Commissioner=s Decision #1354
Décision du Commissaire #1354

TOPIC: O00; B20; B00
SUJET: O00; B20; B00

Application No. : 2,252,439
Demande n^{o} : 2,252,439

IN THE CANADIAN PATENT OFFICE

DECISION OF THE COMMISSIONER OF PATENTS

Patent application number 2,252,439 having been rejected under subsection 30(3) of the *Patent Rules*, has consequently been reviewed in accordance with subsection 30(6) of the *Patent Rules* by the Patent Appeal Board and the Commissioner of Patents. The findings of the Board and the ruling of the Commissioner are as follows:

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INTRODUCTION

[1] Patent application number 2,252,439 relates to plant-based vaccines useful against enteric bacterial pathogens. It stands rejected for three reasons:

(1) because certain claims use an indefinite article and are therefore ambiguous;

(2) because the invention has been claimed too broadly in certain claims since it embraces not only the use of a particular protein found in one strain of pathogen, but also ones like it that are found in other types of pathogens; and,

(3) because the claimed invention is considered obvious in view of two prior publications.

[2] The application has been referred to the Patent Appeal Board for review. Although offered, the Applicant declined an opportunity to be heard before the Board and has elected not to make any further submissions. The review is therefore based on the record as it presently stands.

BACKGROUND

[3] Enteric bacterial pathogens can cause serious illness. So-called Ahamburger disease@ is one such illness that is often contracted by ingesting undercooked ground beef. The pathogen responsible for the disease is a virulent strain of the bacterium *E. coli*.

[4] The inventors of the subject patent application propose that plants be genetically engineered to produce a vaccine against such pathogens. The idea is that a patient would eat the engineered plant material, thus triggering the production of antibodies in their gastrointestinal mucosa which would prevent the germs from attaching at their sites of infection. The active agent in the vaccine (the antigen) would be an Aintimin@ B a type of protein found on the outer surfaces of enteric bacterial pathogens, which are required in order for the bacteria to adhere to intestinal

cells and eventually cause disease.

CLAIM CONSTRUCTION

[5] We begin our analysis with a purposive construction of claims in order to determine their meaning and scope.

[6] During purposive construction, the elements of the claimed invention are identified as either essential or non-essential: *Free World Trust v Electro Santé Inc*, 2000 SCC 66 [*Free World Trust*].

The Person Skilled in the Art and the Relevant Common General Knowledge

[7] Claims are construed in an informed and purposive manner from the viewpoint of the notional Aperson skilled in the art@ in light of that person=s common general knowledge and based on the patent specification itself without resort to extrinsic evidence (*Free World Trust* at para. 66). Likewise, the four-step approach to obviousness set out by the Supreme Court in *Apotex Inc v Sanofi-Synthelabo Canada Inc*, 2008 SCC 61 [*Sanofi*] mandates an analysis from the same viewpoint.

[8] The Examiner prepared a Summary of Reasons (SoR), which was supplied to the Applicant, that follows the four-step approach. It identifies the skilled person as Aa research team committed to scientific discovery and includes immunologists familiar with enterohemorrhagic *E. coli* (EHEC) infections and concerned with the development of an effective EHEC vaccine, as well as research scientists with experience in molecular biology.@ We agree with this definition and note that the skilled person=s team does not include a scientist familiar with plant-based vaccine technology, nor does it seem that it could, given the infancy of the plant-based vaccine art and the information provided by the Applicant during prosecution to that effect.

[9] As a point of clarification, an A**e**ntero**h**emorrhagic ***E***. ***c****oli* (EHEC) infection@ is the medical term for bloody diarrhea or, more colloquially, Ahamburger disease.@ Although the description indicates that it is a preferred target disease, it is not the sole focus of the claims of the

application. Related conditions caused by other pathogens, such as EPEC strains of *E. coli* (**e**ntero**p**athogenic **E**. **c**oli B a diarrheal disease that typically affects infants), are also discussed in the description and have been claimed. As such, it is fair to say that the skilled person would be familiar with infections caused by enteric bacterial pathogens in general and would be concerned with developing vaccines against these other pathogens as well.

[10] As for the common general knowledge, the SoR states that the Aperson skilled in the art would be aware of the needs in the field and motivated to find an effective vaccine against EHEC.@ We generally agree with this statement. However, we do not find the suggestion which immediately follows to be accurate; i.e., to the effect that the two particular publications (referred to as documents AD1@ and AD2@) cited in the Final Action as state of the art for the purpose of obviousness under section 28.3 of the Act would constitute common general knowledge:

> Therefore, prior art concerned with intimin, in particular D1 [the *McKee* dissertation], which establishes the pivotal role of intimin in bacterial adherence would be known to said person.

[11] The two prior art documents, in particular document D1, thus appear to have been identified as forming part of the common general knowledge, but have also been identified as forming part of the state of the art under step 3 of the *Sanofi* approach to obviousness.

