the patent describes various aspects of the invention in further detail. Human Antibodies that Bind Human IL-12 are the first to be discussed:

> I. Human Antibodies that Bind Human IL-12
>
> This invention provides isolated human antibodies, or antigen-binding portions thereof, that bind to human IL-12. Preferably, the human antibodies of the invention are recombinant, neutralizing human anti-hIL-12 antibodies. Antibodies of the invention that bind to human IL-12 can be selected, for example, by screening one or more human V_L and V_H cDNA libraries with hIL-12, such as by phage display techniques as described in Example 1.

. . .

(a detailed description of phage display follows).

[36] At page 47 and following, there is a discussion of the stickiness of the antigen and its determination by a PHA assay.

[37] A long discussion of mutagenesis follows.

[38] At pages 108 through 110, there is a shopping list of diseases in which IL-12 is said to play a critical role. It begins at page 108:

> Interleukin 12 plays a critical role in the pathology associated with a variety of diseases involving immune and inflammatory elements. These diseases include, but are not limited to…
>
> (page 110)
>
> Preferably the antibodies of the invention or antigen-binding portion thereof, are used to treat rheumatoid arthritis, Crohn's disease, multiple sclerosis, insulin dependent diabetes mellitus, and psoriasis, as described in more detail in section VII.

[39] Those particular disorders are discussed in detail commencing at page 118 of the patent. That discussion is preceded at pages 117 to 118 by the following:

> As used herein, the phrase "a disorder in which IL-12 activity is detrimental" is intended to include diseases and other disorders in which the presence of IL-12 in a subject suffering from the disorder has been shown to be or is suspected of being either responsible for the pathophysiology of the disorder or a factor that contributes to a worsening of the disorder. Accordingly, a disorder in which IL-12 activity is detrimental is a disorder in which inhibition of IL-12 activity is expected to alleviate the

symptoms and/or progression of the disorder. Such disorders may be evidenced, for example, by an increase in the concentration of IL-12 in a biological fluid of a subject suffering from the disorder (*e.g.*, an increase in the concentration of IL-12 in serum, plasma, synovial fluid, *etc.* of the subject), which can be detected, for example, using an anti-IL-12 antibody as described above. There are numerous examples of disorders in which IL-12 activity is detrimental. In one embodiment, the antibodies or antigen binding portions thereof, can be used in therapy to treat the diseases or disorders described herein. In another embodiment, the antibodies or antigen binding portions thereof, can be used for the manufacture of a medicine for treating the diseases or disorders described herein. The use of the antibodies and antibody portions of the invention in the treatment of a few non-limiting specific disorders is discussed further below:

[40] The discussion respecting psoriasis appears at page 120 of the patent:

E. *Psoriasis*

Interleukin-12 has been implicated as a key mediator in psoriasis. Psoriasis involves acute and chronic skin lesions that are associated with a TH1-type cytokine expression profile. (Hamid et al. (1996) J. Allergy Clin. Immunol. 1:225-231; Turka et al. (1995) Mol. Med. 1:690-699). IL-12 p35 and p40 mRNAs were detected in diseased human skin samples. Accordingly, the antibodies or antigen binding portions thereof of the invention may serve to alleviate chronic skin disorders such psoriasis.

The present invention is further illustrated by the following examples which should not be construed as limiting in any way. The contents of all cited references, including literature references, issued patents, and published patent applications, as cited throughout this application are hereby expressly incorporated by reference. It should further be understood that the contents of all the tables attached hereto (see Appendix A),

[41] A number of specific Examples, ten in all, follow. The most important for this case is Example 9, which discusses a human subject who was subject to testing of the antibody J695 and, "by chance", received that antibody, not a placebo. That person suffered from psoriasis, which was treated by the administration of J695. It must be noted that Example 9 DID NOT appear in the

priority patent application. It only appeared in the PCT (effectively the Canadian) application as filed March 24, 2000. It says:

EXAMPLE 9: Clinical Pharmacology of J695

In a double blind, crossover study, 64 healthy, human male subjects were administered ascending doses of J695 or placebo. Measurement of complement fragment C3a prior to and 0.25 h after dosing did not demonstrate activation of the complement system. CRP and fibrinogen levels were only increased in subjects in whom symptoms of concurrent infections were observed.

All subjects survived and the overall tolerability of J695 was very good. In no case did treatment have to be stopped because of adverse events (AEs). The most commonly observed AEs were headache and common cold/bronchitis, neither of which were categorized as severe.

One of the study subjects, a 33-year-old single male, was suffering from psoriasis guttata at the start of the study. According to the randomized study design, this subject by chance received 5mg/kg J695 by SC administration. Ten days prior to administration of the antibody, the subject showed only small discrete papular lesions on the arms and legs. At the time of the antibody administration, the subject displayed increased reddening, thickness of the erythematous plaques, and increased hyperkaratosis. One week after J695 administration, the subject reported an improvement in skin condition, including flattening of the lesions and a decrease in scaling. Shortly after the second administration of J695 (5 mg/kg IV), the subject's skin was totally cleared of psoriatic lesions, in the absence of any local treatment. Erythematous plaques covered with white scales reappeared concomitant with the expected clearance of J695 after the second administration of antibody.

[42] After Example 10 at page 169 is a paragraph respecting equivalents:

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

[43] Many pages of "Sequence Listings", directed to J695, follow; then the 223 claims and then fourteen tables and graphs.

THE CLAIMS AT ISSUE

[44] The '281 patent contains two hundred and twenty-three (223) claims. The Plaintiffs AbbVie have focused on two of those claims; claims 143 and 222. These two claims are written in dependent form so as to incorporate by reference earlier claims of the patent; thus, claim 143 incorporates by reference claim 138; and claim 138 incorporates by reference any one of claims 1 to 38, 49, 56 to 62, 65 to 117 or 119. Claim 222 incorporates by reference claim 217, and claim 217 incorporates by reference any one of claims 144 to 169. Of these many choices, AbbVie has chosen to assert claim 143 as read by incorporating claims 78, 80, 84 and 138; and claim 222 as read by incorporating claims 158, 165, 166 and 217.

[45] At trial Janssen's Counsel agreed to restrict Janssen's Counterclaim as to invalidity to these claims.

[46] With the selected incorporations, claim 143 reads as follows:

> *143. The use of a neutralizing isolated human antibody, or antigen-binding portion thereof, that binds to human IL-12 and dissociates from human IL-12 with a k_{off} rate constant of 1×10^{-4} s^{-1} or less, as determined by surface plasmon resonance and which inhibits phytohemagglutin blast proliferation in an <u>in vitro</u> PHA assay with an IC_{50} of 1×10^{-9} M or less, to treat psoriasis.*

[47] Claim 222 with the selected incorporations reads as follows:

> *222. The use of an isolated human antibody, or antigen-binding portion thereof, which binds to a human interleukin comprising a p40 subunit and dissociates from the human interleukin with a* k_{off} *rate constant of* $1 \times 10^{-2}\ s^{-1}$ *or less, as determined by surface plasmon resonance, and which inhibits phytohemagglutinin blast proliferation in an in vitro PHA assay with an* IC_{50} *of* 1×10^{-9}*M or less, which neutralizes the activity of the interleukin, to treat psoriasis.*

THE EVIDENCE

[48] The evidence consisted of witnesses appearing in person, reports or affidavits of witnesses who did not appear in person, agreed-upon documents entered as exhibits, other exhibits entered at trial, and portions of examination for discovery deemed to be read in. The evidence in chief of the expert witnesses was provided in the form of affidavits or statements which were deemed to be read into the record. The parties agreed that certain documents would be entered into the record without formal proof. These documents were given an exhibit number with the letter A as a prescript. These documents are to be considered as true copies of the originals, to be authored and where indicated, received, by the persons so noted at the date apparent from the document. Their relevance, if any, is for the Court to determine.

[49] AbbVie provided the evidence of four expert witnesses and three fact witnesses. No challenge was made by Janssen to the fact that the experts were called as such, although the nature and extent of their expertise was not conceded.

[50] AbbVie presented the evidence of the following witnesses as expert witnesses:

(a) Dr. Mark Shlomchik: Professor of Immunology, Pittsburgh, Pennsylvania.

AbbVie proposed the following as a statement as to his expertise:

> *Dr. Mark Shlomchik is a clinical and research immunologist, as well as the Chairman of the Department of Immunology at the University of Pittsburgh. AbbVie proposes that Dr. Shlomchik be qualified as an expert immunologist, including the development and assessment of human antibodies using phage display and transgenic mice technology. AbbVie further proposes that Dr. Shlomchik be qualified as an expert in the use of antibodies to treat autoimmune and inflammatory diseases. Dr. Shlomchik will be qualified to provide opinions about the state of the art, other knowledge of the skilled person, the meaning of words in Canadian Patent No. 2,365,281 and to express opinions set out in his affidavits as of March 25, 1999, and today.*

Dr. Shlomchik testified both as to infringement (Exhibit P-95) and validity (Exhibit P-96) of the '281 patent.

(b) Dr. Louis Weiner: Physician and Professor, Washington, District of Columbia. AbbVie proposed the following as a statement as to his expertise:

> *Dr. Louis Weiner is currently a clinical and research oncologist as well as a Professor of Oncology at Georgetown University in Washington. Dr. Weiner directs the Lombardi Comprehensive Cancer Center at Georgetown, which is one of only 41 US National Cancer Institute designated Comprehensive Cancer Centers. Dr. Weiner has expertise developing novel therapeutic antibodies. AbbVie proposes that Dr. Weiner be qualified as an expert in antibody engineering and the*

development of human antibodies including therapeutic monoclonal antibodies, phage display and transgenic mice. Dr. Weiner will be qualified to provide opinions about the state of the art, other knowledge of the skilled person, the meaning of words in Canadian Patent No. 2, 365,281 and to express opinions set out in his affidavit as of March 25, 1999 and today.

Dr. Weiner testified as to validity (Exhibit P-101) of the '281 patent.

(c) Dr. Richard Chizzonite: Consultant, Biotech/Pharma , South Kent, Connecticut. AbbVie proposed the following as a statement as to his expertise:

Dr. Richard Chizzonite was, in the 1990's, part of a team who identified IL-12 and developed novel biologic assays (including PHA blast proliferation) for evaluating the biological characteristics of IL-12. Dr. Chizzonite was directly involved in the development of antibodies directed towards IL-12 to potentially treat diseases and was a leading author on the use of, and inhibition of, IL-12 to treat diseases. Dr. Chizzonite was also the author of the chapter dealing with PHA blast proliferation assays for IL-12 in Current Protocols in Immunology. AbbVie proposes that Dr. Chizzonite be qualified as an expert immunologist, including IL-12, and the biologic assays described in Canadian Patent No. 2,365,281. Dr. Chizzonite will be qualified to provide opinions about the state of the art, other knowledge of the skilled person, the meaning of words in Canadian Patent NO. 2,365,281 and to express the opinions set out in his affidavits as of March 25, 1999, and today.

Dr. Chizzonite testified both as to infringement (Exhibit P-106) and validity (Exhibit P-107) of the '281 patent.

(d) Dr. Gregory De Crescenzo: Full Professor, Montreal, Quebec. AbbVie proposed the following as a statement as to his expertise:

> *Dr. Gregory De Crescenzo is currently a Professor in the Department of Chemical Engineering at Ecole Polytechnique de Montreal. AbbVie proposes that Dr. De Crescenzo be qualified as an expert in surface Plasmon resonance technology, including the use of BIAcore machines to analyze the interactions between molecules (including the measurement of K_D and k_{off} for protein-protein interactions). Dr. De Crescenzo will be qualified about the meaning of the words in Canadian Patent No. 2,365,281 from the point of view of the skilled person and to express the opinion set out in his affidavits as of September, 2000 and today.*

Dr. De Crescenzo testified as to infringement (Exhibit P-120) and validity (Exhibit P-121) of the '281 patent. Certain explanatory notes were entered into evidence by agreement between Counsel as Exhibit A-165.

[51] AbbVie called three witnesses as to factual matters:

(a) Dr. Stuart Friedrich: Scientist, Morpeth, Ontario. He is one of the named inventors in the '281 patent. He testified as to some of the development work to the patent. He appeared in person and was examined and cross-examined.

(b) Dr. Richard Hughes: Scientist Project Leader, Cambridge, United Kingdom. He conducted an experiment to determine the IC_{50} for STELARA as measured in an *in vitro* PHA blast proliferation assay.

He did not appear in person. His evidence was provided by way of an affidavit (Exhibit P-105). There was no cross-examination as Janssen declined to cross-examine him even though Letters Rogatory permitting cross-examination had been issued by me prior to trial.

(c) Suping Jin: Senior research Associate, San Antonio, Texas. She conducted an experiment to determine the k_{off} rate for STELARA, dissociating from human IL-12 using a BIAcore machine.

Her evidence was contained in her report, which was an attachment to her affidavit (Exhibit P-122). She appeared in person and was examined and cross-examined.

[52] In addition, AbbVie tendered in evidence portions of the examination for discovery of Janssen (Exhibit P-163).

[53] Janssen provided the evidence of three expert witnesses and two fact witnesses. No challenge was raised by AbbVie as to the experts having been called as such, although the nature and extent of their expertise was not conceded.

