Commissioner’s Decision #1414

Décision du Commissaire n^{o} 1414

TOPIC: O00 – Obviousness

SUJET: O00 – Évidence

Application No.: 2,622,609

Demande n°.: 2,622,609

IN THE CANADIAN PATENT OFFICE

DECISION OF THE COMMISSIONER OF PATENTS

Patent application number 2,622,609 having been rejected under subsection 30(3) of the *Patent Rules*, has subsequently been reviewed in accordance with paragraph 30(6)(*c*) of the *Patent Rules*. The recommendation of the Patent Appeal Board and the decision of the Commissioner is to refuse the application.

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INTRODUCTION

[1] This recommendation concerns the review of rejected patent application number 2,622,609, which is entitled "The Use of an Erythropoietin Moiety to Treat Neurodegenerative Disorders" and owned by F. Hoffmann-La Roche AG. The outstanding defect to be addressed is whether the claimed invention is obvious. A review of the rejected application has been conducted by the Patent Appeal Board pursuant to paragraph 30(6)(*c*) of the *Patent Rules*. As explained in more detail below, our recommendation is that the application be refused.

BACKGROUND

The Application

[2] Patent application 2,622,609 was filed in Canada on September 18, 2006 and published on April 12, 2007.

[3] The application relates to the use of a chemically modified hormone known as erythropoietin ("EPO") to treat neurodegenerative disorders. EPO is a naturally-occurring proteinaceous hormone produced in the human body that promotes the production of red blood cells. As such, it is typically used as a therapeutic agent to treat iron deficiency or low levels of red blood cells, i.e. anemia.

[4] In the present case, EPO has been chemically modified through the attachment of polyethylene glycol ("PEG") groups, or "moieties", and is used to treat human neurodegenerative disorders, such as stroke or Alzheimer's disease. Attachment of PEG moieties is generally thought to extend a molecule's activity by increasing its half-life in the bloodstream and by protecting it from degradation. A PEG-modified, or "PEGylated", molecule is necessarily larger and more hydrophilic than an unmodified one.

[5] Although EPO itself had been indicated in the prior art to be useful for treating neurodegenerative disorders before the filing of the application, it appears that no one had used PEGylated EPO in such treatments. The present inventors undertook to establish that PEGylated EPO could be so used if it were to be injected it into the bloodstream of a patient. However, in order for PEGylated EPO to exert a biochemical effect and be useful for treating a neurodegenerative disorder, it must cross what is known as "the blood-brain barrier" ("BBB") when moving from the bloodstream into the central nervous system. That PEGylated EPO could in fact cross the BBB appears not to have been demonstrated prior to the filing of the application.

[6] The BBB is a protective structure that regulates the exchange of substances between the blood and the brain. Movement of molecules across the BBB can occur via several routes. Small molecules such as sugar and alcohol move across the BBB by simple diffusion. Larger molecules such as proteins usually need to use a more complicated transport mechanism in order to move across the BBB. In such instances, a receptor molecule on the bloodstream side of cells of the BBB specifically binds the molecule, transports it through the cells of the BBB, and then releases it on the other side into the cerebrospinal fluid of the central nervous system. For the purposes of this review this process is termed "receptor-mediated transport involving endocytosis."

[7] The inventors conducted experiments establishing that PEGylated EPO can cross the BBB despite its large size. They disclose the results of their experiments in the application and claim the use of such molecules for the treatment of neurodegenerative disorders as their invention.

Prosecution history

[8] On April 15, 2013, the Examiner wrote a Final Action ("FA") pursuant to subsection 30(4) of the *Patent Rules*. The FA states that the application is defective for one reason: because the claims define subject matter that is obvious in view of three prior art documents, contrary to section 28.3 of the *Patent Act*.

[9] In its response to the FA ("R-FA") dated October 14, 2014, the Applicant submitted an amended claim set and argued that the claimed invention was not obvious, generally submitting that the inventors' establishment that PEGylated EPO can cross the BBB was unexpected and therefore the use of PEGylated EPO for treating neurodegenerative disorders was not obvious.

[10] As the Examiner considered the application not to comply with the *Patent Act*, pursuant to subsection 30(6) of the *Patent Rules* the application was forwarded to the Patent Appeal Board ("the Board") for review on May 15, 2015, along with a Summary of Reasons ("SOR") that explains why the skilled person would have expected that PEGylated EPO would be transported across the BBB.

[11] In a letter dated July 27, 2015 (the "Acknowledgement Letter") the Board forwarded the Applicant a copy of the SOR and offered the Applicant the opportunity to make further written submissions and/or attend an oral hearing. On October 27, 2015 the Applicant provided written submissions addressing the SOR and declined the offer to attend an oral hearing.