[12] Although the distinction between common general knowledge and the state of the art Atends to diminish in modern times because of the sophistication of search engines and the availability of electronic publications and databases@, it remains that Athe degree to which a particular publication was >generally regarded as a good basis for further action= ... is still very relevant when one considers issues such as obviousness@: *Eli Lilly and Company v Apotex Inc*, 2009 FC 991 at para. 104 [*Eli Lilly*]. A piece of particular knowledge becomes common general knowledge Awhen it becomes part of their common stock of knowledge relating to the art@: *British Acoustic Films Ltd et al v Nettlefold Productions*, (1936) 53 RPC. 221, at 250 cited with approval in *General Tire & Rubber Co v Firestone Tyre & Rubber Co Ltd*, [1972] RPC 457, [1971] FSR 417 (UKCA.), in turn cited with approval in *Eli Lilly* at para. 97.

[13] With respect to document D1, we note that it is a particular doctoral dissertation whose simple existence would not likely have been widely known in the art and there is nothing on record to suggest otherwise. With respect to D2, we note that it is a particular patent application which post-dates D1 and that it does not support, as explained more thoroughly as part of our

obviousness analysis, a finding that intimin was commonly accepted as playing the pivotal role in bacterial adherence. According to D2, another molecule played that role and intimin was not the primary molecule. Therefore, the common general knowledge does not appear to acknowledge that the molecular mechanism of bacterial adherence had unquestionably been established.

[14] Beyond knowledge of EHEC strains of *E. coli*, we also believe the common general knowledge more generally includes knowledge of enteric bacterial pathogens including, for example, knowledge of EPEC strains of *E. coli*. But it has not been established that methods of preparing plant-based vaccines formed part of the skilled person=s common general knowledge.

[15] We therefore conclude that the common general knowledge includes the knowledge that EHEC and EPEC and other enteric bacterial pathogens somehow adhere to intestinal cells and that adherence involves cellular molecules.

The Claims

[16] The application claims the therapeutic use of one particular type of cellular molecule found on the surface of enteric bacterial pathogens: intimin proteins. These types of proteins are encoded by A*eae*@ (***E****. coli* **a**ttach and **e**ffface) genes and the specification teaches that intimin proteins are responsible for pathogen adherence and are associated with the production of Aattaching and effacing@ (AA/E@) lesions at sites of adherence. On that basis the specification goes on to teach that plants can be genetically engineered to produce an intimin protein by first incorporating an *eae* gene into a plant DNA vector, followed by transformation of plant cells and, ultimately, the regeneration of whole plants. The plant material, or portions of it, can then be fed to subjects, thereby generating a protective mucosal immune response in the gastrointestinal tract.

[17] Claim 1 of the application is representative of the claimed invention:

> 1. Use of a plant, or a portion thereof, transformed with a vector comprising an *eae* gene chosen from the *eae* genes of Enteropathogenic *Escherichia coli* (EPEC), Enterohemorrhagic *Escherichia coli* (EHEC), *Citrobacter freundii*, and *Hafnia alvei*, or a portion of said *eae* gene encoding at least the C-terminal third of the protein product of said *eae* gene, which retains the ability to bind to gastrointestinal epithelial cells, wherein said plant or portion thereof expresses said *eae* gene or portion thereof from said vector, for stimulation of a protective immune response in a patient against

> pathogenic bacteria expressing an *eae* gene. [emphasis added]

[18] One key aspect concerning the meaning and scope of claim 1 is worth explaining.

[19] As we have emphasized in the claim, we note that it initially refers to Aan *eae* gene@ chosen from a list of four such genes but concludes with a second reference to Aan *eae* gene.@ Although the claim twice mentions Aan *eae* gene@, each occurrence is in reference to a different claim element. The first occurrence is a reference to an *eae* gene *per se* while the second is used to describe another element of the claim: a Abacterial pathogen@ which happens to express an *eae* gene. This language provides a broader claim than one in which the *eae* gene expressed in the pathogenic bacteria is the same as Athe chosen *eae* gene@. This means that, according to the Applicant, immunization of a subject with an intimin protein expressed in a plant from the Achosen@ *eae* gene will produce antibodies that are protective and cross-reactive, not just against bacteria expressing the particular chosen *eae* gene, but more broadly against any bacterial pathogen that expresses an *eae* gene. As will become apparent, this is important to remember.

[20] There was no dispute between the Examiner and the Applicant as to the essentiality, or not, of the elements of claim 1. Since we see no reason to conclude otherwise, we will therefore proceed on the basis that all of the elements are essential.

ISSUE 1: CLAIM AMBIGUITY

[21] The first issue can be dealt with in relatively short order. It concerns ambiguity in claims 1, 3, 14 and 22 and compliance with subsection 27(4) of the *Patent Act*. That subsection reads:

> The specification must end with a claim or claims defining distinctly and in explicit terms the subject-matter of the invention for which an exclusive privilege or property is claimed.

