Commissioner’s Decision #1384

Décision du Commissaire #1384

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Application No.: 2,389,321

Demande n°.: 2,389,321

IN THE CANADIAN PATENT OFFICE

DECISION OF THE COMMISSIONER OF PATENTS

Patent application number 2,389,321 having been rejected under subsection 30(3) of the *Patent Rules*, has been reviewed in accordance with paragraph 30(6)(*c*) of the *Patent Rules*. The recommendation of the Board and the decision are as follows:

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Introduction

[1] Patent application number 2,389,321 (the ’321 application) entitled “Neisserial Antigenic Peptides” was filed on October 30, 2000 by Chiron S.P.A. and is currently owned by Novartis Vaccines and Diagnostics. This application was rejected in a Final Action because the claimed invention was considered to lack utility.

[2] The Applicant’s amendments and arguments in response to the Final Action were considered unpersuasive and the ’321 application was therefore referred to the Patent Appeal Board.

[3] For the reasons that follow we recommend that the ’321 application be refused.

Background

[4] *Neisseria meningitidis* is a bacteria that can cause meningitis, an inflammation of the membranes covering the brain and spinal cord. Several different serogroups of *Neisseria meningitidis* have been identified on the basis of structural differences in the capsular polysaccharide. At the time of filing of the ’321 application, successful polysaccharide-based vaccines had been developed against some serogroups but not for serogroup B (meningitis B, herein “menB”). Polysaccharide-based vaccines are not effective against menB because the menB polysaccharide is identical to a human polysaccharide and is therefore poorly immunogenic. Consequently, menB remains a significant cause of morbidity and mortality.

[5] The ’321 application is concerned with identifying new menB antigens by large scale sequencing of the menB genome. The focus of this work is to identify new menB antigens that could serve as a potential vaccine component.

Procedural History

[6] The Final Action was written on April 8, 2013. In response, on September 23, 2013, the Applicant submitted an amended claim set containing 8 claims (the claims on file) along with written submissions. The amended claims were not considered to overcome the defects indicated in the Final Action. Consequently, the case was transferred to the Patent

Appeal Board along with a Summary of Reasons on January 15, 2014. This panel provided the Applicant with the Summary of Reasons on January 31, 2014 and the Applicant provided further written submissions in response on April 14, 2014.

[7] After conducting an initial review of the case a letter was sent to the Applicant on July 23, 2014 summarizing the panel's initial observations. This letter identified additional defects relating to the clarity of claims 7 and 8 and to overlap of all the claims on file with the claims of co-pending Canadian application 2,650,642. The Applicant was also asked to clarify whether or not claims 3 and 6, which are directed to pharmaceutical compositions, promised a therapeutic utility.

[8] In response to the panel`s letter the Applicant, on September 22, 2014, provided proposed amendments to the claims on file, written arguments and additional documents in support of its view of the common general knowledge (CGK) of the person skilled in the art.

[9] On November 4, 2014 the panel sent a second letter to the Applicant identifying two additional documents it considered to be part of the CGK and inviting comments from the Applicant on the relevance of these documents. On November 17, 2014 the Applicant provided comments and also submitted several more documents it considered relevant to the CGK.

[10] A hearing was held November 18, 2014. Following the hearing, on December 2, 2014, the Applicant submitted further proposed claims, provided arguments, and submitted several further documents in relation to the CGK.

Proposed Claims

[11] As mentioned above, following an initial review, in the letter of July 23, 2014, the panel asked the Applicant to address the promised utility of pharmaceutical composition claims 3 and 6 and also identified a defect relating to the clarity of claims 7 and 8. Claims 7 and 8 were suggested by the panel to lack clarity because they were directed to polypeptides of 100 amino acids or less while claims 1 and 4, upon which they were dependent, were limited to polypeptides of 21 amino acids or less. In the Applicant's response of September 22, 2014 they did not provide arguments to address the lack of utility of claims

3 and 6 or the lack of clarity of claims 7 and 8. Instead the Applicant proposed deleting these claims, resulting in proposed claims 1-4, which are identical to claims 1, 2, 4 and 5 on file.