[12] The present panel was formed to review the application under paragraph 30(6)(*c*) of the *Patent Rules* and make a recommendation to the Commissioner as to its disposition. In a letter dated July 28, 2016 (the "Panel Letter"), we set out our preliminary analysis and rationale as to why, based on the record before us, the subject matter of the claims is obvious and does not comply with subsection 28.3 of

the *Patent Act*. On September 8, 2016 the Applicant replied to the Panel Letter (its "Reply to the Panel Letter") and provided additional submissions to support their position that the claimed subject matter is not obvious.

ISSUE

[13] There is one issue to address in this review: whether or not the subject matter defined by the claims is obvious, contrary to subsection 28.3 of the Act.

LEGISLATION AND LEGAL PRINCIPLES

Purposive construction

[14] In accordance with *Free World Trust v Électro Santé Inc*, 2000 SCC 66, essential elements are identified through a purposive construction of the claims done by considering the whole of the disclosure, including the specification and drawings. (see also *Whirlpool Corp v Camco Inc*, 2000 SCC 67 at paras 49(f) and (g) and 52.) In accordance with the *Manual of Patent Office Practice*, §13.05, the first step of purposive claim construction is to identify the person skilled in the art and their relevant common general knowledge. The next step is to identify the problem addressed by the inventors and the solution put forth in the application. Essential elements can then be identified as those required to achieve the disclosed solution as claimed.

[15] In the Panel Letter, we expressed our view that the construction of the claims did not appear to be at issue and that the claim terminology was clear. The Applicant did not comment on the construction of the claims or their terminology in its Reply to the Panel Letter.

Obviousness

[16] The *Patent Act* requires that the subject matter of a claim not be obvious to a person skilled in the art. Section 28.3 of the Act provides:

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

[17] In *Apotex Inc v Sanofi-Synthelabo Canada Inc*, 2008 SCC 61 at para. 67 (*Sanofi*), the Supreme Court of Canada stated that it is useful in an obviousness inquiry to follow the following four-step approach:

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

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

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

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

ANALYSIS

The person skilled in the art and the relevant common general knowledge of that person

[18] In the Panel Letter, we noted that the identity of the skilled person and their common general knowledge did not appear to be at issue. Nor did the Applicant's Reply to the Panel Letter dispute either of these aspects of the analysis.

[19] In brief, we agreed with the Examiner's identification of the skilled person as "a clinician with experience treating neurodegenerative disorders" and that such a person "would have significant and extensive knowledge in experimental medicine and would be well versed in treatment options for patients with neurodegenerative disorders."

[20] We clarified that the common general knowledge would also include an understanding of the structure, function and physiology of the BBB, including an understanding that molecules may move across the BBB by simple diffusion and, in the case of larger molecules such as proteins, by receptor-mediated transport involving endocytosis.

The inventive concept

[21] In the Panel Letter, we noted that there was agreement between the Examiner and the Applicant that the inventive concept of all of the claims "relates to the use of a PEGylated EPO molecule to treat neurodegenerative disorders" and clarified, as specified in the claims, that the neurodegenerative disorder is "of the brain and spinal cord", and that the PEGylated EPO is for "administration in the blood circuit of the brain of a patient".

[22] The Applicant's Reply to the Panel Letter did not indicate disagreement with this assessment.

Differences between the matter cited as forming part of the "state of the art" and the inventive concept

[23] Three references were applied in the FA:

- European patent application 1525889 A1, published April 27, 2005; inventor: Apollon Papadimitriou [*Papadimitriou*]

- WIPO international patent application WO 02/49673 A2, published June 27, 2002; inventors: Josef Burg et al. [*Burg et al.*]

- WIPO international patent application WO 00/61164 A1; published October 19, 2000; inventors: Michael Brines et al. [*Brines et al.*]

[24] In the Panel Letter, we noted that *Papadimitriou* and *Burg et al*. each disclose PEGylated EPO molecules that are suitable for therapeutic applications and which are within the scope of the claims. Neither reference indicates whether PEGylated EPO is able to cross the BBB and treat neurodegenerative disorders.

[25] In the Panel Letter we also indicated that *Brines et al*. discloses that EPO can be administered to the blood stream and is able to cross the BBB, rendering it useful for the treatment of a number of neurodegenerative disorders without the need to directly inject it into the central nervous system (*Brines et al.*, at page 4, lines 9-13). A suitable EPO molecule is defined comprehensively by *Brines et al.* as any one of a number of naturally-occurring, synthetic and recombinant forms of EPO (page 9, lines 24-30); however, a PEGylated form of EPO is not explicitly mentioned.