(a) Dr. Michael Eck: Scientist/Professor, Brookline, Massachusetts. He gave evidence as to amino acid sequences and three-dimensional structures of two antibodies: STELARA and J695. His evidence was given by way of a Report

in two volumes; Exhibit D-123, which was deemed to be read into evidence. He did not appear in person. There was no cross-examination.

(b) Dr. Marie (Marika) Sarfati: Scientist/Professor, Montreal, Quebec. Janssen prepared the following statement as to her expertise :

> *Marie Sarfati will be qualified to testify on immunology in humans with a focus on IL-12, including the regulation of the immune response, human antibodies, human interleukins, antibody affinity, antibody neutralization, and the use of fully human antibodies in the treatment of disease.*

Dr. Sarfati appeared in person and testified as to validity (Exhibit D-152) and infringement (Exhibit D-153) of the '281 patent. She was cross-examined.

(c) Dr. Andrew J. J. George: Professor of Immunology, Richmond, United Kingdom. Janssen prepared the following statement as to his expertise:

> *Andrew J. T. George will be qualified to testify on basic immunology, antibodies and therapeutic antibodies, antibody engineering including the use of recombinant techniques to generate antibodies in phage display and transgenic mouse technology, the analysis, detection and measurement of immune cells and molecules, including the affinity and kinetics of antibody/antigen interactions.*

Dr. George appeared in person and testified as to validity (Exhibit D-155 in four volumes) and infringement (Exhibit D-156) of the '281 patent. Some corrections were entered as Exhibit D-157. He was cross-examined.

[54] Janssen called two fact witnesses:

(a) Dr. John Ghrayeb: Retired Scientist, Downingtown, Pennsylvania. He was involved in the development of the drug known as STELARA and gave evidence as to that development. He appeared in person and was examined and cross-examined.

(b) George Treacy: Retired Toxicologist, Downingtown, Pennsylvania. He was involved in some of the development work in the early stages leading up to the drug now known as STELARA. He testified as to certain memoranda he prepared in 1999 (Exhibit 147) and was cross-examined.

[55] In addition, Janssen tendered in evidence portions of the examination for discovery of AbbVie (Ex D-162).

COMMENTS AS TO THE EVIDENCE AND WITNESSES

a) Comments as to the Expert Witnesses

[56] I am satisfied that each of the persons called by each of the parties as experts were qualified to give evidence as experts within their qualifications as put forward by Counsel as set out earlier in

these Reasons. I am also satisfied that each of the experts for each of the parties has read and has endeavoured to adhere to the Code of Conduct for Expert Witnesses as provided for in Rule 52.1(1)(c) and the Schedule to Form 52.2.

[57] With respect to the experts put forward by AbbVie, I place the greatest reliance on the evidence of Dr. Weiner. He was a person working in the relevant area at the relevant time, and gave his answers with great candour. I was also impressed by Dr. Chizzonite, who also has substantial experience at the relevant time and has authored many scientific papers on relevant subject matter at the relevant time. I do not discount the evidence of Dr. Shlomchik, as he has impressive qualifications, but he did not play an important role in the field at the relevant time. His evidence appears to have been viewed more with hindsight. He appeared to be somewhat nervous in the witness box; a matter I ascribe to this probably being the first time that he has testified as an expert witness in open court. I have no hesitation in accepting Dr. De Crescenzo's evidence; it was largely uncontested.

[58] With respect to Janssen's expert witnesses, Dr. George was clearly a practiced and experienced witness, with impressive qualifications in the relevant field at the relevant time. He has obviously testified as an expert several times. I found him to be somewhat too practiced. In cross-examination, he was taken to portions of his written evidence in chief which, despite his statements in that evidence that certain matters could be found in supporting documents, they could not, in fact, find such support. This suggests that he was perhaps a little over confident in respect of some of his evidence and should have been more careful.

[59] Dr. Sarfati, Janssen's other expert witness, appears to have been a minor player in the relevant area at the relevant time. She appeared to be somewhat confused and flustered at times during cross-examination. Her evidence is largely based on hindsight; I do not give her evidence as much weight as that of other experts.

[60] Dr. Eck, another expert put forward by Janssen, did not appear personally; his evidence is uncontested.

[61] In all, I was most impressed with Dr. Weiner and I will prefer his evidence unless I state otherwise.

b) Testing the Janssen STELARA Product

[62] Only AbbVie conducted tests on the Janssen STELARA product. Notwithstanding that STELARA is Janssen's product, and that Janssen undoubtedly has the means to perform the necessary tests on its product, it did not provide in evidence the results of any such tests. Janssen chose only to offer criticisms of the tests performed at the request of AbbVie. Accordingly, I must weigh the AbbVie tests only against criticisms, and not against other tests. If Janssen clearly believed that its product did not fall within certain parameters, I would have expected it to provide evidence as to testing that demonstrated that fact.

[63] Janssen made a motion to be dealt with at trial to exclude the evidence as to this testing conducted by third parties at the request of AbbVie. In particular, Janssen moved to exclude the evidence of Ms. Jin and Dr. Hughes.

[64] Unlike the practice in the United Kingdom as described in the "White Book", Civil Procedure, Volume 2, 2013, Sweet & Maxwell, London at page 730, there is, as of yet, no Federal Courts of Canada Rule specifically directed to testing conducted for the purposes of trial. In *Omark Industries (1960) Ltd v Gouger Saw Chain Co*, (1965) 1 Ex C R 457 at page 516, Justice Noel discussed a "salutary" rule to the effect that an opposite party should be given notice of and an opportunity to attend at such experiments. He did, however, also say that an *ex parte* test may be admissible, subject to weight, particularly where, in his case the opposite party could readily have conducted the same test. Most recently Justice O'Reilly of this Court in *Apotex Inc. v. Pfizer Canada Inc.*, 2013 FC 493 at paragraph 40,held that where a party had ample notice as to the testing and ample knowledge as to what would be done, a party cannot be held to say that the testing results are inadmissible because the party did not attend.

[65] AbbVie provided evidence of testing conducted at two independent laboratories. One was conducted by Ms Suping Jin at the University of Texas Health Centre, where she measured the k_{off} rate constant of STELARA dissociating from human IL-12 as 0.76×10^{-4} s^{-1}. Her cross-examination satisfied me that she conducted the test properly and her result is reliable. Dr. De Crescenzo, an expert called by AbbVie, particularly at paragraphs 37 to 45 of Exhibit P -121, supports Ms. Jin's conclusions. Dr. George, an expert called by Janssen in paragraph 8 of his second affidavit, Exhibit D-156, criticizes Ms. Jin's analysis only in that it provides limited information (paragraph 8), but agrees that her experiments do accord with the protocol of Example 5 of the '281 patent (paragraph 13).

[66] It is to be noted that the original affidavits of De Crescenzo and George refer to the evidence of other persons – Dr. Vinitsky and Dr. Rich – neither of whom were called as witnesses by either party. These comments were redacted from the affidavit now appearing as Exhibit P-121.

[67] Another set of experiments was conducted at Quotient Bio Analytical Sciences in Cambridge, United Kingdom by Dr. Richard Hughes. AbbVie's Counsel conceded that no prior notice of this testing was given to Janssen's Counsel and, of course, Janssen did not attend.

[68] The evidence of this testing was provided by the filing of Dr Hughes' affidavit (Exhibit P-105); he did not appear in person, and, though I issued Letters Rogatory to permit cross-examination, Janssen chose not to cross-examine. He conducted PHA assays of Janssen's STELARA product and concluded that STELARA inhibits PHA blast proliferation in a PHA assay with an IC_{50} of less than 1×10^{-9}. Dr. Chizzonite, an expert called by AbbVie, in his first affidavit (Exhibit P-106) at paragraphs 45 to 64, reviewed Dr. Hughes' work and concurred with his conclusion.

[69] Dr. Sarfati, an expert called by Janssen, in her second statement (Exhibit D-153), criticized Dr. Hughes' work largely because she would want further experiments conducted on further samples. At paragraph 16, she appears to agree that the tests that were performed were well performed, but should be treated only as preliminary.

[70] Given the evidence that I have, and having reviewed the criticisms made by Janssen and, given that Janssen did have a opportunity to cross-examine Dr Hughes, and that Janssen has

provided no test results whatsoever, I conclude that the evidence of both tests is admissible and that the evidence shows that:

- STELARA exhibits a k_{off} rate constant dissociating from human IL-12 as 0.76 x 10^{-4} s^{-1};

- STELARA inhibits PHA blast proliferation in a PHA assay with an IC_{50} of less than 1 x 10^{-9}M.

c) <u>Developments Leading to the '281 Patent</u>

[71] AbbVie called only one of the persons named as an inventor in the '281 patent; Dr. Stuart Friedrich. There were some twenty-two persons named as inventors of the '281 patent. Another of the named inventors, Dr. Veldman, was questioned by Janssen's Counsel on discovery and some of those answers appear in the portions of discovery read in by Janssen at trial. Apparently there were discussions between Counsel as to whether Dr. Veldman would appear as a witness at trial (Exhibit D-119). She did not. Janssen did not seek Letters Rogatory to examine her. Other named inventors were also examined on discovery and portions of their examinations were read in at trial on consent of AbbVie's Counsel.

[72] Developments began in Germany in an organization known as BASF. It collaborated with a company known as Genetics Institute.

[73] Dr. Friedrich joined the team at what was then known as Genetics Institute (which subsequently became part of a company known as Wyeth) in 1998. He left the organization in July 2001. During the period when he was with the organization, Dr. Friedrich work involved determining the pharmacokinetic and toxicokinetic properties of the antibody known as J695. He conducted studies in which J695 was administered to monkeys. The results of some of those studies are reported in the '281 patent. The research at that time was primarily focused at the time on rheumatoid arthritis, Crohn's disease and multiple sclerosis. Dr. Friedrich identified a study where, apparently by chance, one of the persons upon whom human tests were being performed, had psoriasis that disappeared when J695 was being administered. The result is set out in Example 9 of the '281 patent.

[74] I have no hesitation in accepting Dr. Friedrich's evidence as truthful; however, his involvement, both as to scope and period of time in the project, was limited.

d) <u>Developments Leading to the STELARA Product</u>

[75] Janssen led the factual evidence of Dr. Ghrayeb and Mr. Treacy, both now retired, both of whom were scientists at an organization called Centocor, later acquired by Johnson & Johnson; of which Janssen also is a member. They testified as to the development of antibodies which would attach to human IL-12. Centocor used transgenic mice in this development. At least at the time, Centocor did not possess phage display technology.

[76] Dr. Ghrayeb was one of the persons personally involved in the project, as well as in supervising others involved in the project. He has been retired for some time, and had some

difficulty in remembering dates and sequence of events unless aided by a document. He was a witness in proceedings in the United States Courts, and, in cross-examination before me, admitted that some of the answers he gave in the United States proceedings as to the chronology of events were not correct (Transcript, Volume 6, pages 971 – 976). I will, therefore, be cautious in accepting Dr. Ghrayeb's testimony where it is not supported by documents in evidence.

[77] Mr. Treacy also was a scientist involved in the STELARA project. He recently retired from Centocor. He was apparently approached by Counsel for Janssen only a few weeks before this trial began, and was asked as to his recollections of events. Apparently motivated by this discussion, he went home, where he found a computer in a storage area; and, in the memory of that computer, located two memoranda that he wrote in May 1999 reflecting a search of the prior art as to IL-12 and psoriasis that he conducted at the time. Those memoranda were tendered in evidence at trial. He admitted that he did not have a depth of expertise in the particular area that he had searched.

[78] I give Mr. Treacy's evidence, in particular his memoranda, little weight. Those memoranda apparently never appeared, and were never referred to, in any reports or summaries made by the Centocor research group. What use, if any, was made of these documents is unknown. They were never produced by Janssen in discovery, and were never referred to by Dr. Ghrayeb in his narrative of events. The exact nature and function, if any, of these documents in the STELARA project at Centocor is not clear; there is no evidence that they were ever used. The appearance of these documents only a few days before trial, especially when they were never produced on discovery in Canada, or in the United States proceedings, and apparently played no part in the developments at Centocor, leads me to give them little weight.

e) A Comparative Timeline as to Events at AbbVie and Janssen

[79] AbbVie, in its Statement of Claim, paragraphs 12 and 13, alleges that it was the first company to develop human antibodies that neutralize IL-12, and that Janssen's product was developed after that. Janssen, in its Defence, denied these allegations and alleged that it developed its product in 1997. Because the pleadings put the timing of developments by each of the parties at issue, I permitted evidence to be led in respect of this matter, although its relevance appears to be marginal.

