Citation: The Curators of the University of Missouri (Re), 2024 CACP 2
Commissioner's Decision #1661
Décision du commissaire nº 1661
Date: 2024-01-11

TOPIC:	B00	Ambiguity or indefiniteness (incomplete)
	G00	Utility
	O00	Obviousness

SUJET :	B00	Caractère ambigu ou indéfini description (incomplet)
	G00	Utilité
	O00	Évidence

Application No. 2836288
Demande nº 2 836 288

IN THE CANADIAN PATENT OFFICE

DECISION OF THE COMMISSIONER OF PATENTS

Patent application number 2,836,288 having been rejected under subsection 199(1) of the *Patent Rules* (SOR/2019–251), has consequently been reviewed in accordance with paragraph 86(7)(c) of the *Patent Rules*. The recommendation of the Patent Appeal Board and the decision of the Commissioner are to refuse the application.

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INTRODUCTION

[1] This recommendation concerns the review of rejected Canadian patent application number 2,836,288, which is entitled “Porcine reproductive and respiratory syndrome virus resistant animals”. The Curators of the University of Missouri is the sole Applicant. A review of the rejected application has been conducted by a Panel of the Patent Appeal Board (the Board) pursuant to paragraph 86(7)(c) of the *Patent Rules*.

[2] As explained in more detail below, our recommendation is that the Commissioner of Patents refuse the application.

BACKGROUND

The application

[3] The present application was filed under the Patent Cooperation Treaty (PCT) and has an effective filing date in Canada of May 16, 2012. It was laid open to public inspection on November 22, 2012.

[4] The claims of the rejected application relate to genetically modified swine cells comprising inactivating mutations in one or both alleles of a *CD163* gene, wherein swine comprising said genetically modified swine cells exhibit increased resistance to a porcine reproductive and respiratory syndrome virus (PRRSV).

[5] The application has 70 claims on file that were received at the Patent Office on December 23, 2020.

Prosecution history

[6] On September 24, 2021, a Final Action was written under subsection 86(5) of the *Patent Rules*. The Final Action states that the subject-matter of claims 1 to 70 on file at the time of the Final Action is obvious contrary to section 28.3 of the *Patent Act* and that claims 1, 8 to 13, 15, 31, 34, 52, 59 and 61 are also indefinite and do not comply with subsection 27(4) of the *Patent Act*.

[7] The Response to the Final Action dated January 24, 2022 disagrees with the

obviousness assessment, addresses the indefiniteness issues and further includes an amended claim set containing proposed claims 1 to 69 (proposed claims set-1), it submits is allowable.

[8] On September 15, 2022 the application was forwarded to the Patent Appeal Board for review under paragraph 86(7)(c) of the *Patent Rules* along with a Summary of Reasons explaining that the rejection is maintained and that the proposed amendments presented in the Response to the Final Action do not overcome all of the defects identified in the Final Action.

[9] In a letter dated September 16, 2022, the Patent Appeal Board forwarded a copy of the Summary of Reasons to the Applicant and requested that they confirm their continued interest in having the application reviewed.

[10] In a letter dated December 14, 2022, the Applicant confirmed their interest in having the review proceed and further submitted a second set of proposed claims (proposed claims set-2).

[11] The present Panel was formed to review the rejected application under paragraph 86(7)(c) of the *Patent Rules*. On August 9, 2023, the Panel sent a Preliminary Review letter detailing our preliminary analysis and opinion that the subject-matter of claims 1 to 3, 5 to 17, 19 to 35, 37 to 48, 50 to 54 and 56 to 70 on file is obvious and that claims 1, 8 to 13, 15, 30, 34, 52, 59 and 61 suffer from indefiniteness, ambiguity and/or lack of clarity contrary to section 28.3 and subsection 27(4) of the *Patent Act*, respectively. Further, and pursuant to subsection 86(9) of the *Patent Rules*, the Preliminary Review letter notified the Applicant that it is our preliminary view that the utility of the claimed subject-matter has not been established by demonstration or a sound prediction across the entire scope of claims 1, 2, 4 to 7, 15, 16, 18 to 21, 23 to 34, 36 to 39, 41 to 47, 49 to 53 and 55 to 70 and thus these claims contravene section 2 of the *Patent Act*. Finally, the Preliminary Review letter expressed the preliminary view that the proposed amendments do not meet the requirements of a necessary amendment under subsection 86(11) of the *Patent Rules*.

[12] The Preliminary Review letter also provided the Applicant with an opportunity to make oral and/or written submissions.

[13] On September 29, 2023 the Applicant provided a written Response to the

Preliminary Review letter and a virtual oral hearing was held on October 5, 2023.

Issues

[14] In view of the above, the following issues are considered in this review:

- whether the utility of the subject-matter of the claims on file has not been established by demonstration or a sound prediction across their entire scope contrary to section 2 of the *Patent Act*;
- whether the claims on file are obvious contrary to section 28.3 of the *Patent Act*; and
- whether claims 1, 8 to 13, 15, 31, 34, 52, 59 and 61 on file are indefinite contrary to subsection 27(4) of the *Patent Act*.

[15] In addition to the claims on file, the proposed claims have also been considered.