[12] Noting that the Applicant did not dispute that claims 7 and 8 lack clarity (and instead proposed their deletion) we are of the view that, based on their inconsistency with the claims upon which they depend, these claims do not comply with subsection 27(4) of the *Patent Act*.

[13] Noting that the Applicant did not respond to our concerns regarding the lack of utility of claims 3 and 6, and in light of our conclusion below with respect to the utility of the remaining claims, which contain a lower threshold of promised utility, we are of the view that claims 3 and 6 lack utility and do not comply with the *Patent Act.*

[14] The panel`s letter of July 23, 2014 identified the claims on file as overlapping with the claims of co-pending application 2,650,642. In their response of September 22, 2014 the Applicant informed the panel that the claims of the co-pending application had been amended to avoid overlap. In the panel's view this amendment to the co-pending application was sufficient to eliminate overlap with the claims on file.

[15] At the hearing the Applicant indicated that they may wish to provide further submissions to address issues raised during the hearing. Following the hearing, on November 19, 2014, a letter was sent to the Applicant inviting them to provide such submissions and stipulating that if the Applicant wished to submit new claims they should ensure that i) there was a clear correspondence between any new proposed claim and one of the claims on file, and ii) the new claims did not introduce new defects or reintroduce defects that were overcome by the proposed claims submitted September 22, 2014.

[16] The Applicant submitted written comments on December 2, 2014 and also proposed 5 new claims. Contrary to guidance of the panel outlined above, these proposed claims did not each correspond to claims on file and defects previously overcome were reintroduced. Specifically, proposed claim 5 did not correspond to any of the claims on file because it was directed to a polypeptide with only 85% identity to SEQ ID NO: 11076 (the third polypeptide claimed) while the claims on file were defined to have at least 95% identity to

said sequence. Also, proposed claims 1-4 were broadened to the extent that they once again overlapped with the claims of co-pending application 2,650,642.

[17] Because these post-hearing proposed claim amendments did not correspond with the previous claims on file and reintroduced defects that had been overcome by the previously proposed deletion of claims, they are not considered "necessary" under s. 30 (6.3) of the *Patent Rules* and so are not further considered. Nevertheless, in light of the finding below that the claims on file lack utility, since these broader proposed claims would have had the same utility as those on file, they would also have been found to lack utility.

[18] In summary, the only outstanding issue is with respect to the utility of claims 1, 2, 4 and 5 of the claims on file. It is these claims that will be the subject of the analysis below. Since proposed claims 1-4 are identical to claims 1, 2, 4 and 5 on file they do not require a separate analysis.

Issue

[19] This review addresses the following question:

- Do claims 1, 2, 4 and 5 lack utility?

Legal Principles

Claim Construction

[20] Purposive construction is an interpretive exercise in determining the meaning and scope of the claims. Claim construction is antecedent to consideration of validity: *Whirlpool Corp v Camco Inc, 2000 SCC 67* at paragraph 43 ["*Whirlpool*"]. Purposive construction requires that the claims be interpreted from the point of view of the person skilled in the art, who possesses the common general knowledge of the particular art: *Whirlpool* at paragraph 53. Construction is based on the patent specification itself without resort to extrinsic evidence: *Free World Trust v Électro Santé Inc,* 2000 SCC 66, at paragraph 66 ["*Free World Trust*"]. Further, recourse should be had to the description to gain insight into what was meant by a particular word or phrase. During purposive construction, the elements of the claimed invention are identified as essential or non-essential: *Free World Trust* at paragraph 31. An

element is considered non-essential if, based on a purposive construction, the skilled person would appreciate an element of the claim could be omitted or substituted without having a material effect on the working of the invention: *Free World Trust* at paragraph 55. According to the Examination Practice Respecting Purposive Construction - PN2013-02, the essential elements of a claim are those elements that contribute to the proposed solution to the problem identified in the application.