[22] Claim clarity can be assessed based on the guidance in *Minerals Separation North American Corp v Noranda Mines Ltd.*, [1947] Ex.C.R. 306 at 352 wherein Thorson P. stated:

> By his claims the inventor puts fences around the fields of his monopoly and warns the public against trespassing on his property. His fences must be clearly placed in order to give the necessary warning and he must not fence in any property that is not his own.

> The terms of a claim must be free from avoidable ambiguity or obscurity and must not be flexible; they must be clear and precise so that the public will be able to know not only where it must not trespass but also where it may safely go.

[23] According to the Final Action, the claims lack clarity since they first refer to Aan *eae* gene@ selected from a list of four such genes but also conclude with a second reference to Aan *eae* gene@ that is not so limited.

[24] The claim language is said to be problematic because Athe second introduction (use of an indefinite article) of an element already introduced causes ambiguity.@ To remedy the problem, the Final Action asks that the claim be amended to use a definite article in the second instance of the term, e.g., Athe chosen *eae* gene@, not Aan *eae* gene.@

[25] The Applicant takes the position that no amendment is necessary and says that the claims are directed to a skilled artisan who, with a mind willing to understand the invention, Awould understand the meaning and scope of claims 1, 3, 14 and 22, and in particular that the final clause of the claims provides functional language to specify that the mentioned pathogenic bacteria expresses an *eae* gene regardless of the previously-mentioned *eae* genes selected from a specific group.@

Analysis

[26] In our estimation there is no lack of clarity in the claims. As explained above as a matter of claim construction, each occurrence of the term Aan *eae* gene@ is in reference to a different claim element. That this has the effect of defining broader claims than ones in which both instances of the term A*eae* gene@ refer to the same element does not mean that the claims are unclear. By adopting this language, the Applicant has deliberately indicated that immunization of a subject with an intimin protein expressed in a plant from the Achosen@ *eae* gene will produce a broadly protective immune response. Any concern in that regard will be addressed, as explained below, as a question of utility and sound prediction.

[27] The claims are therefore compliant with subsection 27(4) of the Act.

ISSUE 2: OVERBREADTH OF CLAIMS

[28] The second issue concerns whether the scope of claims 1, 3, 14 and 22 is too broad. In

general, a claim may be considered too broad for a variety of reasons, including in view of the prior art (i.e., because the applicant has fenced-off subject matter that is known or obvious) or in view of what has been disclosed in the description. The present issue is of a type that falls within the latter class.

[29] There are two types of claiming too broadly in view of what has been disclosed in the description. One type is to find the claim too broad because information necessary to enable the skilled person to make and practise the invention across its entire breadth has not been provided in the description. This is best termed an *Ainsufficiency@* problem under subsection 27(3) of the *Patent Act*.

[30] A second type of over-claiming can arise if a claim encompasses subject matter whose utility has not been established based on the information found in the description B something that the courts currently say is a separate and distinct *utility* problem under section 2 of the *Patent Act*. It is apparent from the prosecution that the perceived defect in the present case specifically relates to this second type.

[31] We gather from the Final Action and SoR that it did not appear to the Examiner that, in view of the information provided in the description, a Asound prediction of utility@ existed upon which the utility of everything within the scope of the claims could be based. Consistent with subsection 17.03.04 of the *Manual of Patent Office Practice* (AOffice actions relating to utility@) a rejection under section 84 of the *Patent Rules* and subsection 27(3) of the *Patent Act* was considered appropriate because the claims were too broad and did not appear to be Afully supported by the description.@ That subsection also encourages the identification of section 2 of the Act when making such rejections. Based on the current state of the law, we now know that an identification of such defects under section 2 of the Act is clearly warranted.

[32] In response to the Final Action, the Applicant likewise framed the issue as one of sound prediction of utility.

[33] No matter how the issue has been identified during prosecution, we believe that the correct underlying legal principles of sound prediction have been considered and debated by both the Examiner and the Applicant. Therefore, the second issue can be resolved by considering whether the *AZT* test (*infra*) for predicted utility has been satisfied. Further arguments, submissions or separate analyses on this point are not required. We would clarify, however, that the issue actually falls under section 2 of the Act.

[34] In order to comply with section 2 of the Act, as of the filing date of the application there must be either a demonstration or a sound prediction of the utility of everything that falls within the scope of a claim: *Apotex Inc. v. Wellcome Foundation Ltd.*, 2002 SCC 77 [*AZT*]. In the present case, there is a lack of demonstrated utility for everything within the scope of the claim and the Applicant must therefore rely on a sound prediction to establish utility (see *Teva Canada Ltd v Pfizer Canada Inc*, 2012 SCC 60, at para. 37).

[35] An invention that relies on a sound prediction of utility must satisfy three requirements (*AZT*):

> (1) there must be a factual basis for the prediction;
>
> (2) the inventor must have at the date of the patent application an articulable and Asound@ line of reasoning from which the desired result can be inferred from the factual basis; and
>
> (3) there must be proper disclosure.