[80] I am setting out in tabular form a chronology of some of the events occurring in respect of each party's developments as they appear from the Record in this case:

AbbVie				Janssen		
Document type				Document type		
name	category	Document	Date	name	category	Document
milestone 1 report	work leading up to the patent	Report on progress (isolation of antibodies binding to Il-12)	13/09/1995			
milestone 2 report	work leading up to the patent	Report on progress (neutralization of isolated anti-ill-12 antibodies)	12/12/1995			
milestone 3 report	work leading up to the patent	Report on progress (1 linage chosen with right characteristics)	15/07/1996			
			10/04/1997	Janssen	Laboratory workbook	Genpharm injections of Il-12 and TNF (claimed by Janssen that its mouse injections, but I do not see the evidence)
			01/10/1997	Janssen	Laboratory workbook	Stelara antibody purified
milestone 4 report	work leading up to the patent	Report on progress (Y61 chosen as one of best 2)	28/11/1997			
Status report	work leading up to the patent	J695 proposed as candidate	07/05/1998			
			22/05/1998	Janssen meeting	Scientific Advisory Board meeting	Stelara presented to SAB, no comment on psoriasis indication
milestone 5 report	work leading up to the patent	Affinity maturation of Y61 that lead to J695	26/08/1998	Centocor	Interoffice memorandum	psoriasis mentioned in clinical indication by Il-12 team
			05/11/1998	Centocor	Interoffice memorandum	psoriasis mentioned as a clinical indicator
281 Patent	**Priority date**	Priority date to US60/126,603	25/03/1999			
		Phase 1 of J695 and the first time Patient 62 administered with J695	09/09/1999			
			05/10/1999	Centocor	interoffice correspondence	Discussion of possible phase 1 trial for psoriasis.
		Amendment to the application to add Example 9 showing that the J695 was used to treat psoriasis in humans	03/11/1999			
			27/01/2000	Centocor Interoffice Memo	Tech Update	Phage display considered to advance Centocor technology
			10/02/2000	interoffice memo	recommened clinical indication for FIH	prosiasis and Crohn's considered by the team to have potential for FIH clinical study
281 Patent	**PCT (Canada) Filing date**	PCT filing datefor '281 Patent in Canada	24/03/2000			
			07/08/2000	US Patent Office	Provisional patent application number 60/223358	No specific claim for Psoriasis only (claimed within a large group in claim 25) and mentioned in a similar group in description
281 Patent	**Publication date**	publication of '281 in Canada, no psoriasis only claim but have example 9.	28/09/2000			
			05/10/2000	Centocor email from George Heavner	Literature Search	John Grayeb received email regarding WO 00/56772

AbbVie				Janssen		
Document type				Document type		
name	category	Document	Date	name	category	Document
			xx/12/2000	Undertaking	answers upon undertaking	Protocol for psoriasis finalized
			06/04/2001	Undertaking	answers upon undertaking	start of phase 1 study with patients with psoriasis
			09/05/2001	Undertaking	answers upon undertaking	Stelara first administered to humans with psoriasis
			01/07/2001	Centocor report	Monthly report	Phase II and III trials - Psoriasis program shows no achieved or expected achievements
Management Committee meeting	Briefing document	Clinical trial for psoriasis is contemplated, experts have been contacted in relation to trial	14/02/2001			
J695 Development recommendations	Summary of PEC meeting	"Do not initiate a proof of concept study in psoriasis at this time"	13/06/2002			
			14/04/2004	Journal Publication	J Invest Dermatol	Publication of Stelara phase 1 results in psoriasis
United States Patent issues	6,914,128	US patent without psoriasis only claims BUT contains Example 9	05/07/2005			
Canadian Patent application document	response to examination report	New set of claims for '281 patent, but have no speific claim for psoriasis only	28/08/2006			
Canadian Patent application document	response to examination report	New set of claims for '281 patent, with specific psoriasis only claims	27/06/2007			
			01/09/2006	Centocor email from Fidelus-Gort	research report	J695 (results from AbbVie) failed to show efficacy in Phase 3 study in MS
			12/12/2008	Canadian Patent Document	Notice of compliance	Stelara NOC
Uunited states Patent issues	7,504,485	US patent issues with psoriasis claims	17/03/2009			
Canadian Patent Document	**2,365,281**	Canadian '281 Patent issues	04/08/2009			
Federal Court application	statement of Claim	T-1310-09 initiated	10/08/2009			

[81] From the evidence at trial, in particular the factual evidence of Dr. Friedrich, Dr. Ghrayeb and Mr. Treacy; as well as the exhibits to their evidence, the documents put into evidence by agreement, and the discovery portions read into evidence, I conclude:

- the developments at AbbVie and its predecessors respecting J695, and at Janssen respecting STELARA, were separate developments;

- there is no good evidence that Janssen's decision to direct work to psoriasis was in any way motivated by the publication of the '281 patent application, or the publication of a similar application in any other country;

- there is no good evidence that AbbVie's decision to include claims in the '281 patent application were motivated by any publication of Janssen's work on STELARA;

- the delay by AbbVie in pursuing clinical work on psoriasis was not attributed to lack of confidence; rather, AbbVie chose to pursue research respecting other diseases for pragmatic reasons; and

- the delay by Janssen in pursuing clinical work on psoriasis was equally not motivated by lack of confidence, but for other pragmatic reasons.

f) Comparison Between STELARA and J695

[82] Janssen is selling a product in Canada, which it calls STELARA; it contains as an active ingredient a biological material which it calls ustekinumab, an almost unpronounceable name. I will refer to the product - in particular, its active ingredient - as STELARA.

[83] AbbVie has developed a biological material which it calls J695. That material is described at some length in the "281 patent.

[84] I will compare STELARA and J695, both in respect of their similarities and their differences, based on the evidence presented in the Record at trial. This exercise is not to be confused with the exercise I will do later in comparing STELARA with the claims at issue. That is quite a different exercise.

[85] Therefore, in comparing STELARA and J695:

- both are human antigens which bind to human IL-12;
- both have similar stickiness and potency in respect of binding to human IL-12;
- they have been derived quite differently; STELARA has been derived using transgenic mouse technology; J695 has been derived using phage display technology;
- each of STELARA and J695 bind to human IL-12 but, at different places (epitopes);
- STELARA and J695 have different genetic make-up their amino acid sequences are, at best, only 50% similar;
- the binding sites at the tip of the Y structure of each of STELARA and J695 are of a different character; and

- STELARA has been approved by the relevant Canadian government authorities for sale in Canada for the treatment of psoriasis; J695 has not. In fact, J695 has not been approved for sale by the relevant authorities in any country; the evidence does not show why this is the case.

UNITED STATES DECISION

[86] There have been filed as Exhibits A11 and A12 copies of an Amended Memorandum and Order on Cross-Motions on Summary Judgment, and an Order on Motion for Judgment as a Matter of Law, respectively, by Judge Saylor of the United States District Court, District of Massachusetts, Court Action No. 09-11340-FDS, between *Abbott GmbH & Co et al and Centocor Ortho Biotech Inc et al*. That decision is between parties that are also parties in this action or their privies and two United States Patents that are, in many respects, the same as or similar to the '281 patent at issue here. The claims at issue there are different from the two claims at issue here The trial in the United States was a jury trial.

[87] I am advised by Counsel that the matter is on appeal before the United States Court of Appeal for the Federal Circuit (US CAFC).

[88] While I take note of these decisions, they have not been taken into account in my coming to a decision in the case before me.

ISSUES

[89] The Plaintiffs allege that claims 143 and 222 of the '281 patent are valid and infringed. The Defendant denies these allegations and, as a Plaintiff-by-Counterclaim, alleges that those claims ought to be declared to be invalid.

[90] By a very broad Order of this Court dated September 26, 2011 it has been Ordered that this trial is restricted to issues of validity and infringement only; and that if any asserted claim has been found to be valid and infringed, then the issue of (i) the Plaintiffs' right to elect as between profits and damages, (ii) the Plaintiffs' entitlement to an injunction, (iii) the extent of infringement, and (iv) the quantum of any damages or profits, shall be determined at a second trial at a date to be agreed or fixed.

[91] Therefore, the issues before me are the infringement and validity of claims 143 and 222 of the '281 patent.

[92] As to validity, Janssen has reduced the grounds upon which it asserts invalidity to three (paragraph 46 of its Closing Submissions), namely:

- covetous claiming (claims broader)
- Insufficiency and lack of enablement, and
- obviousness

[93] In order to address these issues, I must first define the person of ordinary skill in the art (POSITA) to whom the patent is addressed, and construe claims 143 and 222.

PERSON OF ORDINARY SKILL IN THE ART (POSITA)

[94] There appears to be little contention between the parties as to the definition of a person of ordinary skill in the art (POSITA).

[95] I will define such a person in terms of a team of persons having a reasonably high level of knowledge and experience in dealing with human antibodies, including those in the fields of immunology and dermatology; particularly psoriasis, and including those with good technical skills in performing the types of tests as described in the patent respecting stickiness and potency.

CONSTRUCTION OF THE CLAIMS

[96] At issue are claims 143 and 222. I repeat those claims as they are read by incorporating the other claims as referenced in those claims:

> *143. The use of a neutralizing isolated human antibody, or antigen-binding portion thereof, that binds to human IL-12 and dissociates from human IL-12 with a k_{off} rate constant of 1×10^{-4} s^{-1} or less, as determined by surface plasmon resonance and which inhibits phytohemagglutin blast proliferation in an in vitro PHA assay with an IC_{50} of 1×10^{-9} M or less, to treat psoriasis.*
>
> . . .
>
> *222. The use of an isolated human antibody, or antigen-binding portion thereof, which binds to a human interleukin comprising a p40 subunit and dissociates from the human interleukin with a k_{off} rate constant of 1×10^{-2} s^{-1} or less, as determined by surface plasmon resonance, and which inhibits phytohemagglutinin blast proliferation*

> *in an <u>in vitro</u> PHA assay with an IC_{50} of 1 x 10^{-9}M or less, which neutralizes the activity of the interleukin, to treat psoriasis.*

[97] Both of these claims are "use" claims. They are directed to the use of a substance to treat psoriasis.

[98] That substance is an "isolated human antibody" or portion thereof which binds and dissociates to and from human IL-12 (claim 143) or a human interleukin comprising a p40 subunit (claim 222). There is no material difference in the wording of the two claims in this regard; both refer to IL-12.

[99] That isolated human antibody (or portion) must have at least a certain stickiness, or greater; and at least a certain potency, or greater; as determined by the tests as defined in the claims.

[100] Neither claim restricts itself to a human antibody as prepared by a certain method, such as phage display, or through use of transgenic mice. While Janssen, relying on its experts, argues that the human antibody of these claims, must be restricted to that created by phage display, I do not find anything in the claims or in the patent to restrict these two claims in this manner. The patent describes the preparation of the human antibody by phage display in some detail; however, it does also make reference to the modified mouse method. There are claims in the patent that are restricted to human antibodies created by phage display; however, there is no such restriction in either of claims 143 or 222.

[101] Thus, I construe claims 143 and 222:

- as directed to the use of
- human antibodies, however created;
- which antibodies bind and dissociate from IL-12;
- at a stickiness of at least 1×10^{-4} s^{-1} (claim 143) or at least 1×10^{-2} s^{-1} (claim 222);
- and which antibibodies have a potency of at least 1×10^{-9} M;
- to treat psoriasis.

INFRINGEMENT

[102] The burden of proving infringement of a patent lies with the person alleging infringement, (e.g. *Varco Canada Ltd v Pason Systems Corp.*, 2013 FC 750 at para. 208). Here that person is AbbVie.

[103] Janssen, in its Closing Submissions at paragraphs 48 and 103, essentially concedes that, if I construe claims 143 and 222 as covering human antibodies made by any method, including, for

instance, the transgenic mouse method, then STELARA would fall within the scope of the claims at issue, subject to testing as to the level of stickiness and potency.

[104] I have found that the testing as to stickiness and potency submitted by AbbVie is admissible. The level of stickiness and potency as so found falls within the parameters of each of claims 143 and 222.

[105] Janssen submits that it does not use STELARA to treat psoriasis. That is correct; but its customers do. Janssen promotes and sells STELARA in Canada precisely for the purpose of administering it to humans to treat psoriasis.

[106] The law in Canada is clear. A person, such as Janssen, who sells a product for an infringing use by another, which product has no other significant commercial use, has induced that infringement, and is itself an infringer (see eg. *Dableh v Ontario Hydro* (1996), 68 CPR (3d) 129, at pages 148-149 (FCA)).

[107] I find that, if claims 143 and 222 are valid, Janssen has infringed these claims.

VALIDITY

a) Burden

[108] The *Patent Act*, subsection 43(2), provides that a patent is presumed to be valid in the absence of evidence to the contrary. There is an onus upon a party alleging invalidity to lead some evidence tending to prove those allegations; if it has done so the Court will determine the matter on

the usual civil burden of proof (e.g. *Tye-Sil Corp. Ltd v Diversified Products Corp.*(1991), 35 CPR (3d) 350 at pages 357-359 (FCA)). Once some evidence has been led, the presumption disappears (e. g. *Rubbermaid (Canada) Ltd v Tucker Plastic Products Ltd.* (1972), 8 CPR (2^{nd}) 6 at page 14 (FC)).

[109] In the present case I am satisfied that Janssen has led sufficient evidence such that the presumption shall not be taken into account and that the matter shall be considered on the usual civil burden of proof with Janssen to bear the burden of proof since it is asserting invalidity..

[110] Only claims 143 and 222 of the '281 patent are at issue in respect of validity (and infringement) therefore even if I were to find either or both claims to be invalid that finding does not affect the remaining claims or the patent generally (*Patent Act*, section 58).

b) <u>Obviousness</u>

[111] Janssen alleges that what is claimed in claims 143 and 222 of the '281 patent is obvious and not an invention.