Utility

[21] Utility is required by section 2 of the *Patent Act* which defines a patentable invention as:

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

[22] The meaning of the term "useful" in the section 2 definition of a patentable invention was considered by the Supreme Court of Canada in *Consolboard Inc. v. MacMillan Bloedel (Sask.) Ltd.*, [1981] 1 S.C.R. 504. The Court held that an application can be considered not useful if "the invention will not work, either in the sense that it will not operate at all or, more broadly, that it will not do what the specification promises that it will do" (quoting from *Halsbury's Laws of England*, (3rd ed.), vol. 29 pg. 59.). This led to a consideration by the Courts of the "promise of the patent".

[23] The promise of the patent was considered in *Apotex Inc. v. Sanofi-Aventis Canada Inc* 2013 FCA 186 ["*Plavix FCA"*], where the Court discussed that determining the standard against which utility will be measured:

> […] requires the Court to construe the patent to determine if a person skilled in the art would understand it to contain an explicit promise that the invention will achieve a specific result. If so, the inventor will be held to that promise. If there is no explicit promise of a specific result, then a mere scintilla of utility will do.

[24] The nature of an explicit promise was clarified in *Apotex Inc. v. Pfizer Canada Inc.* 2014 FCA 250 at paragraph 67 "…it is not enough to merely label a promise as "explicit" if it

can only be supported on the basis of equivocal inferences and ambiguous indications (*Plavix FCA* at paras. 64-66)".

[25] At paragraphs 96-99 of *AstraZeneca Canada Inc. v. Apotex* 2014 FC 638, affirmed 2015 FCA 158 ["*AstraZeneca"*] the Court established that the promise of utility for a compound must be related to how the patent will ultimately be used rather than to a property of that compound:

> [97]… The promise of the patent, it must be recalled, is related to the patent's utility. Thus, the promise must be related to how the patent will ultimately be used (assuming there is an explicit promise made, which both experts agreed on). The patent in this case is not *useful* for possessing the chemical property of being stable against racemization; it is useful as a pharmaceutical drug in therapy. Stability against racemization merely enables that use and is not a use in itself.
>
> [99] Before leaving this point, I note that in the *Nexium NOC* Justice Hughes makes the same observation in respect of the '653 patent:
>
> > It is important to distinguish between the utility promised by the patent – "<u>improved therapeutic profile, such as lower degree of interindividual variation</u>" – and the particular property that makes that possible "<u>high stability towards racemization</u>" (*Nexium NOC*, at para 84; emphasis in original).

[26] A claimed invention must be useful on the basis of either demonstrated or soundly predicted utility: *Apotex Inc. v. Wellcome Foundation Ltd.*, 2002 SCC 77 ["*AZT"*]. Whenever a claimed invention is not based on demonstrated utility, it becomes necessary to determine whether the utility was soundly predicted.

[27] As outlined in *AZT*, in order for utility to be soundly predicted it must satisfy three criteria:

1) There must be a factual basis for the prediction;

2) There must be an articulable and "sound" line of reasoning from which the desired result can be inferred from the factual basis; and

3) There must be proper disclosure.

Purposive Construction of the Claims

The Person Skilled In the Art

[28] The ’321 application is focused on the identification, through genome sequencing, of new Neisserial proteins that may be useful in the diagnosis, treatment or prevention of *Neisseria meningitides* infection. The person skilled in the art is therefore experienced in the sequencing of bacterial genomes, the identification of potential protein coding sequences in said genomes and in the search for novel means to diagnose, treat or prevent bacterial infections.

The CGK of the Person Skilled In the Art

[29] The following paragraphs outline what the CGK of the person skilled in the art was at the time the ’321 application was filed.

[30] Novel proteins can be identified from genomic sequence data by searching for open reading frames (ORFs); these are sequences of DNA that stretch between a start codon and a stop codon. Once an ORF is confirmed to code for a protein it is referred to as a gene.

[31] In bacteria, most ORFs longer than 300 nucleotides will code for proteins (*Alimi et al.* Genome Research, 2000 July; 10(7), pg. 959-66, supplied by Applicant with correspondence of December 2, 2014). Moreover, a bacterial ORF that is highly conserved between species or between different subtypes of a species is more likely to be a gene because the chance of an ORF that does not code for a protein to be conserved throughout evolution is small (*Alimi et al.* pg 960, left column, last paragraph).