[26] Importantly, we noted that *Brines et al*. do not believe that EPO crosses the BBB by simple diffusion. *Brines et al.* disclose that EPO is believed to be actively transported across the BBB via receptor-mediated transport involving endocytosis (page 11, line 28 – page 12, line 1).

[27] In the Panel Letter, we summarized the differences between the cited references, considered individually, and the inventive concept as follows:

- Neither *Papadimitriou* nor *Burg et al.* suggest that PEGylated EPO crosses the BBB so as to treat neurodegenerative disorders; and

- *Brines et al.* do not disclose the use of PEGylated EPO.

[28] We noted that when the references are combined there are no differences between the state of the art and the inventive concept – any deficiency in *Brines et al.* as regards PEGylated EPO is bridged by the disclosure of such molecules in either *Papadimitriou* or *Burg et al.*

[29] The Applicant's Reply to the Panel Letter did not express disagreement with our assessment of the differences between the matter cited as forming part of the state of the art and the inventive concept.

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

[30] In the Panel Letter, we framed the question at this point of the analysis by asking whether the skilled person would have combined the cited references and taken the step of substituting PEGylated EPO, as disclosed in either *Papadimitriou* or *Burg et al*., in place of non-PEGylated EPO in the method of treating neurodegenerative

disorders as disclosed by *Brines et al.* Based on a review of the record, the answer to the question principally considers whether it would have required inventive ingenuity on the part of the skilled person to take that step based on the expectation that PEGylated EPO would cross the BBB and thereby become available within the central nervous system to treat neurodegenerative disorders of the brain and spinal cord. Our preliminary view was that the step of substituting PEGylated EPO in the method disclosed by *Brines et al.* would have been obvious to the skilled person.

[31] We expressed that opinion because, in our view, the common general knowledge, the *Brines et al.* reference and the disclosure of the present application are all consistent in terms of their disclosure of the expected manner of movement of EPO molecules across the BBB, and because the skilled person would expect the same in the case of a PEGylated EPO molecule. We explained that the skilled person understood from their common general knowledge that receptor-mediated transport involving endocytosis was the expected manner of transport of large proteinaceous molecules such as EPO, and that *Brines et al*. believed that EPO crossed the BBB by that mechanism thereby rendering EPO useful in treating neurological disorders through administration in the blood stream. Our preliminary view was that the skilled person would not see any negative indicators of success if PEGylated EPO were to be used instead of non-PEGylated EPO, and would have been motivated to substitute PEGylated EPO for EPO to realize the known and expected advantages associated with PEGylated molecules. We also observed that the instant application itself posited that the ability of PEGylated EPO to cross the BBB was likely due to receptor-mediated transport involving endocytosis.

[32] In the Panel Letter, we acknowledged the Applicant's arguments that the skilled person would not have expected PEGylated EPO to cross the BBB because of its large size and increased hydrophilicity, and for that reason an inventive step had been taken by the inventors when they demonstrated that it did. We indicated that, in our view, the skilled person would have only carried that expectation if the mechanism of movement of PEGylated EPO across the BBB had been by simple

diffusion. Because the record establishes that the expected manner of movement is by receptor-mediated transport involving endocytosis, which would be selective for the molecule in question and which can operate independent of a molecule's size or hydrophilicity, we were not persuaded by the Applicant's arguments.

[33] In its Reply to the Panel Letter, the Applicant disagreed with our preliminary opinion and maintained "that the claimed subject matter is non-obvious for the reasons already of record."

[34] The Applicant's Reply to the Panel Letter began by suggesting that an incorrect approach had been undertaken: "In order to assess obviousness of the claims Applicant respectfully submits that a 'could-would' approach should be used for the assessment, and not a 'could-could' approach." No further explanation was provided as to why the approach to the question of obviousness outlined in our Panel Letter should be regarded as impermissible or wrong in principle.