[36] In order to consider whether the Applicant=s prediction is sound, it is first necessary to identify the claimed invention=s predicted utility. Predictions are measured taking into account any explicit Apromises@ made in the specification; however, Aif there is no explicit promise of a specific result, then a mere scintilla of utility will do@ (see *Sanofi-Aventis v Apotex Inc*, 2013 FCA 186 at para. 50).

Analysis

What is the predicted utility?

[37] According to the description, Aan object of the invention is to express intimin in a host organism, which host will be administered or fed, directly or after processing, to animals or humans in order to stimulate an immune response to intimin@ (page 12, last paragraph). The immune response will protect the host against illness caused by EHEC and other pathogens that have the ability to bind epithelial cells through proteins having some degree of homology with EHEC intimin (page 12, last paragraph). The degree of protection is unimportant; it is not a promise of the specification, and will vary with the type of intimin used and the particular species treated (page 13, second paragraph).

[38] The claimed invention is limited to an intimin-expressing *eae* gene which is chosen from four such genes, or portions thereof that retain binding functionality.

[39] The claims conclude with an indication that the engineered plant material will stimulate an immune response which protects subjects against Apathogenic bacteria expressing an *eae* gene@; meaning that the intimin protein expressed from the chosen *eae* gene is predicted to produce a broad immune response that will be protective, to some degree, against a variety of such pathogens. For instance, expression of EHEC intimin will not only protect against EHEC pathogens, but will also cross-protect against EPEC, *Citrobacter freundii, Hafnia alvei* and other types of *eae*-expressing pathogens.

Factual Basis

[40] The Examiner and the Applicant disagreed on whether the factual basis for the predicted utility is adequate. Resolution of the second issue turns primarily on this first part of the *AZT* test. The dispute centres on the nature of the intimin protein expressed by the chosen *eae* gene; the plant-based nature of the invention is not in dispute.

[41] EHEC strains of *E. coli* are responsible for hamburger disease. The use of its *eae* gene and corresponding intimin protein are discussed at length in the specification, and the Final Action takes no issue with the operation of that particular gene and protein in the stimulation of an immune response which provides protection when consumed by patients in plant-expressed form. However, the Final Action does take issue with the fact that the claims include an *eae* gene not only from EHEC strains, but also homologous *eae* genes from other pathogenic *E. coli* strains and bacteria. The contentious homologous *eae* genes mentioned in the claims are those that were known to exist at the time of filing. They are derived from *Citrobacter freundii, Hafnia alvei*, and EPEC strains of *E. coli*.

[42] The Final Action concludes that the successful operation of the invention, when carried out using these other homologues, is not soundly predicted: Athe underlying factual support is insufficient to provide a basis from which a sound line of reasoning for the predicted use of the proteins encoded by the *eae* genes of EPEC, *Citrobacter freundii* and *Hafnia alvei* for stimulation of a protective immune response can be inferred.@

[43] The Final Action acknowledges that the contentious *eae* homologues encode intimin proteins whose C-terminal regions behave in a manner similar to that of EHEC intimin, in that

they were also known to play a role in adhesion to epithelial cells. It also acknowledges that the description discloses that anti-EHEC intimin antibodies are capable of blocking EHEC attachment to epithelial cells.

[44] However, the Final Action notes that the immunogenic site(s) (the eptiope) on the EHEC intimin protein that is responsible for producing the blocking antibodies has not been disclosed. It further notes that the C-terminal regions of the other intimin proteins have limited amino acid sequence identity with the EHEC intimin protein. Thus, it is argued that there is no disclosure of a common structural element that would be capable of producing a protective immune response and the skilled person would be unable to know or predict whether the *eae* homologues would have the same utility as EHEC *eae*.

[45] The Applicant maintains that there is a sound prediction for the operability of the *eae* homologues, noting that the specification teaches that intimin protein is necessary for pathogens to adhere to human epithelial cells and cause characteristic Aattaching and effacing@ (AA/E@) lesions at their point of attachment. The specification also mentions that *eae* genes and intimin proteins are structurally similar and that the role of the C-terminal portion of the intimin protein in cell adhesion was well established at the time the application was filed.

[46] In our view, both the Examiner and Applicant are correct in their line of thinking, but neither completely so. In brief, we find that the factual basis is sufficient to predict that expression of the *eae* gene chosen to prepare the vaccine will produce a protective immune response against a bacterial pathogen expressing the same chosen *eae* gene but not, as the claims broadly indicate, against any bacterial pathogen that expresses an *eae* gene. The claims are too broad on the basis of the latter prediction.

[47] We come to these conclusions, as more fully explained below, after having considered the facts as revealed in the specification and several scientific articles discussed therein.

[48] The Examiner correctly reasons that there is structural dissimilarity in the critical C-terminal binding regions of the intimin proteins mentioned in the claims. This means the skilled person would not expect that expression of one type of intimin protein would produce antibodies cross-protective against the intimin found on another *eae* expressing pathogen because the two intimin proteins would not be antigenically similar enough.