[32] Potential surface exposed proteins can be identified by searching for a signal peptide sequence within an ORF (*Pugsley*, Microbio. Rev. 1993 pg. 53: “*Pugsley”*, supplied by Applicant with correspondence of September 22, 2014). Bacterial signal peptides are found at one extreme end of the protein (the amino terminus) and have a highly conserved structure (*Pugsley*, pg. 53).

[33] It was also commonly known to the skilled person that polypeptides and proteins are both composed of chains of amino acids. Polypeptide chains are generally shorter than proteins.

Both proteins and polypeptides are generally antigenic because they can act as antigens by inducing an immune reaction when injected into a host animal, provided the protein or polypeptide is foreign to said host. Immune reactions induced by a protein or polypeptide can include the production of antibodies which specifically bind said protein or polypeptide.

[34] Antigenic determinants, also known as epitopes, are the small regions within a protein or polypeptide that are specifically recognized by antibodies or other elements of the immune system and that actually induce the production of said antibodies. Not all regions of a protein are equally capable of forming antigenic determinants. Proteins are intricately folded three dimensional structures with some of the component amino acids buried deep within the structure and some being exposed to the surface. It is the surface exposed regions which can contain antigenic determinants that bind to antibodies.

[35] Polypeptide fragments that contain an antigenic determinant from a protein may be capable of inducing the production of antibodies that will cross react with that protein (page 1, right hand column, last paragraph of Van Regenmortel and Pellequer, Peptide Research, 1994; 7(4): 224-8, discussed below at paragraph 61 and supplied by the panel in correspondence of November 4, 2014). Conversely, such fragments may also be capable of binding to some of the antibodies induced by the protein itself.

[36] A number of different algorithms can be used to predict which regions of a protein are considered most likely to contain antigenic determinants (see pages 34-35 of the description). These algorithms, and the differences of opinion that existed with respect to the reliability of their predictions at the filing date, form a critical part of the utility analysis and will be discussed in detail below.

The problem and solution that the invention addresses

[37] As mentioned above, there were no menB proteins known at the time of filing which were capable of generating an effective vaccine. There was, therefore, a need to identify new menB proteins. At the time of filing the ’321 application, technology which allowed the rapid sequencing of whole genomes was relatively new. The Applicant employed this technology to sequence large portions of the menB genome (as well as large portions of the

genomes of menA and the related *Neisseria gonnoroheae*). A large amount of sequence data was obtained, and over 2,000 ORFs, each representing a possible novel protein, were identified. This data was filed in international patent applications WO9957280 and WO0022430 (published less than 1 year before the ’321 application and herein referred to as the “international applications”).

[38] The ’321 application states that “the invention provides fragments of the proteins disclosed in international patent applications WO99/57280 and WO00/22430… wherein the fragments comprise at least one antigenic determinant” (page 1, 2nd last paragraph). These fragments were identified using the epitope prediction algorithms mentioned above at paragraph 36. Therefore, the skilled person would understand that the problem the ’321 application set out to address was;

- A need to provide fragments of novel menB proteins that comprise at least one antigenic determinant.

[39] The ’321 application identifies over 37,000 different polypeptide fragments predicted as containing antigenic determinants from the more than 2,000 menB ORFs identified in the earlier filed international applications. Over the course of prosecution the claims have been narrowed to encompass only a single fragment from a single ORF. The presently claimed fragment is defined by SEQ ID NO. 11076. It is one of 33 fragments predicted, by at least 1 of 3 separate algorithms, from an ORF identified in WO9957280 (see page 1205-1207) and therein termed ORF 741. The skilled person would therefore understand the solution provided by the claimed invention to be;

- The identification of the fragment defined by SEQ ID NO: 11076, which comprises a predicted antigenic determinant of the potential menB protein defined by ORF 741.

The claims, purposively construed.

[40] Claims 1, 2, 4 and 5 read as follows.

1. A recombinant polypeptide comprising a Neisserial antigenic epitope and having at least 95% sequence identity to SEQ ID NO: 11076, wherein SEQ ID NO: 11076 and said recombinant polypeptide comprise a Neisserial antigenic determinant.