[112] I recently reviewed the law in respect of obviousness in Canada in my decision in *Novartis Pharmaceuticals Canada Inc v Cobalt Pharmaceuticals Co*, 2013 FC 985 at paragraphs 60 to 66. I incorporate here that review without setting it out again. In particular, I addressed the Supreme Court of Canada decision in *Sanofi-Synthelabo Canada Inc v Apotex Inc*, 2008 SCC 61; and the decision of the Federal Court of Appeal in *Pfizer Canada Inc v Apotex Inc*, 2009 FCA 8; and *Apotex Inc v Sanofi Aventis Canada Inc*, 2013 FCA 186.

[113] I will, therefore, having regard to the evidence in the present case:

a. Identify the notional person skilled in the art;

b. Identify the relevant common general knowledge of that person;

c. Identify or construe the inventive concept of the claims at issue;

d. Identify what, if any, differences exist between the matter forming the state of the art and the inventive concept of the claims as construed;

e. Without any knowledge of the invention as claimed, were these steps obvious to a person skilled in the art, or do they require a degree of invention; in particular:

- was it more or less self-evident?

- what was the nature and extent of the effort required – was it routine, or not?

- was there motive in the prior art to find the solution not just based on a possibility that it might work, but whether it was more or less self-evident?

i) <u>Identify the Notional Person Skilled in the Art</u>

[114] I have already done this earlier in these Reasons at paragraphs 94 and 95.

ii) State of the Art

[115] The evidence of both AbbVie and Janssen focussed on the state of the art as of March 1999. I have no evidence that such state would be different as of March 2000.

[116] The '281 patent itself disclosed some of the relevant background and state of the art. I accept Dr. George's summary as to those disclosures as set out in Volume 1, paragraph 202 of his first report (Exhibit D-155):

> *202. The 281 Patent itself expressly specifies certain common or standard techniques:*
>
> *(a) Methods for preparing recombinant human IL 12. The 281 Patent states at page 37 that recombinant human IL 12 can be prepared by standard methods. Reference is made to articles as early as 1989 describing the structure of human IL 12.*
>
> *(b) Methods for preparing and screening phage display libraries. The 281 Patent notes at page 58 that such methods were 'known in the art', and reference is made to commercially available kits for doing such screening.*
>
> *(c) Methods of creating scFvs. This is noted at page 100 of the 281 Patent with reference to articles from 1988 and 1990.*
>
> *(d) Methods of modifying CDR sequences. The 281 Patent notes at page 54 that modification can be done by standard molecular biology techniques such as PCR mutagenesis, targeting individual contact or hypermutation amino acid residues in the Heavy or Light chain CDRs, followed by kinetic and functional analysis of the antibodies. Further information about mutagenesis methods is provided at page 81 of the 281 Patent.*
>
> *(e) Standard antibody manipulation techniques were known in the art. The 281 Patent notes at page 73 that the selective mutagenesis approach used to generate J695 from*

Y61 "can be used in standard antibody manipulation techniques known in the art. Examples include, but are not limited to, CDR grafted antibodies, chimeric antibodies, scFV fragments, Fab fragments of full length antibodies and human antibodies from other sources, e.g., transgenic mice".

(f) Obtaining V_H and V_L genes, and incorporating them into expression vectors. This is noted at page 98 of the 281 Patent, and reference is made to a standard laboratory textbook.

(g) Sequences of Heavy and Light chain constant regions were known. This is noted at pages 99 and 100 of the 281 Patent, with reference to Kabat.

(h) CDR positions that are frequent sites of somatic mutation and that might play a role in antigen binding. The 281 Patent notes at page 68 that certain positions in the CDR regions are "frequent sites of somatic mutation", citing Tomlinson et al. (1996) J. Mol. Biol. 256: 813-817[61]. Also noted on page 69 is MacCallum et al. (1996) J. Mol. Biol. 262: 732-745[62], which identified certain residues as being involved in antigen binding. Yet further, on page 69, the inventors note that Pini et al. (1998) J. Biol. Chem. 283: 21769-76[63] describe eight positions that led to increased antibody affinity.

(i) Expression of Light and Heavy chains in an expression vector. As noted on page 102 of the 281 Patent, this was known as a standard technique.

(j) Assays for determining IL 12 activity in vitro or in vivo. The 281 Patent notes (at pages 40 and 69) that indicators of human IL 12 "biological activity can be assessed by one or more of several standard in vitro or in vivo assays known in the art." This statement is made with reference to the assays in Example 3, discussed in more detail below. Also noted in Example 3 at page 144, the human peripheral blood mononuclear cells (PBMC) were collected from a healthy donor and activated in accordance with established practices in Kanof et al., 1996 Current Protocols in Immunology, Unit 7.1, Coligan et al. (eds), and Gately et al., 1995 Current Protocols in Immunology, Unit 6.16, Coligan et al. (eds). The principal assays referenced in the 281 Patent which were used are the IL 12 Receptor Binding Assay (at page 145), the PHA Blast Proliferation

> *Assay (at page 146), and the Interferon-γ Assay (at page 147).*

[117] Statements such as summarized above that have been made in the patent at issue are binding on the patentee (e.g. *Novartis Pharmaceuticals Canada Inc v Cobalt Pharmaceuticals Co*, 2013 FC 985, at para 31, and the cases referred to in that paragraph).

[118] With respect to the state of the art as it would be known to the person skilled in the art, and set out in the literature as would have been found by such a person, I accept what Dr. George has said at paragraph 217 of the same affidavit subject to the corrections made by him which I have incorporated. However, I must add to that some very important observations made by Dr. Weiner in paragraph 88 of his affidavit, Exhibit 101. Dr. George said at paragraph 217:

> *217. In summary, the following knowledge particular to the 281 Patent was common to the skilled artisan by March 1999:*
>
> > *(a) IL 12 was known to be part of the ~~anti-~~inflammatory pathways and to have clinical involvement.*
> >
> > *(b) IL 12 was known to consist of two sub-units which were 40 kDa and 35 kDa respectively, and it was known that monoclonal antibodies that specifically bind the p40 sub-unit will block receptor binding and biologic activity on activated lymphoblasts;*
> >
> > *(c) the idea of anti-IL 12 antibodies for inhibition of IL 12 activity was known, and the ability of human antibodies to bind to human IL 12 has been reported;*
> >
> > *(d) to block receptor binding, the antibody must bind with sufficient affinity so as to have a biological or inhibitory effect, and the routine approaches to measuring affinity levels (including ~~plasma~~ surface plasmon resonance by BIAcore and various assays);*

> *(e) with either transgenic mice or phage display techniques, strong antibodies having as low as 10^{-11} M affinities could be obtained, and lower affinity human antibodies could be improved through well-established practises involving CDR mutations, chain shuffling, mutagenesis; and*
>
> *(f) monoclonal antibodies were generally known to be used as therapeutic agents. Many expected that an antibody without murine sequences would have the potential to be a better therapeutic agent than a humanised antibody, though others did not believe that there would be a difference.*

[119] Dr. Weiner's important observations as set out in paragraph 88 of his affidavit were:

> *88. In March 1999, the skilled person of the '281 Patent would have understood that:*
>
> > *(a) the role of cytokines in human disease is complicated and many cytokines have redundant properties;*
> >
> > *(b) many therapeutic antibodies that have been implicated in particular diseases (such as sepsis, multiple sclerosis and cancer) have failed to have any human clinical effect;*
> >
> > *(c) more than 22 cytokines had been identified in psoriatic lesions;*
> >
> > *(d) effective antibody therapy could require targeting a combination of cytokines; and*
> >
> > *(e) neither the IL-12 literature nor the psoriasis literature postulated that IL-12 was a cause of psoriasis.*

[120] I accept Dr. Weiner's concise summary respecting the state of the art as set out in paragraph 90 of his affidavit:

> *90. With respect to the Claims in issue, the skilled person would have understood that the primary difference was that the state of the art did not teach that anti-IL-12 antibodies would be useful to treat psoriasis.*

[121] When cross-examined, Dr. Weiner provided an insightful answer with respect to the state of the art in which a person skilled in the art would be operating as of March 1999. He said at pages 399 to 400 of Volume 2 of the Trial Transcript in response to a question put to him by Janssen's Counsel:

> *Q. And had you been a person of skill in the art as of March 25th, 1999, with that hope, would you have had any expectations that that antibody would be successful for the treatment of psoriasis?*
>
> *A. As of March 25th, 1999, I do not believe that it would have been possible to predict in a robust way that it would work because it hadn't yet been tested and nobody yet knew whether it would work.*
>
> *There was no – it was – IL-12 at that time was one of a large case of cytokine characters, if you will, that had been documented to be associated with psoriasis. And so there was hope that it might be useful, but there was probably in the – and I know the field, there were hopes that other antibodies directed against other cytokines might be useful to treat inflammatory or autoimmune diseases as well.*

[122] Some of the other experts have also given their views as to the state of the art, but I believe that the evidence of Dr. George and Dr. Weiner, as referred to above, adequately summarizes the evidence and opinions as to the state of the art.

iii) Identify or Construe the Inventive Concept of the Claims at Issue

[123] It is important to keep in mind that the series of questions posed by the Supreme Court of Canada in *Sanofi-Synthelabo*, supra, in respect of the inquiry as to obviousness, includes the identification of the inventive concept of the claims. The Court is required to focus on the invention as claimed in the claims at issue, and not on some generalized concept of invention as expressed in the patent as a whole.

[124] The '281 patent was previously reviewed. It begins at page 3 by summarizing the invention as providing human antibodies that bind human IL-12; it also relates to the treatment or prevention of acute or chronic diseases or conditions where pathology involves IL-12 using the human anti-IL-12 antibodies of the invention. At pages 117 to 120, the patent states that another embodiment of the invention provides a method for inhibiting IL-12 activity in a wide variety of diseases (including) psoriasis.

[125] As construed, claims 143 and 222 claim an invention which is the use of a human antibody that binds to IL-12 and has at least a certain level of stickiness and potency, for the treatment of psoriasis.

[126] Dr. Weiner addressed the invention as claimed at paragraph 89 of his affidavit (Exhibit 101):

> *89. I was asked to review the '281 Patent to understand the Claims and the inventive concepts of them. The skilled antibody engineer would have understood that the inventive concept of the*

> *Claims is that certain human antibodies to IL-12 can be used to treat psoriasis in humans, and in particular:*
>
> > *(a) for Claim 143 those antibodies are ones with a k_{off} rate constant of 1 x 10^{-4} s^{-1} or less, as determined by surface plasmon resonance according to Example 5 and which inhibit PHA blast proliferation in an in vitro PHA assay according to Example 3 with an IC_{50} of 1 x 10^{-9} M or less; and*
> > *(b) for Claim 222 those antibodies are ones which bind to a human interleukin comprising a p40 subunit and dissociate from the human interleukin with a koff rate constant of 1 x 10^{-2} s^{-1} or less, as determined by surface plasmon resonance in accordance with Example 5, and which inhibit phytohemagglutinin blast proliferation in an in vitro PHA assay according to Example 3 with an IC_{50} of 1 x 10^{-9} M or less.*

[127] Dr. *Shlomchik* also gave evidence as to the inventive concept of the claims at paragraphs 105 and following of his affidavit (Exhibit P-96). I repeat paragraph 105 and the first part of paragraph 106:

> *105. I have been asked to identify the inventive concepts of the Claims.*
>
> *106. In my opinion, the skilled immunologist reading the patent as a whole would understand that the inventive concepts of claims 143 and 222 would include the use of certain human antibodies that bind to IL-12 and neutralize its activity for the treatment of psoriasis in humans.*
>
> . . .