[49] This finding is supported by an article published by Jerse and Kaper (1991; Infect. Immun. 59: 4302) discussed on page 3 of the description. The article indicates on page 4308 that

anti-EPEC intimin antibodies are not able to bind to EHEC intimin:

> Although EHEC strain 933 (O157:H7) and strain RDEC-1 both hybridized with the *eae* [DNA] probe, neither produced detectable levels of proteins that were recognized by the serum raised to the [EPEC intimin] 128-kDa Eae-PhoA fusion protein.

[50] This observation is said by the authors to be consistent with those of other researchers (Sherman et al., Infect. Immun. 1991, 59: 890) who Areported that antiserum specific for the EHEC 94-kDa [intimin] protein was unable to inhibit the FAS activity of EPEC strain E2348/69.@ The authors conclude that Aalthough [EPEC and EHEC intimins] may serve similar functions in the production of A/E lesions, they differ antigenically.@

[51] An article published by Yu and Kaper (1992, Mol. Microbiol. 6: 411; discussed on page 26 of the description) is to the same effect. That article concludes with following statement:

> These results suggest that a 94 kDA protein encoded by *eae* genes of both EPEC and EHEC strains mediate adhesion and A/E activity on eukaryotic cells but that immunodominant epitopes are contained in the divergent C-terminal ends.

[52] Therefore, there is no basis for predicting immunological cross-reactivity between EPEC and EHEC intimin proteins B the two are antigenically dissimilar in their key C-terminal binding regions even though they are structurally similar elsewhere and perform similar functions. Since EHEC intimin and EPEC intimin are the two most similar to each other of those mentioned in the claims, the same conclusions can be drawn in respect of all intimins.

[53] But this does not mean, as the Final Action suggests, that the claims must be limited to the *eae* gene from EHEC *E. coli*. The Applicant points out that EHEC *E. coli,* EPEC *E. coli*, *Citrobacter freundii* and *Hafnia alvei* have common modalities of pathogenesis and all produce the same characteristic Aattaching and effacing A (AA/E@) lesions at their point of attachment. The articles referred to in the description establish these facts. There is also agreement between the Applicant and the Examiner that expression of EHEC intimin will protect at least against EHEC *E. coli* because there is necessarily antigenic identity between the immunizing intimin and the one found on the infecting organism. It therefore stands to reason that expression of EPEC intimin will likewise generate antibodies protective at least against EPEC *E. coli*. The same would be true of *Citrobacter freundii*, or *Hafnia alvei* intimin protein (or the functional C-terminal portion of any one of the intimin proteins). This is further supported by the second

paragraph on page 4 of the description that describes a study which indicates that prior exposure to EPEC intimin protects patients against subsequent EPEC *E. coli* infections (see Levine et al., 1985, J. Infect, Dis. 152: 550).

[54] These facts mean that the invention need not operate immunologically in precisely the same way for each chosen *eae* gene. The admitted utility of the invention in respect of EHEC intimin does not mean that the invention, when worked with another chosen intimin, must stimulate an immunological response completely equivalent to that of EHEC intimin; i.e., in the sense that there must be immunological cross-reactivity amongst all the claimed intimins. That is a fine level of commonality that the description neither prescribes nor would have been understood by the skilled person to be something essential for the successful operation of the invention. Commonality amongst the claimed intimins rests at least in their A/E modality of pathogenesis, meaning that, contrary to the Final Action, the particular immunoreactive sites found in the C-terminal portion of the EHEC intimin protein (Aepitopes@, or Acommon structural element@) need not be found in the other non-EHEC intimins mentioned in the claims. The claims need not be restricted to the *eae* gene from EHEC *E. coli* (as suggested in the Final Action) because the *eae* gene chosen to prepare the vaccine is soundly predicted to be useful for protecting against bacteria expressing the same *eae* gene.

[55] In sum, the factual basis provided in the description is insufficient to allow the skilled person to conclude that expressing one type of intimin gene in a plant will protect patients against bacterial pathogens that express any type of intimin gene, but is sufficient to predict that protection will be afforded against a pathogen expressing the particular type of intimin gene which has been chosen to prepare the plant-based vaccine.

Line of reasoning

[56] The line of reasoning from which the desired results can be inferred was not specifically debated by either the Examiner or the Applicant. For the purposes of this decision, suffice to say that, in view of the discussion above, there does not exist a sound line of reasoning for inferring that a protective immune response would be stimulated by a chosen *eae* gene against <u>any type</u> of pathogen expressing an *eae* gene.

[57] At the same time, there is a sound line of reasoning that supports the inference that a protective immune response would be stimulated against a pathogen that expresses the <u>same</u>, chosen *eae* gene, regardless of the fact that the chosen *eae* gene is not that from EHEC *E. coli* but is instead a homologous *eae* gene from *Citrobacter freundii*, *Hafnia alvei*, or EPEC strains of *E.*

coli.