2. The recombinant polypeptide of claim 1 comprising amino acid sequence SEQ ID NO: 11076.

4. A purified polypeptide comprising a Neisserial antigenic epitope and having at least 95% sequence identity to SEQ ID NO: 11076, wherein SEQ ID NO: 11076 and said purified polypeptide comprise a Neisserial antigenic determinant.

5. The purified polypeptide of claim 4 comprising amino acid sequence SEQ ID NO: 11076.

[41] These claims are directed to either a recombinant polypeptide (claims 1 and 2) or a purified polypeptide (claims 4 and 5). The skilled person would understand that a recombinant polypeptide is simply one that is produced in the laboratory using well known molecular cloning techniques while a purified polypeptide is that which is extracted or isolated from cells or tissues which express it. There is no difference in the amino acid structure of a recombinant polypeptide and a purified polypeptide when they are both defined by the same sequence, as they are in claims 1, 2, 4 and 5.

[42] Claims 1 and 4 are restricted to polypeptides with "at least 95% sequence identity to SEQ ID NO: 11076". The percent identity that any given polypeptide sequence would have to SEQ ID NO: 11076 is determined by examining the number of amino acid differences between the two sequences. Any deleted or additional amino acids would be considered differences. SEQ ID NO: 11076 is 20 amino acids in length. A polypeptide of 20 amino acids in length and comprising one difference over SEQ ID NO: 11076 would be 95% identical (19/20 = 95%), any more differences and the identity would fall below 95%. A polypeptide that is 21 amino acids in length, with the only difference over SEQ ID NO: 11076 being the extra amino acid, would be 95.2% identical (20/21 = 95.2%). Addition of any more amino acids would lower the identity below 95%. Similarly, a polypeptide of 19 amino acids would be 95% identical, any less amino acids and identity would fall below 95%. For these reasons the polypeptides encompassed by claims 1 and 4 must be no

smaller than 19, and no larger than 21, amino acids.

[43] Claims 1 and 4 use the terms "antigenic epitope" and "antigenic determinant". The skilled person would understand these terms to be equivalent. As mentioned above at paragraph 34, the terms "epitope" and "antigenic determinant" are used interchangeably in the art. Adding the term "antigenic" to "epitope" does not change its meaning as any epitope would be understood to be antigenic.

[44] Claims 1 and 4 stipulate that the claimed polypeptide comprises a "Neisserial antigenic determinant". Based on the CGK summarized above at paragraphs 34 and 35, the skilled person would understand this to mean that the claimed polypeptide possesses an antigenic determinant of a protein from *Neisseria* bacteria, and because of this it may be capable of inducing the production of, and being bound by, antibodies against this Neisserial protein.

[45] In the panel's view, the skilled person would consider the following elements as being essential to the solution of the problem identified for the '321 application with respect to claims 1 and 4;

- a polypeptide having at least 95% sequence identity to SEQ ID NO: 11076 and
- comprising a Neisserial antigenic epitope.

[46] Dependent claims 2 and 5 are more narrowly focused on the polypeptide defined by SEQ ID NO: 11076 rather than to a polypeptide that has 95% sequence identity to it. These claims, therefore, are directed to a polypeptide having the following essential features;

- a polypeptide having 100% sequence identity to SEQ ID NO: 11076 and
- comprising a Neisserial antigenic epitope.

What is the Promise of the Patent?

[47] While the problem and solution, as discussed above at paragraphs 37-39, are related to the search for a new therapeutic agent (i.e. a vaccine) against menB, the Applicant can only be held to this utility if they have explicitly promised it. In our view, the skilled person would not find an explicit promise of therapeutic utility in claims 1, 2, 4 and 5. Likewise, no

explicit promise of a therapeutic utility is made in the description. A broad discussion of potential embodiments spanning pages 2-4 of the description is reflected in the statement that the polypeptides "may be suitable as vaccines, for instance, or as diagnostic reagents, or as immunogenic compositions" (page 3, 2nd last paragraph, emphasis added). Because these uses are all presented as possible alternative embodiments, and because the term "may" is used, the skilled person would not consider these explicit promises of a therapeutic utility or any other utility.