[35] In the Panel Letter, as well as this recommendation, we have followed the structured four-step approach to obviousness set out by the Supreme Court of Canada in *Sanofi*. The Applicant now submits that we have undertaken what it considers an impermissible "could-could" approach. However, as indicated in the Panel Letter, the assessment of what the skilled person "would" have done was based on evidence of sufficient motivation found in the record, not based on what the skilled person "could" have done; for instance:

> Having reviewed the record, we have formed the preliminary view that the step of substituting PEGylated EPO in the method disclosed by Brines et al. would have been obvious to the skilled person, that there is nothing indicating to the skilled person that PEGylated EPO would not cross the BBB, and that the known advantages (as discussed in the description on page 2, lines 20-22) that would be afforded by the use of

> PEGylated EPO provided sufficient motivation for the skilled person to take that step. [emphasis added; page 7, Panel Letter]
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> . . .
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> Therefore, the skilled person, wishing to achieve transport of PEGylated EPO across the BBB from the blood stream, and being motivated to provide an improved therapy, would have substituted such molecules for those mentioned by *Brines et al.* and thereby realize the advantages they afford in the treatment of neurodegenerative disorders of the brain and spinal cord. [emphasis added; page 9, Panel Letter]

[36] Thus, our preliminary opinion expressed in the Panel Letter was informed by the *Sanofi* approach, having regard to the forward-looking perspective of the skilled person, and evidence of sufficient motivation for that person to take what we considered would have been an obvious step of substitution.

[37] The Reply to the Panel Letter also provided a brief discussion of one of the prior art references, *Brines et al.*, and the Applicant's view of the inventive nature of the claimed subject matter.

[38] The Applicant submitted that the *Brines et al.* document describes "that EPO or derivatives associated with compounds that are known to enhance penetration of endothelial barriers, or compositions using such compounds, are useful to deliver these substances to the brain and cause neuroprotective effects. The document does not describe that increase in molecular weight or content of polyethylene glycol, or increased hydrophilicity could be useful for such a purpose." According to the Applicant, "the person of ordinary skill in the art will not find any hint in [*Brines et al*.] which would lead them to the current invention."

[39] The Applicant also reiterated that none of the prior art documents "predicts blood brain barrier penetration and neuroprotective activity of pegylated erythropoietin derivatives as defined in present claim 1, which are molecules substantially larger

than erythropoietin, more hydrophilic than erythropoietin and containing polyethylene glycol" and that "the person of ordinary skill in the art would expect that smaller molecules should be used in order to cross the blood brain barrier."

[40] We have considered the Applicant's Reply to the Panel Letter but are not persuaded that the claimed subject matter would not have been obvious to the skilled person.

[41] The question here is obviousness and the inventive concept differs from what is disclosed in any one of the prior art documents. In that regard, the *Brines et al*. reference admittedly did not disclose the use of PEGylated EPO in their method of neuroprotection. However, we disagree with the Applicant that *Brines at al*. provided no hint or suggestion of the Applicant's claimed subject matter, because, apart from the failure to disclose PEGylated EPO, *Brines et al.* disclosed subject matter that is otherwise within the claims and part of the inventive concept. As indicated in the Panel Letter, *Brines et al.* also broadly suggested the use of any EPO derivative in their method. As also explained previously, in our view the shortcomings of *Brines et al.* would have been bridged through the skilled person's substitution of PEGylated EPO, as disclosed in either one of *Papadimitriou* or *Burg et al.*, for non-PEGylated EPO.

[42] The Applicant continues to argue that "the person of ordinary skill in the art would expect that smaller molecules should be used in order to cross the blood brain barrier." However, as explained in the Panel Letter, this argument appears to refer only to movement of molecules across the BBB by simple diffusion (which the skilled person admittedly would expect to be limited by a molecule's size), and fails to take into account the existence of a mechanism that is selective for EPO, and which is not restricted to the movement of small molecules, i.e., through receptor-mediated transport involving endocytosis. In our estimation, the skilled person would have understood from *Brines et al.* as well as their common general knowledge, that it is through that mechanism that EPO is able to cross the BBB. As explained in the

Panel Letter, the skilled person would expect the same in the case of PEGylated EPO.

Conclusion

[43] In our view, the subject matter defined by the claims on file would have been obvious to the skilled person, contrary to subsection 28.3 of the *Patent Act*.

RECOMMENDATION OF THE BOARD

[44] In view of the above, we recommend that the application be refused on the basis that the claims on file are not compliant with subsection 28.3 of the *Patent Act*.

Ed MacLaurin	Marcel Brisebois	Andrew Strong
Member	Member	Member

COMMISSIONER'S DECISION

[45] I concur with the findings and the recommendation of the Board and its recommendation that the application should be refused because the claims on file do not comply with subsection 28.3 of the *Patent Act*. Accordingly, I refuse to grant a patent on this application. Under section 41 of the *Patent Act*, the Applicant has six months within which to appeal my decision to the Federal Court of Canada.

Johanne Bélisle
Commissioner of Patents
Dated at Gatineau, Quebec,
this 16th day of December, 2016