[128] Dr. Chizzonite did not address the matter squarely in his affidavit (Exhibit P-107). At best, one can imply that he considered the inventive concept to be the identification that an anti-IL-12 antibody would be therapeutically useful in treating psoriasis in humans. I repeat paragraphs 45 and 48 of his affidavit:

> *45. As of March 25, 1999, there was no human clinical data using an anti-IL-12 antibody or IL-12 antagonist which resulted in effective treatment in a human disease. As of March 25, 1999, the skilled person would have no idea what disease, if any, would benefit from an IL-12 antagonist in a human clinical trial.*
>
> . . .
>
> *48. Accordingly, as of March 25, 1999, in my opinion the person of ordinary skill in the art would not know whether or not an anti-IL-12antibody or an IL-12 antagonist would be therapeutically effective for treating psoriasis in humans.*

[129] Dr. George, in his Statement (Exhibit D-155) gave a more generalized opinion as to the invention without focusing in particular on the claims at issue. He wrote at paragraphs 173 to 179:

> ***V. WHAT IS THE INVENTION MADE?***
>
> *173. I have been asked to identify and describe the invention made by the inventors of the 281 Patent. To do so, I have considered the entire 281 Patent, including all the claims. Also, I have considered this question as of September 2000. Of note, my analysis would not change if I considered it as of March 1999.*
>
> ***(A) J695 Sequence***
>
> *174. The 281 Patent includes sequence data, affinity data, and neutralization data for only the J695 lineage from the Joe 9 lineage. The 281 Patent discloses the isolation of Joe 9 from a phage display library, and the engineering steps culminating in J695 to increase the affinity.*
>
> *175. The 281 Patent specifically acknowledges that the inventors did not invent the concept or use of anti-IL 12 antibodies and are not claiming a humanised antibody for clinical use.*
>
> *176. Rather, the 281 Patent focuses on the use of a human anti-IL 12 antibody.*
>
> *177. On reading the 281 Patent, in my view, the invention made by the inventors is the production of a particular family of antibodies against human IL 12, sharing a similar sequence (and so structure).*

> *These antibodies were produced from a particular human phage display library, and mutated to improve and retain the properties of the anti-IL 12 antibody.*
>
> *178. In my opinion, the invention is J695 and other related antibodies and antibody fragments from the same lineage. The simplest and clearest way to describe those antibodies is by their sequence (i.e. their amino acid sequence), which the inventors have done for only these antibodies in the 281 Patent.*
>
> *179. The 281 Patent promises that the J695 and related antibodies will be useful in human therapy and diagnostics. The inventors specifically say that they are creating a human antibody to IL 12 (as opposed to the murine, chimeric, and humanised antibodies of the prior art), which must be intended for the purposes of human therapy and disease, as referenced in various claims.*

[130] Dr. Sarfati in her Statement (Exhibit D-152) did not identify what she believed the inventive concept to be. By implication in reading paragraphs 71 to 74, I infer that she believed the concept to be the neutralization of IL-12 by a suitable antibody in the treatment of psoriasis:

> ***2. IL-12 Concepts that Were Known***
>
> *71. Example 4 of the Abbvie 281 Patent uses murine anti-human mAb (clone C8.6.2, high affinity) as standard gold reference to J695. As already shown, murine anti-human mAb (clone C8.6.2, high affinity) and J695 bind to IL-12p40. In other documents provided to me, it is seen that both J695 and C8.6.2 inhibit binding of iodinated IL-12p70 to IL-12Rβ1-expressing cells and neutralize function of rIL-12p70 (PHA blast proliferation on IFN-γ production):*
>
> . . .
>
> *72. Also, the concept that human anti-IL-12p40 mAb can be used in therapeutic use as referenced in the 281 Patent, especially to treat psoriasis, was known as of March 1999:*
>
> . . .

> *73. It was well known that effective neutralization of IL-12 activity could be achieved by a high affinity Ab that is a IL-12p40 binder.*
>
> ***3. Self-Evident Success***
>
> *74. The Abbvie 281 Patent did not focus on how to use human transgenic technology to generate a fully human antibody by those with skill and experience. Although, as demonstrated in the accessible literature, transgenic mice technology was a very reasonable approach to create a fully human antibody.*

[131] I was impressed with the answer that Dr. Weiner gave in his cross-examination as recorded at page 394 of the trial transcript, Volume 21:

> *Q. And in your view, the sole difference between the inventive concept of those two claims and the prior art, the literature, is psoriasis, the use for psoriasis?*
>
> *A. No, no. I think the basis, as I understand it, was that for the first time, the inventors described the development of a high-affinity immunoglobulin molecule that bound to IL-12, was capable of neutralizing IL-12, and it was able to do so both in standard in vitro assays but also in vivo in animal models. And it was thought initially that such an antibody or antibodies like it would be capable of being used to treat a variety of autoimmune diseases.*
>
> *The truly stunning observation that, serendipitously, a person treated with J695 had a dramatic clearance of psoriatic plaques was really transformative.*

[132] Having regard to all of the evidence before me, including the portions recited above, I find that the inventive concept of claims 143 and 222 of the '281 patent is that psoriasis may be treated by the use of human antibodies that bind to human IL-12, which antibodies have a stickiness of at least the claimed amount and a potency of at least the claimed amount.

iv) What, if any, are the Differences between the Prior Art and the Invention as Claimed?

[133] The difference is that between hope and certainty. The experts are in apparent agreement that before the invention was made, there was a *hope* that, among the "soup" of cytokines in the human body, if an antigen was found to bind to one or more of them, then certain human diseases *might* be treatable. The invention here was that it was found that a particular cytokine should be bound by an antigen having certain properties, and then psoriasis *would* be treatable. I repeat portions of the answers given by Dr. Weiner in his cross-examination, beginning at page 394, is a continuation of the answer set out previously in these Reasons, over to page 398, which explains the differences very well:

> *I have been doing antibody therapy research since 198—well, depending on when you want to start counting, it was either '81 or '84, and had the privilege of participating in many of the earlier clinical trials. And in my entire career, I have had one transformative moment like that where a patient treated with an antibody had a dramatic, in this case, anti-cancer response that was just, you know, just came out of, seemingly out of the blue and actually led to the ultimate clinical development of a useful antibody to treat colon cancer.*
>
> *The ability to demonstrate that there was this extraordinary outcome in this individual really was able to provide a proof of concept that has subsequently been validated that antibodies directed against IL-12 indeed are useful to treat psoriasis.*
>
> *And so this was – the antibody that was developed had a set of properties, and this patient example, Number 9, was the evidence that such an antibody could be useful to treat patients with a particular disease and provided guidance to those who would follow that this was the direction in which to go.*
>
> . . .
>
> *Q. So let's be very precise about this, sir. In your view, the inventive concept was generated by the person who observed the result in the patient?*

A. No, no, no, no, no. The inventive -- I am sorry, please, do you want to finish?

Q. No, that's fine. Your answer to that was "no".

A. The invention was the production of the antibody that would have the properties of neutralizing the biological activity of IL-12. It was hoped for by the inventors that such an antibody would be useful to treat various rheumatologic diseases and other autoimmune diseases specified in the patent that included psoriasis, it included multiple sclerosis, it included many other diseases. This example provided evidence that this antibody, and instructed others in the future, this antibody and others like it could be, with the appropriate properties, could be useful to treat psoriasis.

And the invention, as – the inventors were clearly the people who made the drug, had it tested, there was an observation made; and therefore, that was confirmation, if you will, that they were heading in the right direction.

Q. And so it's your view, I take it, that you wouldn't have known until Example 9 that this antibody would treat psoriasis; correct?

A. One could have hoped that the antibody would be used to treat psoriasis or any other disease where IL-12 was a critical part of the pathogenesis of the illness.

But it would, this was the experiment, if you will, that demonstrated utility in a particular use case.

v) <u>Were the Differences More or Less Self-Evident?</u>

[134] I turn again to the answers given by Dr. Weiner in his cross-examination as recorded at pages 399 to 401 of the trial transcript:

A. Could you repeat that question? I am not sure I understood it.

Q. Sure. As I understood your evidence, you referred to there would be a hope that the antibody would treat psoriasis and that Example 9 was the confirmation of that; correct?

A. Yes.

Q. Yes. And so that hope would have existed as of, for example, March 25th, 1999?

A. The hope existed previous to the demonstration that it worked, yes.

Q. And had you been a person of skill in the art as of March 25th, 1999, with that hope, would you have had any expectation that that antibody would be successful for the treatment of psoriasis?

A. As of March 25th, 1999, I do not believe that it would have been possible to predict in a robust way that it would work because it hadn't yet been tested and nobody yet knew whether it would work.

There was no – it was – IL-12 at that time was one of a large cast of cytokine characters, if you will, that had been documented to be associated with psoriasis. And so there was hope that it might be useful, but there was probably in the – and I know in the field, there were hopes that other antibodies directed against other cytokines might be useful to treat inflammatory or autoimmune diseases as well.

Q. So with respect to that hope that you have described as of March 25th, 1999, and the inventors themselves tell us there were five preferred indications that they were interested in as of that date; yes?

A. That's my understanding.

Q. And psoriasis was one of those five.

And so to the extent that the inventors had a hope as of March 25th, 1999, it would have focused on those five indications; fair?

A. One would assume that if they felt that these were fully "preferred embodiments", that those would be the areas where

> *they imagined there might be the greatest potential utility of an antibody that was targeting IL-12 and neutralizing it*.

[135] This case is a good example of the differences between the *worth a try* approach and the *more or less self-evident* approach. The latter approach is that adopted by the Canadian jurisprudence as to whether a claimed invention was obvious.

[136] The evidence shows that many persons were directing their efforts towards identifying an antibody that would adhere to one or more of the soup of cytokines, and in doing so, might treat one or more human diseases. Dr Chizzonite's evidence is that there were many failures in this area of research and very few successes. AbbVie's researchers got lucky; they found an antibody that bound to a particular cytokine IL-12 and in so doing, treated psoriasis. They did so some time between September 1999 and March 2000 when they recorded that, by luck, one of the persons being clinically studied was given the antigen called J695 and was, in so doing, treated for psoriasis. Some patent agent, presumably, was astute enough to record this event as Example 9 in the patent application filed as of March 24, 2000. There is no evidence as to who put Example 9 into the application, or when, other than that, it was between March 25, 1999 and March 24, 2000, the date that the PCT application was filed.

[137] In the field of antibody research, a lucky hit such as this one is apparently rare. Dr. George, an experienced researcher for over twenty years, has never experienced the discovery of an antibody that actually worked and cured a disease (cross-examination, pages 1122 – 1123). Dr. Chizzonite had been working in the very area from 1982 to 1998 and concluded at paragraphs 48 and 49 of his affidavit (Exhibit P-107):

> *48. Accordingly, as of March 25, 1999, in my opinion the person of ordinary skill in the art would not know whether or not an anti-IL-12 antibody or an IL-12 antagonist would be therapeutically effective for treating psoriasis in humans.*
>
> *49. In fact, after March 1999, there have been many examples where IL-12 was implicated in a disease which ended up not to be causative, including cancer, multiple sclerosis and asthma.*

[138] As I said previously I give Mr Treacy's memoranda little weight. He is not an expert. His memoranda apparently found no support at Centocor nor were never relied upon. His opinions have no weight and certainly he did not demonstrate that, in fact, IL-12 was the culprit that was sought in the treatment of psoriasis.

[139] The reasons of Pigeon J of the Supreme Court of Canada in *Farbwerke Hoechst A/G v Halocarbon (Ontario) Ltd*, [1979] 2 SCR 929 at page 944 are as appropriate today in respect of the present issue, as they were when written:

> *In my view, the true doctrine was clearly stated by the Privy Council in Pope Appliance Corporation v. Spanish River Pulp and Paper Mills [[1929] A.C. 269], where Viscount Dunedin said (at pp. 280-281):*
>
> > *"…After all, what is invention? It is finding out something which has not been found out by other people. This Pope in the present patent did. He found out that the paper would so stick, and the practical problem was solved. The learned judges below say that all this might have been done by any one who experimented with "doctors" and air blasts already known. That is that someone else might have hit upon the invention. There are many instances in various branches of science of independent investigators making the same discovery. That does not prevent the one who first applies and gets a patent from having a good patent…"*

[140] I find that the invention, as claimed in claims 143 and 222 of the '281 patent, was not self-evident having regard to the prior art. It was not obvious.

BREADTH AND FORM OF CLAIMING

a) The Issues and Evidence

[141] This is the most substantial issue in this case. Is the claim overly broad? The issue has been couched in many ways by Counsel during argument; including utility, sound prediction, overbreadth, sufficiency and ambiguity.

[142] To frame the question clearly, I first turn to the constraints placed upon the invention by the manner in which claims 143 and 222 of the '281 patent have been drafted:

- the antibody must be a human antibody
- the antibody must bind to human IL-12
- the antibody must possess certain minimum levels of stickiness and potency
- the antibody is effective to treat psoriasis

[143] The manner in which claims 143 and 222 are not constrained is that *any* antibody, however created, that meets these parameters, comes within the scope of the claims. The patent describes in great detail one such antibody, J695, which is created by phage display. The patent also says that

antibodies may be created using a transgenic mouse method, but does not identify any particular such antibody.

[144] The issue is, therefore, having described in great detail a phage-display-created antibody, can a claim that is not constrained by the method by which the antibody is created, be valid?

[145] I have concluded earlier in these reasons that it was inventive to determine that a human antibody which bound human IL-12 with the stickiness and potency as set out in the claims, was useful in treating psoriasis.

[146] The evidence also shows:

- the techniques used to create antibodies of this type; in particular, phage display and transgenic mice, were well known in the art at the relevant time

- the techniques for measuring stickiness and potency, as set out in claims 143 and 222, were well known at the relevant time

[147] There is no evidence that:

- anything that falls within either of the claims was not useful in treating psoriasis

- a person skilled in the art, given the patent, could not have created an antibody that meets the parameters of either of these two claims

[148] There is nothing that is indeterminate in the claims at issue; there is nothing that, in the evidence, lacks utility, or cannot be soundly predicted. The issue, therefore, is one of overbreadth, or covetousness. Having claimed the invention without reference to the specific antibody described in the patent, or even the specific method by which it was described to be made in the patent, can the claim be so broad as to cover whatever antibody falls within the constraints as I have set them out above and still be valid?

[149] With respect to the parameters that are set out in the claims, the question arises as to whether they are sufficient to define a workable antibody to treat psoriasis. Janssen's expert, Dr. Eck, raises questions as to whether further parameters are required in paragraph 70 of his affidavit (Exhibit D-123).