[48] In our view, in accordance with the claim language itself, the skilled person would construe the claims as explicitly promising that the polypeptide comprises "a Neisserial antigenic determinant" (emphasis added). As mentioned above at paragraph 44, the skilled worker would understand this expression to mean that the claimed polypeptide comprises an antigenic determinant from a Neisserial protein and would therefore be capable of both generating antibodies which cross-react with said Neisserial protein as well as cross-reacting with antibodies generated by said Neisserial protein.

[49] The Applicant submitted that the promised utility is merely that the claimed polypeptide is antigenic. For example, in correspondence of November 17, 2014 the Applicant states that "the promised utility is for the peptide to be antigenic, i.e. capable of being bound by an antibody" (see correspondence page 1, 2nd paragraph). We find, however, that this position is inconsistent with the claim language, which clearly states that the claimed polypeptide comprises "a Neisserial antigenic determinant", not simply that it be antigenic.

[50] While the claim language promises a polypeptide comprising an antigenic determinant from a Neisserial protein, a simple promise of antigenicity would not require any connection to a Neisserial protein and thus would not be related to the ultimate use (*AstraZeneca, supra*). In short, the Applicant's proposed promise effectively disconnects the claimed polypeptide from any use related to *Neisseria* bacteria.

[51] In our view, antigenicity, as an inherent property of almost all proteins and polypeptides, cannot define the utility of a protein or polypeptide. As was the case in *AstraZeneca* (see paragraph 25 above), the promised utility of a patent must be related to how the patent will ultimately be used and not to a particular property that makes the ultimate use possible. If

the utility requirement could be satisfied for proteins or polypeptides by the non-specific, inherent property of antigenicity alone, then almost all proteins and polypeptides would have utility. Conversely, almost no protein or polypeptide could ever be found to lack utility.

[52] We conclude that the skilled person would find an explicit promise in the claims that the polypeptide comprises an antigenic determinant from a Neisserial protein. The skilled person would recognize that the Neisserial protein from which the antigenic determinant comes is the predicted protein defined by the 741 ORF, since the claimed polypeptide sequence SEQ ID 11076 is a fragment taken directly from this predicted protein.

Does the Claimed Invention Lack Utility?

[53] The claimed polypeptide was predicted on the basis of algorithms that will be further discussed below and there is no evidence that any tests were conducted to verify the prediction before the filing date. As such, since the promised utility was not demonstrated, the Applicant must rely on a sound prediction to satisfy the utility requirement. Utility will be established if the skilled person reading the description would be satisfied the prediction was sound. As discussed above, the Supreme Court of Canada clarified that a sound prediction requires a factual basis, a sound line of reasoning and a proper disclosure.

The Factual Basis

[54] The skilled person would identify the following facts to have been established in the ’321 application:

- menB is a pathogenic bacteria that causes meningitis (page 1, 2nd paragraph).
- The claimed polypeptide defined by SEQ ID NO: 11076 is a fragment of a predicted protein sequence defined by an ORF that was termed ‘741’ in international application WO9957280 (pages 291-292).
- The 741 ORF is a DNA sequence identified from menB that is 825 nucleotides in length and contains a predicted signal peptide sequence immediately following the start codon (page 1205 of international application WO9957280).

- The sequence of the predicted full length protein defined by the 741 ORF is highly conserved between menB and menA (95.6% identity) and moderately conserved between menB and *Neisseria gonorrhoea* (61.4% identity) (page 1206-1207 of international application WO9957280).

- The sequence of the claimed polypeptide fragment (SEQ ID NO: 11076) of the 741 ORF is 95% identical between menB and menA and 85% identical between menB and *Neisseria gonorrhoea* (based on sequence comparisons between amino acids 192-211 of a741.pep on page 1206 and 1207 of WO9957280).

Sound Line of Reasoning

[55] As mentioned above, the 741 ORF represents a predicted Neisserial protein. In order for there to be a sound prediction the skilled person must first have a sound line of reasoning, based on the factual basis above, that the 741 ORF is a real gene encoding a real Neisserial protein, and then also must have a sound line of reasoning that the claimed polypeptide defined by SEQ ID NO: 11076 comprises a Neisserial antigenic determinant of this protein.