[58] It is thus apparent that the claims can be remedied in a manner consistent with our conclusions on sound prediction if the second instance of the term A*eae* gene@ were to be amended in the manner suggested by the Examiner (albeit as a matter of clarity; see the first issue discussed above) in order to refer to Athe chosen *eae* gene@ instead of more generally Aan *eae* gene.@ In that way the claims would be limited to subject matter whose utility is soundly predicted.

Disclosure

[59] This aspect of the *AZT* test was also not specifically debated by the Examiner and the Applicant. We are satisfied that this part of the *AZT* test is met because the facts and line of reasoning would be evident to the skilled person after having read the specification.

[60] In summary, the claimed invention is not compliant with section 2 of the Act, but as noted above, the claims can be amended so as to comply.

ISSUE 3: OBVIOUSNESS

[61] All of the claims on file are considered by the Examiner to be obvious. Claim 1 is a medical use claim representative of the inventive concept. It shares features common to the other independent claims on file which are directed to things such as plant DNA expression constructs, plant cells and methods of making the transformed plant cells. Neither the Examiner nor the Applicant drew a distinction between claim 1 and the other claims. Accordingly, in this case they will all either stand or fall together based on the outcome of our analysis of claim 1.

[62] Section 28.3 of the *Patent Act* sets out the conditions under which a claim may be found to be obvious:

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

(a) in such a manner that the information became available to the public in Canada or elsewhere.

[63] Our obviousness assessment follows the four-step approach set out in *Apotex Inc v Sanofi-Synthelabo Canada Inc*, 2008 SCC 61:

(1) (a) Identify the notional Aperson 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 Astate 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

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

[64] This first step is common to our claim construction and has been explained above.

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

[65] The SoR states that the inventive concept is Athe provision of a plant based vaccine expressing recombinant intimin as the essential component for the stimulation of a protective immune response against a pathogenic bacteria expressing an intimin protein.@

[66] We believe this statement is accurate but see value in pointing out that the inventive concept more broadly includes the use of an intimin protein, not only from EHEC *E. coli*, but also intimins from EPEC *E. coli*, *Citrobacter freundii* and *Hafnia alvei*. The inventive concept also includes the use of the C-terminal third of any of these proteins which retain the ability to bind to gastrointestinal epithelial cells. This is evident from the language of claim 1.

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

[67] The obviousness assessment outlined by the Examiner is based on the combined disclosures of two prior art references which are referred to as documents AD1@ and AD2@ in the Final Action.

[68] The SoR states that the Adifference between the state of the art and the inventive concept is the use of intimin as the sole, essential component in an EHEC vaccine.@ In our view, that is one consideration, but not the only difference.

Document D1

[69] Document D1 is a doctoral dissertation entitled AAdherence of Enterohemorrhagic *Escherichia coli* to Human Epithelial Cells: The Role of Intimin@ (submitted to the Faculty of the Department of Microbiology and Immunology Graduate Program of the Uniformed Services University of the Health Sciences F. Edward Hébert School of Medicine, April 1995). It was authored by one of the inventors of the present application, Marian McKee, and deals in detail with the intimin protein of the *E. coli* EHEC pathogen. Based on her research, she concludes that it is required for intimate adherence of EHEC strains to intestinal cells and that it plays an essential role in pathogenesis. She therefore proposes that the protein would be a suitable vaccine candidate.

[70] While D1 does not generally discuss the use of an intimin from a variety of enteric bacterial pathogensBin a manner similar to the way claim 1 broadly encompasses a variety of intiminsBit clearly discloses the use of one intimin that falls within the scope of the claims. There is no difference between D1 and the inventive concept in that respect.

[71] There was disagreement between the Examiner and the Applicant over one difference between D1 and the claimed invention; that is, whether, as the Examiner says, the dissertation teaches the use of intimin as the sole, essential critical immuno-active component of an EHEC vaccine or, as the Applicant says, it teaches the use of intimin as merely one of several vaccine components.

[72] In our view, there is no difference in this respect between the inventive concept and D1. This

is because D1 speaks of an Aideal@ or Abest@ vaccine as one that includes intimin as well as other immuno-active components, such as inactivated *E. coli* toxins. The skilled person would thus read D1 as clearly focussing on using intimin in a vaccine, meaning that D1 indicates intimin could be used as the sole immuno-active component of a vaccine, albeit not necessarily the best or ideal EHEC vaccine. We note also that the inventive concept does not exclude the presence of other immuno-active components. It is only essential that the vaccine minimally include one of the listed intimin proteins.

[73] The key difference between the inventive concept and D1 is the lack of discussion in D1 of a plant-based vaccine expressing a recombinant intimin protein.

Document D2

[74] Document D2 is international patent application number WO96/00233 jointly filed by a children=s hospital and a state university research foundation. It was published January 4, 1996 (i.e., after D1) and is entitled A*Escherichia coli* O157:H7 Epithelial Adhesin@. The ABackground of the Invention@ discusses the state of the art and the various cellular molecules, including intimins, that were then thought to be potentially involved in adhesion of *E. coli* to intestinal cells. The impetus for filing the application is the discovery of a novel surface protein, termed Aadhesin@, from *E. coli* O157:H7 that the inventors implicate in pathogen colonization of bovine intestines. That protein is encoded by the A*ear*@ (**e**pithelial **a**dherence **r**egion) genetic locus. Although a main strategy is to directly inject cattle with a vaccine comprising recombinant adhesin, D2 alternatively proposes on page 17 that the adhesin antigen be produced in transgenic plants B something that brings D2 closer in line with the inventive concept of the present application.