> *70. The differences in sequence and three-dimensional structure of Stelara as compared with J695 underlie their very different mechanisms and sites of binding to IL-12. Additionally, the differences in their sequence and structure can be expected to yield differences in other properties that are often of functional importance. Antibodies sometimes exhibit "cross-reactivity"; that is they can bind with significant affinity to antigens other than their "intended" target. Because they recognize different epitopes and the structure of their combining sites is different, Stelara and J695 are expected to differ in their respective cross-reactivities. Their sequence and structural differences may lead to differences in biophysical properties such as solubility and propensity to aggregate. The sequence and structure of an antibody also underlie other properties of an antibody that are relevant to its suitability for use as a therapeutic agent, such as antigenicity. Thus the marked differences in sequence and structure of Stelara as compared with*

> *J695 have relevance beyond their function in binding and neutralizing IL-12.*

[150] These comments are speculative; expressed in words such as "can be expected", "often of functional importance", "are expected", and "may lead to differences". There is no evidence to support a conclusion that such speculation is in fact a reality.

[151] Dr. Weiner, at paragraphs 124 and 125 of his Affidavit (ExhibitP-101), refutes Dr. Eck, saying that the differences upon which Dr. Eck speculates are not important; and that neutralization of IL-12, which is one of the parameters of the claim, is what is critical:

> ***B. Dr. Michael Eck***
>
> ***Neutralization is Critical***
>
> *124. Dr. Eck at paragraph 70 asserts that, after comparing the binding sequences of Stelara and J695, "'the sequence and structure of an antibody also underlie other properties' of an antibody that are relevant to its suitability for use as a therapeutic agent". Dr. Eck suggests that there is a biologic significance from the fact that STELARA and J695 do not bind to identical sites on the p40 subunit of IL-12 (albeit overlapping sites). Dr. Eck overlooks the most important functional similarities of the two antibodies – that they both bind to IL-12 and both neutralize IL-12 bioactivity with an IC_{50} value that is 1×10^{-9} M or less as measured in the PHA Assay of Example 3. The precise location on which the antibody binds to IL-12 is not important when the PHA Assay can be used to screen the antibodies and determine whether binding of the antibody to IL-12 has the desired effect – neutralization of the biological activity of IL-12. The PHA assay tells the skilled person that the antibody binds to a relevant location on IL-12 as defined by its ability to neutralize IL-12 biologic activity. The potencies (IC_{50}s) of the different antibodies in the PHA assay allows the skilled person to predict whether a specific antibody has properties similar to J695 and therefore may achieve a similar in vivo result in treating psoriasis.*

> *125. Also at paragraph 70, Dr. Eck states that sequence and structural differences may lead to differences in solubility and propensity to aggregate and to its antigenicity. The Claims do not refer to these properties. In my opinion, the skilled person would not understand the Claims to require an antibody with a particular solubility or propensity to aggregate or antigenicity. Instead, the Claims refer to the use of certain antibodies to treat psoriasis as described in the '281 Patent.*

[152] Dr. Shlomchik, at paragraphs 105(e) and 151 of his affidavit (Exhibit P-96) addresses these issues:

> *150(e) At paragraph 70 of his report Dr. Eck states that "[t]he differences in sequence and three-dimensional structure of Stelara as compared with J695 underlie their very different mechanisms and sites of binding to IL-12". I disagree with Dr. Eck for two reasons:*
>
> *A. The "mechanisms" by which J695 and STELARA are posited to work is identical. Both antibodies neutralize IL-12, i.e. by binding to IL-12 and blocking its ability to properly interact with the IL-12 receptor.*
>
> *B. Even if they approach the ligand from different angles, J695 and STELARA do not have very different sites of binding to IL-12. Both bind to the p40 subunit and not the p35 subunit. Both cover shared amino acids (six). Both neutralize IL-12 in vivo by blocking it from binding to its receptor.*
>
> *151. The skilled immunologist was aware as part of his or her common general knowledge prior to March 1999 and March 2000 that very different antibodies could bind to the same target and achieve a similar clinical result. For example, as of these dates the FDA had approved daclizumab (ZENAPAX) and basiliximab (SIMULECT) as immunosuppressants for organ transplantations. Both antibodies bound to IL-2Rα and were effective (and approved) for the same treatment even though they are different antibodies. The skilled immunologist was well aware that antibodies did not need to be identical to bind to the same cytokine or treat the same disease.*

[153] Dr. Weiner was taken to some of these issues in his cross-examination. I set out what is recorded in the transcript at pages 388 and 389:

> *Q. Would you agree with me, sir, that the inventors of the 281 Patent did not actually make any antibodies using transgenic mice?*
>
> *A. That is correct. They made an antibody utilizing phage display.*
>
> *Q. Would you agree with me, sir, with the proposition that an antibody like Stelara with a VHS heavy chain could not be created from the phage display library described in the patent; do you accept that proposition?*
>
> *A. Not necessarily.*
>
> *Q. Do you say that it's wrong or you just don't know one way or another?*
>
> *A. I don't know one way or another. I would need to understand what was in the phage display library to know if that library contained VHS chains that could have been utilized in the display. And if they were present, it's certainly conceivable that a molecule could have been made.*
>
> ***But again, I would make the point, because I think it's a very important one, that what matters here is function, not the particular structure that achieved that function. And how it's made, what its particular epitope specificity is, what its heavy chain and light chain usage is far less important than what its functional attributes are.*** *(Emphasis added)*

[154] In conclusion on this point, I find that Janssen has not satisfied me that there are parameters beyond those set out in claims 143 and 222 that are essential for the functioning of the antibody to treat psoriasis.

b) <u>The Law</u>

[155] Counsel for each of the parties have put before me not only what they argue to be the relevant Canadian law, but also, at my request, jurisprudence from other countries; including the

United States, Great Britain, Germany and the European Union. The law outside Canada can be informative; but it is the Canadian law which, of course, must be applied here.

[156] Put rather simply, Janssen argues that AbbVie has not paid "hard coinage" for a claim as broad as claims 143 and 222; it argues that AbbVie has disclosed only one antibody that binds to IL-12, but is claiming any such antibody. Janssen cites the "hair on bald man" statement of Binnie J in the Supreme Court of Canada in writing the Reasons of that Court in *Free World Trust v Electro Santé Inc*, [2000] 2 SCR 1024 at paragraph 32:

> *[T]he ingenuity of the patent lies not in the identification of a desirable result but in teaching one particular means to achieve it. The claims cannot be stretched to allow the patentee to monopolize anything that achieves the desirable result. It is not legitimate, for example, to obtain a patent for a particular method that grows hair on bald men and thereafter claim that anything that grows hair on bald men infringes.*

[157] AbbVie's response to that argument is best set out at paragraphs 58 and 59 of its Final Argument Factum:

> *58. The '281 Patent does not claim a mere desired result. Rather, the patent discloses that high affinity, neutralizing anti-IL-12 antibodies deliver the promised result. This is the solution to the problem that the case law requires; based on the in vitro and in vivo neutralization data from Examples 3, 4, 5 and 9, the evidence establishes that one skilled in the art could reasonably predict that <u>all</u> antibodies falling within the scope of the claim would similarly treat psoriasis. Janssen has no contrary evidence.*
>
> *59. By disclosing to the public the first high affinity, neutralizing antibody that successfully treated a human psoriasis patient, AbbVie established the facts which support the breadth of the Claims.*

> *AbbVie paid the hard coinage for its invention and significantly advanced the art. It is entitled to the protection of those Claims.*

[158] The most relevant Canadian authorities are the decisions of the Supreme Court of Canada in *Burton Parsons Chemicals Inc v Hewlett-Packard (Canada) Ltd.*, [1976] 1 SCR 555 and *Monsanto Co v Canada (Commissioner of Patents)*, [1979] 2 SCR 1108.

[159] *Burton Parsons* dealt with a patent claiming an electrocardiograph cream "compatible with normal skin" containing an "ionizable salt". It was argued that the claim was overly broad since the evidence showed that certain salts were not compatible with normal skin and some were fatal; thus, the claim was overbroad. Pigeon J, writing for the Court, put the argument this way at paragraphs 11 and 12 of his Reasons:

> *11 With respect, I cannot agree that Claim 17 is invalid because the words "compatible with normal skin" are found before "comprising" instead of after, so that it would be valid, it seems, if the words were rearranged as follows:*
>
> > *17. An electrocardiograph cream for use with skin contact electrodes comprising a stable aqueous emulsion that is anionic, cationic or non-ionic, containing sufficient highly ionizable salt to provide good electrical conductivity and compatible with normal skin.*
>
> *12 In my view, the rights of patentees should not be defeated by such technicalities. While the construction of a patent is for the Court, like that of any other legal document, it is however to be done on the basis that the addressee is a man skilled in the art and the knowledge such a man is expected to possess is to be taken into consideration. To such a man it must be obvious that a cream for use with skin contact electrodes is not to be made up with ingredients that are toxic or irritating, or are apt to stain or discolour the skin. The man skilled in the art will just as well appreciate this necessity if the cream to be made is described as "compatible with normal skin" as if it is described as containing only ingredients compatible with*

> *normal skin. The situation here is completely unlike that in either the Minerals Separation case or in Société des usines chimiques Rhône-Poulenc v. Jules R. Gilbert Ltd. In those cases the object of the patent was some substances of a definite chemical composition: xanthates in the first, substituted diamines in the second. Unfortunately for the patentees, the claims covered at the same time some xanthates which would not yield the desirable result in one case, and, in the other, some isomers which would not be therapeutically valuable. This is what was held fatal to the validity of the patents.*

[160] At paragraph 16 of his Reasons, Pigeon J put the matter squarely: inventors are not Shylocks claiming a pound of flesh; where nothing has been demonstrated in evidence to mislead a person skilled in the art and such a person would have the means to make a proper selection, a claim is not overly broad:

> *16. It is stressed in many cases that an inventor is free to make his claims as narrow as he sees fit in order to protect himself from the invalidity which will ensue if he makes them too broad. From a practical point of view, this freedom is really quite limited because if, in order to guard against possible invalidity, some area is left open between what is the invention as disclosed and what is covered by the claims, the patent may be just as worthless as if it was invalid. Everybody will be free to use the invention in the unfenced area. It does not seem to me that inventors are to be looked upon as Shylock claiming his pound of flesh. In the present case, there was admittedly a meritorious invention and Hewlett-Packard, after futile attempts to belittle its usefulness, brazenly appropriated it. It was in no way misled as to the true nature of the disclosure nor as to the proper methods of making a competing cream. The objections raised against the claims really are that, except those pertaining to some specific embodiments of the invention, the others are so framed as to cover every practical emdodiment, leaving to the man skilled in the art, the task of avoiding unsuitable materials in the [Page 566] making of the mixture, a task which any man skilled in the art ought to be able to perform without having to be told because any unsuitability depends on well known properties. No unexpected or generally unknown unsuitability was proved or even suggested, which makes this case quite unlike Minerals Separation or Rhône-Poulenc.*

[161] In *Monsanto*, the Supreme Court was dealing with a rejection of a patent application by the Patent Office. That Office had rejected claims directed to a chemical compound to be introduced in the rubber vulcanizing process to inhibit premature vulcanization. The patent contained three specific examples of such compounds. The rejected claims were directed to a family of such compounds containing 126 compounds. Pigeon J, for the majority, wrote that if the evidence demonstrated that all 126 compounds could be soundly predicted to have the same utility as the three exemplified compounds, then the Patent Office should allow claims directed to the 126 compounds. He wrote at paragraph 19:

> *19 Although the report of the Board is quite lengthy, in the end with respect to claim 9 all it says after stating the principle with which I agree, is that a claim has to be restricted to the area of sound prediction and "we are not satisfied that three specific examples are adequate". As to why three is not enough nothing is said. In my view this is to give no reason at all in a matter which is not of speculation but of exact science. We are no longer in the days when the architecture of chemical compounds was a mystery. By means of modern techniques, chemists are now able to map out in detail the exact disposition of every atom in very complex molecules. It, therefore, becomes possible to ascertain, as was done in Olin Mathieson, the exact position of a given radical and also to relate this position to a specific activity. It thus becomes possible to predict the utility of a substance including such radical. As this is a matter of general knowledge among scientists, it will be readily apparent to a competent person that if a patent covers only a few of the substances which yield the desired result, all he has to do is to prepare another which will have the same properties. The report of the Board indicates that it is aware of this. However, it gives no indication of the reasons for which it was not satisfied of the soundness of the prediction of utility for the whole area covered by claim 9. Evidence had been submitted in the form of affidavits based on scientific principles, it does not take issue with those principles, it just says: "We are not satisfied that this is adequate". In my view this is insufficient because, if accepted, it makes the right of appeal illusory. In this respect it is important to note that s. 42 of the Patent Act reads:*

> *42. Whenever the Commissioner is satisfied that the applicant is not by law entitled to be granted a patent he shall refuse the application and, by registered letter addressed to the applicant or his registered agent, notify the applicant of such refusal and of the ground or reason therefor.*

[162] The Federal Court of Appeal dealt with whether the disclosure in a patent was sufficient to support a claim in *Mobil Oil Corp v Hercules Canada Inc*, (1995), 63 CPR (3rd) 473. The patent was directed to a two-layer film - one metallic, the other plastic - of the kind sometimes found, for instance, in potato chip bags. The claim called for a "slip agent" to be introduced in the extrusion process, but did not say much about it. Marceau JA, for the Court, held that a person skilled in the art could fill in the gaps; the claim was not invalid. I repeat part of what he said at page 486:

> *The problem addressed and solved by the inventors was the poor adhesion between metallic coatings and a polypropylene substrate. They found that if the polypropylene was attached to a layer of a copolymer of ethylene and propylene treated by corona discharge, there would be good adhesion, especially in the absence of any slip agent, since slip agents interfere with adhesion. If, because of the use for which the invention was intended, some slip agent was required, the adhesion may still be acceptable but caution should be exercised as to the amount and the location of the slip agent being used, and, for that reason, the specifications describe a test with a standard machine to determine, with non-inventive experimentation, how much can be added without rendering the substrate unfit for the contemplated use.*
>
> *In opening his analysis of the issue of sufficiency, the trial judge had rightly set out the main principles involved: the specifications must be complete enough to allow a person skilled in the art to make successful use of the invention (dictum of Dickson J., as he then was, in Consolboard Inc. v. MacMillan Bloedel (Saskatchewan) Ltd. (1981), 56 C.P.R. (2d) 145, 122 D.L.R. (3d) 203, [1981] 1 S.C.R. 504, as to the basic requirement of s. 36(1), now s. 34(1)) but, at the same time, the disclosure must be given a purposive reading with a view to upholding a useful invention. I fail to see which of these principles could have led him to his conclusion.*

> *It may be striking that the specification and claims use identical language in indicating that some slip agent may be used provided it is insufficient to adversely affect adhesion of the substrate to a metallised coating. But what else is needed?*
>
> *I am not here taking issue with some findings of facts of the trial judge; I would have no basis for doing so. I take issue with his reasoning which appears to be based on a reading of s. 34 which makes its requirements much more severe than what I understand of it. With respect, I think that the trial judge could not, on the evidence, find the patent invalid for insufficiency of the disclosure.*

[163] The decision of the Rouleau J of this Court in *Cabot Corp v 318602 Ontario Ltd*, (1988), 20 CPR (3d) 132 dealt with whether the claims were broader than the invention disclosed. The claims dealt with earplugs which would be compressed, inserted into the ear, and then would expand on their own to form good soundproofing. The claims were said to extend to any earplug meeting certain characteristics as Rouleau J wrote at paragraph 121:

> *121. It is a wide claim as it covers any earplug with these physical characteristics and can be made of any foam which enables the characteristics to be obtained. The onus is however on the defendants to establish a lack of utility or that the claims are broader than the invention.*

[164] Rouleau J found that any expert would be able to identify, without undue trial and error, an appropriate foam. The claims were valid. He wrote at paragraphs 126 to 129:

> *126 There is no evidence that some or any of the foams would not work. On the other hand, there was evidence at trial from all experts that other foams would be recognized as having utility.*
>
> *127 I am of the view that the evidence can support a finding that the breadth of the invention claimed was sound and reasonable. There is no evidence that any embodiment of the claims in suit would not work. The defendants have failed to discharge the onus upon them by*

> *clear and convincing proof . To find otherwise would be to be left with something useless. In Olin Mathieson Chemical Corp. v. Biorex Laboratories, [1970] R.P.C. 157 at 192-193 Graham J. wrote:*
>
> > *Unless, therefore, the original inventor of the -CH(3) substitution can properly be given reasonably broad cover, it is likely that soon after others hear of his success similar bodies will be made by others having as good or better activity. Unless he can control such activities, any reward he may obtain for his invention and research is likely to be of little value.*
>
> *128 In applying this reasoning to the Gardner invention, once it is revealed that a polyvinyl foam with certain physical characteristics is suitable for earplugs, it would be evident to the notionally skilled workman that other foams with similar characteristics could be used.*
>
> *129 As Pigeon J. discussed in Monsanto Co. v. Commissioner of Patents, [1979] 2 S.C.R. 1108 at pp. 1121-1122, 42 C.P.R. (2d) 161, 100 D.L.R. (3d) 385, 28 N.R. 181 and I paraphrase, in the complete absence of any evidence of unsoundness of the prediction to deny claims and limit them to the area of proved utility instead of allowing them to the extent of predicted utility cannot be supported. A patent cannot be refused because an inventor has not fully tested and proved it in all its claimed applications. Only if the inventors have claimed more than what they have invented and included substances which are devoid of utility should the claims be open to attack.*

In its recent decision, *Pfizer Canada Ltd v Novopharm Ltd*, [2012] 3 SCR 625, the Supreme Court of Canada addressed the issue of sufficiency *of the disclosure*. Sufficiency of the claim was not at issue. LeBel J wrote the unanimous decision of the Court. At paragraph 2 of the Reasons he states the main issue:

> *2 The main issue in this appeal is whether Pfizer failed to properly disclose its invention when it obtained the patent for Viagra. For the reasons that follow, I conclude that Pfizer's patent application did not satisfy the disclosure requirements provided for in s. 27(3) of the Act. I would accordingly allow the appeal.*

[165] The invention was that a drug called sildenafil (commercially Viagara) treated erectile dysfunction (ED). The patent disclosed a number of compounds said to be useful for that purpose, but failed to identify sildenafil as the particular compound that served the purpose. Justice LeBel wrote at paragraph 66:

> *66 In this case, if we consider the specification as a whole, there is nothing to support the view that the use of sildenafil for the treatment of ED is a separate invention from the use of any of the other claimed compounds for that same purpose. No specific attributes or characteristics are ascribed to sildenafil that would set it apart from the other compounds. Even if we take into consideration the fact that sildenafil is an "especially preferred compound", there is still nothing that distinguishes it from the other eight "especially preferred compounds". The use of sildenafil and the other compounds for the treatment of ED comprises one inventive concept.*

[166] The present case does not deal with the same issue as the *Viagara* case, nor the *Mobil Oil* case. Those cases dealt with the sufficiency of the disclosure. There is no doubt in the present case that the patent adequately discloses one antibody and how to make it by phage display. It also mentions that antibodies may be made by a transgenic mouse. The claims 143 and 222 are broad enough to include antibodies made by either method; and any other method *provided* that the antibodies *also* meet the other constraints of the claim that I have previously listed. The present case is more like that of *Monsanto* and *Cabot*.

[167] Based on the principles established in *Monsanto* as well as *Cabot*, the claims at issue, 143 and 222, are not overly broad or covetous. Those claims are readily understandable by a person skilled in the art; they know what the parameters are; there is no evidence to indicate that antibodies falling within these parameters will not work to bind to IL-12 so as to treat psoriasis.

[168] Janssen argues, as a policy issue, whether "functional claiming" should be allowable. It argues that, having discovered one antibody that binds to IL-12 so as to treat psoriasis, can AbbVie claim any antibody that binds to IL-12 and treats psoriasis? This argument does not come to grips with the fact that AbbVie was the one who confirmed that if an antibody did bind to IL-12, then psoriasis could be treated. Before AbbVie's confirmation there was only hope or speculation, numerous other cytokines or a combination of one or more of them might have been the proper target. AbbVie confirmed that it was IL-12. Further, the argument does not come to grips with the fact that the claims at issue also define a minimum level of stickiness and potency required to do the treatment. AbbVie was the first to confirm that, if you want to treat psoriasis, you must get an antibody that binds to IL-12 and it must have at least a certain level of stickiness and potency. That is very different from saying - we have a particular antibody (J695), and we put it into people, and it treats their psoriasis; therefore, we want a patent claiming any antibody that does that. There may be many ways to treat psoriasis, but AbbVie's way is to have an antibody that does so by binding to IL-12 with at least a certain level of stickiness and potency. That is the difference.

[169] Janssen also invokes an "it's not fair" argument. Janssen argues that it developed independently an antibody through a very different technique – transgenic mice; that through prolonged clinical studies, it confirmed that its antibodies would treat psoriasis; that only it has received the relevant government approval to sell the drug it developed to treat psoriasis. On the other hand, Janssen argues that AbbVie, at best, had a stroke of luck and, apparently through an astute patent agent, capitalized on that luck and put the lucky break into the patent application before it was officially filed in Canada and many other countries, under the Patent Cooperation

Treaty. The answer lies in the quote from Viscount Dunedin's Reasons in *Pope Alliance* as cited in *Farbwerke Hoechst*, supra.:

> *There are many instances in various branches of science of independent investigations making the same discovery. That does not prevent the one who first applies and gets a patent from having a good patent…*

[170] At my urging, the parties made submissions respecting decisions in the Europe, Germany and the United States. Europe, including Germany and the United Kingdom (as it becomes more aligned with Europe in a patent system). Those countries have developed a different approach: the "technical contribution" approach. It would be unwise to rely too much upon these decisions. I will, however, comment on the *Biogen* saga in the United Kingdom. The decisions in the United States, such as *University of Rochester v G.D. Searle & Co Inc*, 358 F. 3d 916 (Fed. Cir 2004) and *Ariad Pharmaceuticals Inc v Eli Lilly and Company*, 598 F. 3d 1336 (Fed Cir 2010) appear to turn on factual findings as to the adequacy of the disclosure in the patent, and whether the patent simply presented a problem to be solved and not a solution. Particularly, since an appeal respecting similar patents is pending before the United States Court of Appeal for the Federal Circuit, it would be unwise and probably foolish for me to venture into the laws of that country, particularly when I don't need to.

[171] It may be appropriate to comment on the *Biogen* saga in the United Kingdom Courts. Lord Hoffman, a highly respected patent judge, rendered a decision in the House of Lords; adopted by the other Law Lords hearing the case in *Biogen Inc v Medeva PLC*, [1977] ROC 1. A particular passage of Lord Hoffman's decision was seized on in subsequent decisions of the trial Courts as establishing what was called the question of "*Biogen* sufficiency". In that case, Biogen had a patent directed to a

hepatitis B virus antigen. The patent disclosed a particular recombinant molecule, but claimed any recombinant molecule which satisfied particular parameters. Lord Hoffman's decision, as reported at pages 50 – 51,said:

> *But the fact that the skilled man following the teaching of Biogen 1 would have been able to make HBcAg and HBsAg in bacterial cells, or indeed in any cells, does not conclude the matter. I think that in concentrating upon the question of whether Professor Murray's invention could, so to speak, deliver the goods across the full width of the patent or priority document, the courts and the EPO allowed their attention to be diverted from what seems to me in this particular case the critical issue. It is not whether the claimed invention could deliver the goods, but whether the claims cover other ways in which they might be delivered: ways which owe nothing to the teaching of the patent or a principle which it disclosed.*
>
> *It will be remembered that in Genentech I/Polypeptide expression the Technical Board spoke of the need for the patent to give protection against other ways of achieving the same effect "in a manner which could have been envisaged without the invention". This shows that there is more than one way in which the breadth of a claim may exceed the technical contribution to the art embodied in the invention. The patent may claim results which it does not enable, such as making a wide class of products when it enables only one of those products and discloses no principle which would enable others to be made. Or it may claim every way of achieving a result when it enables only one way and it is possible to envisage other ways of achieving that result which make no use of the invention.*

[172] It appears that Lord Hoffman was sufficiently concerned as to how his decision was being applied by the lower courts, that he arranged to sit as a Judge of the Court of Appeal in a subsequent case where the issue arose, so that he could explain and qualify his reasoning in *Biogen* and let the matter go on to be heard by a panel of the House of Lords that did not include him. (I add as an aside that the Supreme Court of Canada appears to deal with such matters more directly as they did

in *Canada (Attorney General) v Bedford*, 2013 SCC 72, and say that there are circumstances where earlier decisions of that Court are no longer binding on that Court).