[56] As mentioned above at paragraph 31 it was CGK that bacterial ORFs longer than 300 nucleotides or that are conserved between species or subtypes are likely to encode a protein. The facts that the 741 ORF is both longer than 300 nucleotides and is conserved between menB, menA and *Neisseria gonorrhoea* would suggest to the skilled person that it likely encodes a protein.

[57] Also, the presence of a signal peptide sequence, immediately after the start codon, would be viewed by the skilled person as another factor which increases the probability that the 741 ORF encodes a protein. The localization of a signal peptide sequence within an ORF would be unlikely to occur by chance in a non-coding sequence. It would be even less likely to be found by chance in the precise location that it is required, immediately after the start codon so that it is found in the amino terminus of the encoded protein.

[58] Given the length of the 741 ORF, its high level of conservation within *Neisseria* bacteria and the presence of a signal peptide within the amino terminal coding region we conclude

that the skilled person would reasonably infer that it is a gene encoding a Neisserial protein, which we will now refer to as "the 741 protein".

[59] Turning now to the second prediction that SEQ ID NO: 11076 comprises an antigenic determinant from this Neiserial protein, the Final Action disputed that a prediction of utility relying on antigenic prediction algorithms could be sound. The Applicant has argued that the results of the algorithms are less of a prediction and more of a certainty. For example the Applicant states "there is no doubt that these predictions were accurate and that the m741 protein is indeed a surface exposed antigen" (correspondence of September 22, 2014, page 2). However, the wording of the description itself confirms that these algorithms are predictive tools. At page 34 the description states "protein sequences disclosed in the International Applications have been, *inter alia*, subjected to computer analysis to predict antigenic peptide fragments within the full-length proteins" (emphasis added). At page 35 the Jameson and Wolf algorithm is described as "a novel algorithm for predicting antigenic determinants" and the Hopp and Woods algorithm is described as for "prediction of protein antigenic determinants from amino acid sequences" (emphasis added in both cases). Both of these methods independently predicted SEQ ID NO: 11076 and the description states that fragments which are predicted by more than one antigenic prediction algorithm are preferred (page 35).

[60] It is necessary then to consider the predictive value of the antigenic prediction algorithms employed. In response to the Final Action the Applicant supplied a reference by Hopp (Peptide Research, 1993, 6(4): 183-90 "*Hopp*"), a review article written by one of the researchers who first developed the Hopp and Woods algorithm. The Applicant states that *Hopp* "concludes that the method works well" (correspondence of September 23, 2013, page 2). This reference explains that the Hopp and Woods algorithm works by identifying the regions of a protein that are most hydrophilic and therefore most likely to be exposed on the external surface of the proteins three dimensional structure. *Hopp* defends the Hopp and Woods algorithm against seven previously published articles which either found the algorithm to lack reliability or described methods of predicting antigenic determinants which worked better (page 185). Table 1 displays the results of *Hopp* and shows that the

top 3 predictions of the Hopp and Woods algorithm are in fact antigenic determinants 84% of the time (*Hopp,* page 184).

[61] In the correspondence of November 4, 2014 the panel brought to the attention of the Applicant the following two references;

D1: Van Regenmortel and Pellequer, Peptide Research, 1994; 7(4): 224-8

D2: Pellequer et al, Methods in Enzymology, 1991; 203: 176-201.

[62] D1 provides criticism of antigen prediction algorithms in general, specific criticism of the Hopp and Woods algorithm, and data on the accuracy of this method and 21 other algorithms (Table 1, page 227). This data calculates the accuracy of the Hopp and Woods algorithm at only 53%. The Jameson and Wolf algorithm is actually a composite index of 5 different algorithms and the accuracy calculated for each of these ranged between 50% and 62%.

[63] D2 is a publication from the same research group as D1 and provides a similar summary of the predictive accuracy of 22 different antigenic determinant prediction algorithms, with the Hopp and Woods method being found to be 51% accurate and the Jameson and Wolf method between 48% and 58% (Table VII, page 200).

[64] It would be apparent to the skilled person reading *Hopp,* D1 and D2 that the CGK related to antigenic prediction algorithms was contentious and unsettled. D1 is a direct criticism of *Hopp,* while *Hopp* itself is a defense against criticisms of the Hopp and Woods method published in D2 and other documents (*Hopp,* page 185, left column).