[75] The difference between the inventive concept of the claims and D2 is that the former includes intimin proteins whereas the latter focusses on a different protein, adhesin, that bears no structural similarity to intimin. The two proteins are also encoded by different genetic loci.

[76] In summary, the differences between the inventive concept of the claims and the matter forming part of the state of the art lies in two areas: (i) with respect to D1, the plant-based means by which the vaccine is to be made; and (ii) with respect to D2, the use of an intimin protein as the active component of the vaccine.

Step 4: Do those differences constitute steps which would have been obvious to the person

skilled in the art or do they require any degree of invention?

[77] The Examiner and the Applicant disagree on the question of whether it would have been obvious for the skilled person to arrive at the inventive concept of the claims.

[78] The Examiner says that the combination of D1 and D2 yields the inventive concept. First, the Examiner argues that D1 discloses intimin as the Apivotal, essential component@ of a vaccine. We agree with the Examiner on this point because, as pointed out above, a fair reading of D1 does not lead to the conclusion suggested by the Applicant that intimin must be used in combination with other components. This is because the skilled person is not necessarily concerned with producing the best possible vaccine.

[79] The Examiner also says that the lack of disclosure in D1 of a plant-based vaccine is remedied through the disclosure of D2, which teaches this feature. It is true that D2 discloses a plant-based vaccine, but, in our view, it does so in a limited manner. Plant-based vaccines are mentioned as one of many proposed immunization methodologies and they do not feature prominently in D2.

[80] The Applicant argues that plant-based vaccines were an unpredictable art at the time the application was filed and that only two publications dealing with plant-based vaccines were available at the time. On this point we agree with the Applicant and find that plant-based vaccines would not have been commonly known to the skilled person due to the immaturity of the art. This finding is supported by the definition of the skilled person not including someone who possesses knowledge of plant molecular biology or plant-based vaccines.

[81] The Applicant also argues that the role of intimin in bacterial adherence was uncertain at the time the application was filed. The Applicant makes the case that Athere was neither unequivocal evidence nor unanimous opinion in the art regarding the role of intimin in bacterial adherence.@ In contrast, the Applicant says that the specification affirmatively points to the use of intimin as the immuno-active component to be used in a vaccine. On this point we agree with the Applicant because D2 asserts that another molecule, adhesin, played a critical role.

[82] Claim 1 accommodates two scenarios under which D1 and D2 might be combined in order to bridge the two differences summarized at para.71 and thereby conclude that the claimed invention is obvious. After having considered both, we find that neither would lead to such a conclusion.

[83] The first scenario involves starting with the later published document, D2, and considers whether the skilled person would have substituted the intimin of D1 for the adhesin of D2 in a plant-based vaccine, also as disclosed in D2. The second manner of combining the references involves starting with the earlier published document, D1, and considers whether the skilled person would have used the EHEC intimin of D1 in combination with the adhesin of D2 in a plant-based vaccine, also as disclosed in D2.

Scenario 1: Accounting for the differences between the inventive concept and the matter forming part of the state of the art by substituting the adhesin of D2 with the intimin of D1

[84] In our view, it would have been unlikely that the skilled person would have followed the path laid out under the first scenario. Key to the inventive concept is that the vaccines are plant-based. According to the definition of the skilled person, this does not fall within the common general knowledge.

[85] The skilled person could find in D2 a plant-based vaccine. To arrive at the inventive concept, the skilled person must then be led to substitute the adhesin of D2 with the intimin of D1. This would not have been likely because, as the Applicant argues, D2 discusses intimin in the ABackground of the Invention@ but points the reader away from an intimin-based vaccine:

> Some investigators have suggested that the epithelial cell adhesion of *E. coli* O157:H7 is encoded by its *eae* gene ... However, data from other groups suggest that the *eae* gene product [i.e., intimin] is not an adhesin for *E. coli* O157:H7 ... Thus, a molecule other than the *eae* gene product in *E. coli* O157:H7 appears to be the primary adhesin of *E. coli* O157:H7 for bovine epithelial cells, enabling this

human pathogen to colonize the bovine gastrointestinal tract.

[86] That is the extent of discussion of intimin in D2. The remainder of the document focusses on the use of the novel adhesin protein. As such, there would be no motivation to substitute intimin for adhesin.

[87] Furthermore, plant-based vaccines are discussed in D2 as one of many possible means of antigen delivery. At the relevant date, plants were not commonly known to the skilled person as suitable vaccine delivery platforms and that person would have been inclined to pursue more well-established methodologies, e.g., those discussed on pages 14-17.