[173] Lord Hoffman took the opportunity to sit as a judge of the Court of Appeal of England and Wales in *H Lundbeck A/S v Generics (UK) Ltd*, EWCA Civ 311, [2008] RPC 19. He gave a decision with which the other judges, Lady Justice Smith, and Lord Justice Jacob (another prominent patent judge), agreed. Lord Hoffman was at pains in his decision to limit *Biogen* to the particular facts of the case; he wrote at paragraphs 34 and 35 of *Lundbeck*:

> *[34] Thus, as a matter of construction, the House of Lords interpreted the claim as being to a class of products which satisfied the specified conditions, one of which was that the molecule had been made by recombinant technology. That expression obviously includes a wide variety of possible processes. But the law of sufficiency, both in the United Kingdom and in the EPO, is that a class of products is enabled only if the skilled man can work the invention in respect of all members of the class. The specification might show that this has been empirically demonstrated or it might disclose a principle which can reasonably be expected to apply across the class: see T 292/85 Polypeptide expression/GENENTECH [1989] OJ EPO 275; T409/91 Fuel Oils/EXXON [1994] OJ EPO 653; Kirin-Amgen Inc v Hoechst Marion Roussel [2005] RPC 169, 202. But the specification in Biogen described only one method of making the molecule by recombinant technology and disclosed no general principle. It was easy to contemplate other methods about which the specification said nothing and which would owe nothing to the matter disclosed.*
>
> *[35] In my opinion, therefore, the decision in Biogen is limited to the form of claim which the House of Lords was there considering and cannot be extended to an ordinary product claim in which the product is not defined by a class of processes of manufacture. It is true that the House in Biogen indorsed the general principle stated by the Board of Appeal in T409/91 Fuel Oils/EXXON [1994] OJ EPO, that "the extent of the patent monopoly, as defined by the claims, should correspond to the technical contribution to the art in order for it to be supported or justified".*

[174] The *Lundbeck* case proceeded to be heard by a panel of the House of Lords that did not include Lord Hoffman (it did include another prominent patent judge, Lord Neuberger). Their decision is reported at *Generics (UK) Ltd v H Lundbeck A/S*, UKHL 12, [2009] RPC 13. Lord Walker, in his Reasons, paid due deference to Lord Hoffman's decision in *Biogen*, but warned that it must be read in context. He wrote at paragraph 31:

> *[31] The Biogen case itself is, I think, a good illustration of this. Before your Lordships Lord Hoffmann's opinion in the Biogen case has been subjected to closer and more searching scrutiny by the House than any that I can recall, with the possible exception of the House's scrutiny in Deutsche Morgan Grenfell Group plc v IRC [2006] UKHL 49, [2007] 1 All ER 449, [2007] 1 AC 558 of the speech of Lord Goff of Chieveley in Kleinwort Benson Ltd v Lincoln City Council [1998] 4 All ER 513, [1999] 2 AC 349. If I may respectfully say so, Lord Hoffmann's opinion in the Biogen case is a tour de force. I have frequently commended it to bar students as an example of how a great judge can suffuse even the most technical subject with intellectual excitement. But its vivid and powerful language must be read in the context of the facts and issues in that case.*

[175] Lord Neuberger warned that *Biogen* should be treated with caution and confined to its facts. He wrote at paragraphs 99 to 101:

> *[99] In my opinion, therefore, in agreement with the Court of Appeal, the opinion of Lord Hoffmann in the Biogen case, though a tour de force as Lord Walker says, is of no assistance to the appellants in this case. It applied in the light of the very unusual nature of the claim in that case. Far from being a straightforward product claim (as in this case) or even a product-by-process claim (as discussed in the Kirin-Amgen case [2005] IP & T 352 at [86]–[91], [101]), the claim was to a product identified in part by how it was made and in part by what it did—almost a process-by-product-by-process claim.*

> *[100] Kitchin J is by no means alone in having taken the mistaken view that the reasoning in the Biogen case is of much wider application, and in particular that it applies to any product claims (at least where they are claims to chemical compounds). I made exactly the same mistake at first instance in the Kirin-Amgen case: see [2001] IP & T 882 at [300]–[312], [2002] RPC 1 at [300]–[312]. A number of articles to which reference was made in the written cases also appear to have proceeded upon the same view.*
>
> *[101] It may be that this is in part attributable to the focussing by Lord Hoffmann in the Biogen case (1996) 38 BMLR 149 at 162–166, [1997] RPC 1 at 42–46 on the 'inventive step' involved in the alleged invention in that case. There is a difference between the 'inventive step' or 'inventive concept', on the one hand, and the 'technical contribution to the art', on the other hand. I respectfully agree with the explanation of the difference between the two concepts given at [29]–[31] of Lord Walker's opinion. When considering the validity of a simple product claim (such as is under scrutiny on this appeal), it may be that concentrating on the identification of the inventive step rather than the technical contribution can lead to error. 'Inventive step' suggests how something has been done, and, in the case of a product claim at any rate, one is primarily concerned with what has been allegedly invented, not how it has been done. On the other hand where the claim is for a process or (as in the Biogen case) includes a process, the issue of how the alleged invention has been achieved seems to be more in point.*

[176] The other Law Lords were in agreement with Lord Walker and Lord Neuberger.

[177] The decision of the Court of Appeal of England and Wales in *Regeneron Pharmaceuticals Inc v Gentech Inc*, EWCA Civ 93, [2013] RPC 28 illustrates how those Courts are dealing with matters now. At issue was a claim directed to the use of a certain antagonist to treat a non-neoplastic disease, comprising a certain class of antibodies. One of the issues was insufficiency. Lord Justice Kitchen (another strong patent judge) wrote the Reasons for the Court. At paragraph 165, he stated the issue as to sufficiency, and at paragraphs 172 and 173 stated his conclusion:

> *[165] The Appellants do not challenge that finding. Their case did not, however, rest there. They also alleged that the specification does not provide directions as to how to make VEGF-Trap.*
>
> . . .
>
> *[172] It follows from all of the foregoing that the skilled team would have regarded chimeric molecules as variants falling within the scope of the claim. The skilled team would have had them well in mind in the light of the teaching in the patent and the common general knowledge and would have been able to produce such molecules across the scope of the claim without any great difficulty. That is not to say they could have produced VEGF-Trap, for I accept this would have required a good deal of ingenuity.*
>
> *[173] This does not, however, mean the patent is insufficient. A claim for an invention of broad application may properly encompass embodiments which may be provided or invented in the future and which have particularly advantageous properties, provided such embodiments embody the technical contribution made by the invention. VEGF-Trap does indeed embody the technical contribution made by the patent; it has a therapeutic effect in patients suffering from ARMD by treating the angiogenesis associated with that condition, and it does so by binding to VEGF and inhibiting its biological activity. VEGF-Trap is therefore one of those improvements which Lord Hoffmann had in mind in Kirin-Amgen [2004] UKHL 46, [2005] RPC 9 at 117.*
>
> *Insufficiency – Conclusion*
>
> *[174] I believe the judge was right to reject all the allegations of insufficiency. It follows he was also right to reject the allegation that the invention is obvious because it does not work and solves no technical problem.*

[178] It therefore appears that the Courts in the United Kingdom are not too far away from where the Courts in Canada stand. The question of sufficiency, or overbreadth, is to be considered on a case-by-case basis. Much will depend on the evidence and opinion put before the Court. There is no simple principle that can be universally applied that would say, for example, that you have shown

only one or two antibodies in your disclosure; you cannot claim all that will do the particular trick that you have in mind.

AMBIGUITY – "OR LESS"

[179] Janssen's Counsel raised in initial argument, but not in final argument, a question as to whether claims 143 and 222 were ambiguous. In particular, were they ambiguous in stating that stickiness and potency should possess certain values "or less" when measured in certain tests.

[180] There is no evidence that a person skilled in the art would be confused by such wording. Again, I turn to the cross-examination of Dr. Weiner, at pages 405 to 410:

> *Q. And Claim 143, as synopsised on the boards, includes a K off of 1 times 10 to the minus 4; yes?*
>
> *A. Or less, yes.*
>
> *Q. Yes. So that claim would include within its scope, antibodies with a K off of 1 times 10 to the minus 5?*
>
> *A. That's correct.*
>
> *Q. And 1 times 10 to the minus 6?*
>
> *A. Yes.*
>
> *Q. And 1 times 10 to the minus 7?*
>
> *A. Yes, if they could be achieved.*
>
> *Q. And essentially, the only limitation on that claim in the "or less" category would be what could be achieved by subsequent antibody engineers; correct?*

A. It's well known that there are likely limits not only in what you can accomplish with antibody engineering but also in analyzing the impact of antibody engineering.

So that 10 to the minus 6 or thereabouts is getting pretty close to the limit of what can functionally be achieved at the current time by using available technologies.

It's conceivable you could get, at some point, somebody could create something that was stickier and where you could measure it and feel confident in the measurement.

Q. But that's an issue of the limits of detection of the technology; fair? There is theoretically antibodies out there that have those K offs; it is just that you are saying we can't measure them at the present date or as of March 25th, 1999?

A. Well, we don't know. You don't know what you can't measure; right?

Q. Right, but what we do know, sir – I would suggest to you that what we do know is that the claim which says 1 times 10 to the minus 4 or less has a limit on one side of the range and no limit on the other end of the range; it encompasses all antibodies that are better than1 times 10 to the minus 4; right?

A. It does, but I think there is an important caveat that I would like to just describe, which is that when you are making an antibody that has a goal, deep tissue penetration, for example, these off rates actually turn out to have very significant impacts on how rapidly an antibody might penetrate deeply into tissue, for example into a tumour cell, and that's listed in my curriculum vitae.

When you are trying to do a neutralization assay, when you are trying to basically neutralize something that circulates in the blood, the kinetic parameter that's likely to matter most is going to be this less sticky end of the system and not the more sticky end of the system.

Because if what your goal is just to neutralize the ability of IL-12 to engage its receptor, if you create a molecule that sticks to the receptor and stays stuck for a long time, that's good, it seems quite plausible and, in fact, I think likely, that if you made something that was even stickier, it would just do that job more efficiently.

And so whether it was 10 to the minus 4, 10 to the minus 5th, 10 to the minus 20th, as far as we know, it would be likely to have the same biological efficacy, meaning that it would be able to inhibit the attachment of interleukin-12 to its receptor all the better, potentially, and neutralize the biological activity, and if were used for therapeutic intent, be useful to treat a disease that was associated with IL-12 biology.

Q. But so back to my original question, sir, which was about the claim itself, would you agree with me that the claim contains a hard stop, if you will, at 1 times 10 to the minus 4 and includes within its scope all antibodies with K offs which are better than 1 times 10 to the minus 4?

A. Well, that's what the claim describes. It describes a lower bounds, and then it is basically anything better than this lower bounds is what is claimed.

Q. And similarly with respect to the scope of the IC50 limitations in the claims, the claims refer to an IC50 limitation of 1 times 10 to the minus 9 molar or less?

A. Um-hmm, yes.

Q. And included within the scope of that claim would be any antibody which has an IC50 that is better than that?

A. Yes, I think properly, the patent describes, as far as I am concerned, it defines a minimum IC50 in that claim that is required in order to achieve an intended purpose. And it is logical to presume that anything that was better than that would have a better, would have an equivalent or better, or some, you know, intended result.

Q. So the inventors, then, as you describe it, are claiming not only the antibody J695, but anything that's better than J695, on the basis of the functional characteristics; fair?

A. My understanding is that the, and again, from a scientific perspective, the important point about J695 that's related to its ability to effectively treat psoriasis was that it was capable of neutralizing the biological activity of IL-12 in vitro and in vivo at these various descriptors.

And by defining it, it gives you essentially a minimum concentration of antibody that would be required to achieve that

> *goal, or minimum kinetic properties, and it is proper to presume that anything that improved upon those properties would likely also be affected.*
>
> *Q. But I was actually asking you a question about the claims, sir. And would you agree with me that the claim covers, 143, covers not only J695 but also any antibody that is better than J695?*
>
> *A. Certainly, it claims things that have a different kinetic property, but as I described, I mean, that would be pretty self-evident from the observation scientifically that having an antibody that neutralizes at a lower concentration, you know, anything that was able to neutralize at a lower concentration would work better, or work well.*
>
> *Q. Sir, let me ask again: Would you agree with me that Claim 143 covers not only J695 but anything that is better than J695 in terms of the functional characteristics that are described in the claim?*
>
> *A. Yeah, I have already said that.*
>
> *Q. Okay, thank you.*

[181] Claims 143 and 222 are setting are minimum standards for stickiness and potency. It may be that at some later time, an antibody will be developed that has vastly greater stickiness and/or potency. Whether or not that would constitute a patentable improvement is best left for another time.

[182] Claims 143 and 222 are not ambiguous.

CONCLUSIONS AND COSTS

[183] As a result, I have concluded that the claims asserted by AbbVie: claims 143 and 222 of the '281 patent, are valid. I will make a declaration to that effect. That declaration shall be as between the parties and their privies, as the *Patent Act* does not provide for such declaration *in rem*.

[184] I will declare that Janssen, by its promotion, offering for sale, and sale in Canada of its product known as STELARA, has infringed and is infringing upon the rights of AbbVie as granted in claims 143 and 222 of the '281 patent.

[185] A number of issues remain outstanding as they pertain to remedies and quantum. Either party, or both, may apply to the Office of the Chief Justice for the fixing of a time and place for a second trial in respect of those issues.

[186] I come to the issue of costs. As I expressed to Counsel during the trial, I am extremely disappointed that they did not take advantage of the Case Management and Trial Management process so as to narrow the issues, make appropriate agreements as to facts, and otherwise get this matter ready for trial; focusing on the important issues. The case has been instituted some four years ago, yet even up to and during the trial, Counsel was going back and forth as to issues and factual concessions. Expert reports were served that never were made part of the record. Letters rogatory were issued, yet never used. Other witnesses, whose names were mentioned from time to time, were never called. Discovery of the parties and named inventors were prolonged and numerous tedious motions were brought to compel yet further discovery. Scant portions of the discovery transcripts were deemed read in at trial; most of which could have been dealt with by an agreement as to facts. In all, the parties have not made full or proper use of the pre-trial process and management procedures, notwithstanding abundant applications to the Court about this or that point. We expect better.

[187] Therefore, each party will bear its own costs, except where there has been a particular Order of this Court awarding costs. Where costs have been left to the Trial Judge or in the cause, there will be no costs.

JUDGMENT

FOR THE REASONS PROVIDED, THIS COURT'S JUDGMENT is that:

1. It is declared that, as between the parties and their privies, claims 143 and 222 of Canadian Letters Patent Number 2,365,281 are valid and have been infringed by the Defendant Janssen Inc. by its promoting, offering for sale, and selling in Canada its product known as STELARA;

2. Either party, or both, may apply to the Office of the Chief Justice for the fixing of a second trial in respect of the remaining issues in this action; and

3. Save where as otherwise previously expressly Ordered by this Court, each party should bear its own costs.

"Roger T. Hughes"
Judge

FEDERAL COURT

SOLICITORS OF RECORD

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PLACE OF HEARING:	TORONTO, ONTARIO
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