[65] In their response of November 17, 2014 the Applicant provides arguments to respond to the conclusions and data of D1 and D2 (pages 7-10 of the response). In essence the Applicant argues that the approach used by D1 and D2 to evaluate the accuracy of the algorithms was incorrect and based on incomplete source data.

[66] To evaluate accuracy, D1 and D2, as well as *Hopp,* analyzed the ability of the algorithms to correctly predict previously validated antigenic determinants in a small pool of well characterized source proteins. The way this analysis was performed, however, was

different in D1 and D2 versus *Hopp*. The Applicant argues that D1 and D2 performed the analysis incorrectly because they considered predictions in regions of the source proteins that did not have a known antigenic determinant to be erroneous. For example, the Applicant states that "the absence of a reported epitope is not the same as concluding that protein region is not antigenic at all" (top of page 8, response of November 17, 2014). The Applicant favors the analysis of *Hopp* which considered predictions in regions without a reported antigenic determinant to be of unknown certainty and not part of the calculation of accuracy.

[67] In the panel's view the skilled person would give less weight to the accuracy rating reported in *Hopp*, compared to the lower accuracy ratings in D1 and D2, because the *Hopp* rating is only for the top 3 predictions. According to the Applicant's description, the SEQ ID NO: 11076 fragment was among 15 different antigenic determinants predicted by the Hopp and Woods algorithm for the 741 ORF (page 291-292) but their scores and rankings were not disclosed. Consequently, the skilled person would not know what the accuracy of the prediction was, based on *Hopp*. Conversely, D1 and D2 estimate accuracy by considering all of the predictions made by the algorithm, not just those with the highest score.

[68] In turning to D1 and D2 we must then determine whether the skilled person would consider the accuracy ratings they report for the algorithms to be sufficient to support a sound line of reasoning that the claimed polypeptide comprises a Neisserial antigenic determinant. D1 and D2 do not consider these values to be high enough to form reliable predictions of antigenic determinants. For instance, D2 concludes that "none of the prediction algorithms in current use gives a high level of correct prediction" (page 197) and "in the absence of any clear-cut superiority for any of the prediction methods in current use (Table VII), there is obviously a need for improving existing algorithms and prediction scales" (page 201).

[69] Given the contentious nature of the CGK related to antigenic prediction algorithms at the filing date, the lower relevance of the accuracy rating of *Hopp* versus that of D1 and D2, and the opinion expressed in D1 and D2 that the algorithms were generally unreliable based on the low level of accuracy reported (ranging from 48% to 62% as per paragraphs 62 and 63 above), the skilled person would not consider the line of reasoning that the

claimed polypeptide comprises an antigenic determinant of the full length 741 protein to be sound.

[70] Consequently, in our view the skilled person would not consider the utility of the claimed polypeptide to be soundly predicted.

Conclusion

[71] The requirements for a sound prediction of utility for claims 1, 2, 4 and 5 are not met and therefore these claims do not comply with section 2 of the *Patent Act.*

[72] Likewise, claims 7 and 8, which are dependent on claims 1 and 4 respectively, lack a sound prediction of utility and also do not comply with section 2 of the *Patent Act*.

[73] Pharmaceutical composition claims 3 and 6, which promise at least the same level of utility as claims 1, 2, 4 and 5, lack a sound prediction of utility and also do not comply with section 2 of the *Patent Act*.

RECOMMENDATION OF THE PANEL

[74] The panel recommends that the ’321 application be refused because the claims on file lack utility and do not comply with section 2 of the *Patent Act.*

Michael O’Hare	Cara Weir	Stephen MacNeil
Member	Member	Member

DECISION

[75] I concur with the Patent Appeal Board's findings and its recommendation that the '321 application be refused because the claims on file do not comply with the *Patent Act*.

[76] In accordance with section 40 of the *Patent Act*, I refuse to grant a patent for 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.

Agnès Lajoie

Assistant Commissioner of Patents

Dated at Gatineau, Quebec,

this 21st day of July, 2015