[88] Therefore, under this first scenario, the claimed invention would not have been obvious to the skilled person. That leaves the second scenario to evaluate.

Scenario 2: Accounting for the differences between the inventive concept and the matter forming part of the state of the art by combining a plant-based adhesin of D2 and the intimin of D1

[89] Both of the differences identified at step 3 of the *Sanofi* approach can also conceivably be accommodated when claim 1 is read as including an intimin used in combination with a second antigen, which could be adhesin. So goes the reasoning that, under the second scenario, the skilled person would be motivated by D1 to adopt intimin as a vaccine. Since D1 discloses the use of additional vaccine components, the skilled person would be open to that possibility. From D2 the skilled person would have appreciated that a plant-based vaccine could be produced. With the realization that intimin is a valuable vaccine component, the skilled person would then have genetically engineered plants to express both an intimin and adhesin.

[90] However, there are problems with this line of reasoning and, on the balance of probabilities, it is difficult to see it as a scenario that would render the claimed invention obvious.

[91] We agree that the skilled person would reasonably see from D1 that multi-component vaccines are Aideal@ and possible because the last paragraph of that document suggests the use

of intimin in combination with other known antigens, e.g., inactivated ASLT@ toxins. However, D1 does not, and cannot by itself, disclose or even suggest an ideal multi-component vaccine based on a combination of intimin and adhesin proteins because the latter=s existence was not known to the author of D1 (as noted earlier, D2 post-dates D1). This, and the need for a teaching of a plant-based vaccine, means that the skilled person could not avoid considering D2 in order to arrive at the inventive concept.

[92] However, we find that the skilled person would not be inclined to attempt to formulate a multi-component vaccine because such vaccines typically arise only after the feasibility of single component vaccines have been established. In that regard, it is apparent from both D1 and D2 that the skilled person was concerned with first identifying the primary factor that was involved in bacterial adherence and using that factor to immunize subjects. Single component vaccines of any type had not been established in the art and it was not clear which antigens might be combined in order to generate an ideal, or improved, vaccine. D1 makes this point on page 165 where it is stated that: AThe role of the other putative adhesins described for EHEC must be firmly established before these factors can be considered as additional vaccines candidates. . .@. Since neither intimin nor adhesin had been firmly established in the art as the key factor responsible for adhesion, a multi-component vaccine would have been that much more elusive.

[93] Consequently, the skilled person would not be inclined to attempt to generate a more complex multi-component vaccine using a sophisticated plant-based system which itself had only been pioneered in the relatively recent past.

Overall Conclusion on Obviousness

[94] In sum, we conclude that the differences between the inventive concept and each cited document cannot be bridged through a reasonable combination of the two. Claim 1 would not therefore have been obvious to the skilled person. The same conclusion applies in respect of the other claims on file.

[95] Before leaving the issue of obviousness we wish to address one additional argument presented in the Final Action. It is based on the grounds that no examples of plant-based intimin vaccines have been provided and that, absent testing of such vaccines, the Applicant Ahas failed to demonstrate any unexpected biological advantages@ that would render the claimed invention non-obvious over D2 and common general knowledge.

[96] There is no general requirement in the *Patent Act* to disclose unexpected advantages. However, in the case of a selection patent, the courts have decided that the recognition of an unexpected advantage forms the basis of the invention and must therefore be disclosed (see *Sanofi* at para. 114; *Eli Lilly Canada Inc v Novopharm Ltd*, 2010 FCA 197 at para. 78). The claimed invention in present case is not a subset, or selection, of a broader previous disclosure and should not be considered *prima facie* obvious on that basis. There is no need in the present case to disclose unexpected advantages in order to support a finding of non-obviousness because, even absent a consideration of any advantages, the claimed invention is not obvious when D2 is considered in light of D1 and the common general knowledge.

[97] Accordingly we find that the application complies with section 28.3 of the Act.

RECOMMENDATION OF THE BOARD

[98] We recommend that the application be refused for lack of compliance with section 2 of the *Patent Act* unless the Applicant submits an amendment under subsection 31(*c*) of the *Patent Rules* such that claims 1, 3, 14 and 22 conclude with a reference to Athe chosen *eae* gene@ instead of Aan *eae* gene@.

Ed MacLaurin	Paul Fitzner	Cara Weir
Member	Member	Member

DECISION OF THE COMMISSIONER

[99] I concur with the findings and the recommendation of the Board. I hereby inform the Applicant that, in order to comply with section 2 of the *Patent Act*, the Applicant must submit an amendment under subsection 31(*c*) of the *Patent Rules* such that claims 1, 3, 14 and 22 conclude with a reference to Athe chosen *eae* gene@ instead of Aan *eae* gene@. The amendment under subsection 31(*c*) of the *Patent Rules* must be submitted within three months of the date of this decision failing which it is my intention to refuse the application.

Sylvain Laporte

Commissioner of Patents
Dated at Gatineau, Quebec
this 29th day of November, 2013