PURPOSIVE CONSTRUCTION

Legal background

[16] According to Free World Trust v Électro Santé Inc, 2000 SCC 66 [Free World Trust] and Whirlpool Corp v Camco Inc, 2000 SCC 67 [Whirlpool], a purposive construction of the claims is performed from the point of view of the person of ordinary skill in the art (POSITA) in light of the relevant common general knowledge (CGK), considering the specification and drawings. In addition to interpreting the meaning of the terms of a claim, purposive construction distinguishes the essential elements of the claim from the non-essential elements. Whether or not an element is essential depends on the intent expressed in or inferred from the claim, and on whether it would have been obvious to the POSITA that a variant has a material effect upon the way the invention works.

[17] In carrying out the identification of essential and non-essential elements, all elements set out in a claim are presumed essential unless it is established otherwise or where such a presumption is contrary to the claim language.

Analysis

The POSITA and the relevant CGK

[18] The Preliminary Review letter, on pages 4 to 8, states the following with regard to the identity of the POSITA and their expected CGK:

> On page 3, the Final Action identifies the POSITA and the relevant CGK:
>
> > The person skilled in the art is a team including researchers in the fields of swine virology, cell biology and immunology.
> >
> > […]
> >
> > The common general knowledge of the person skilled in the art includes techniques for the production of genetically modified porcine cells and animals (reviewed in D7, for example); as well as knowledge of the biology of porcine reproductive and respiratory syndrome virus (PRRSV) infection, including the roles of sialoadhesin and CD163 in the entry of PRRSV into porcine alveolar macrophages (see for example D3, D4 and the review D5). A skilled person having regard to these documents would know that disrupting the function of CD163 reduces or inhibits PRRSV infection in vitro.
>
> For convenience, we introduce here documents D3, D4, D5 and D7.
>
> D3: Van Gorp et al., Journal of General Virology, 89, pages 2943-2953, 2008
>
> D4: Van Gorp et al., Journal of Virology, 84(6), pages 3101-3105, March 2010
>
> D5: Welch and Calvert, Virus Research, 154, pages 98-103, 2010
>
> D7: Aigner et al., Journal of Molecular Medicine, 88, pages 653-664, 2010
>
> D3 discloses that incubation of porcine primary alveolar macrophages with either sialoadhesin or CD163-specific antibodies reduced PRRSV infection by up to 75%, while infection was completely blocked by a combination of

the two antibodies. Analysis of PRRSV entry into nonpermissive cells expressing only sialoadhesin, the product of the SIGLEC1 gene, showed PRRSV internalization but no uncoating. Virus internalization was not observed when only CD163 was expressed, although cells became productively infected. Co-expression of recombinant sialoadhesin and CD163 in nonpermissive cells increased virus production 10-100X compared with cells expressing only CD163, indicating the requirement for both for efficient PRRSV infection.

D4 discloses the use of deletion and chimeric mutants of CD163 to identify the protein domains involved in PRRSV infection. The scavenger receptor cysteine-rich domain 5 (SRCR domain 5) was identified as essential for infection, while the SRCR 1-4 domains were not required. Antibodies specific to SRCR domain 5 were able to reduce PRRSV infection.

D5 reviews the role of CD163 in PRRSV infection. A prediction of the region of SRCR domain 5 involved in binding the virus includes the loop 5-6 region, which is conserved across species. The region is predicted to contain the primary ligand binding pocket, whereas the rest of the SRCR domain 5 may provide a structural scaffold.

D7 reviews the use of transgenic pigs as models for translational biomedical research. D7 discusses the efficient and precise techniques available for the genetic modification of pigs. The techniques include DNA microinjection into the pronuclei of fertilized oocytes, sperm-mediated gene transfer, lentiviral transgenesis, and somatic cell nuclear transfer using genetically modified nuclear donor cells. D7 teaches that further refinement of transgenic techniques is underway, including inducible transgene expression, the Cre/loxP system for conditional transgenic modifications, nonviral episomal expression systems, and Zinc finger nuclease technology. The techniques available allow for the generation of tailored transgenic pigs.

The Response to the Final Action and the response dated December 14, 2022 do not contest or comment on these characterization of the POSITA and their relevant CGK. Further, the Applicant does not propose additional

consideration with regard to either the POSITA or the relevant CGK in these communications.

Given the technical field to which the present patent application relates and the subject-matter of the claims on file, we consider that the characterization of the POSITA as a team comprising researchers in the fields of swine virology, cell biology and immunology is reasonable. We would further add that, in our preliminary view, this team should also include a molecular biologist that is familiar with transgenic animal production techniques and their applications.

Regarding the identification of the CGK, it is well established that the CGK is limited to knowledge which is generally known by persons skilled in the field of art or science to which a patent relates: Apotex Inc v Sanofi–Synthelabo Canada Inc, 2008 SCC 61 at para 37 [Sanofi]; Free World Trust at para 31.

More specifically, we consider that the assessment of CGK is governed by the principles stated in Eli Lilly & Co v Apotex Inc, 2009 FC 991 at para 97, upheld by 2010 FCA 240, citing General Tire & Rubber Co v Firestone Tyre & Rubber Co Ltd, [1972] RPC 457, [1971] FSR 417 (UKCA) at pages 482 and 483 (of RPC):

> The common general knowledge imputed to such an addressee must, of course, be carefully distinguished from what in the patent law is regarded as public knowledge. This distinction is well explained in Halsbury's Law of England, Vol. 29, para 63. As regards patent specifications, it is the somewhat artificial (see per Lord Reid in the Technograph case, [1971] F.S.R. 188 at 193) concept of patent law that each and every specification, of the last 50 years, however unlikely to be looked at and in whatever language written, is part of the relevant public knowledge if it is resting anywhere in the shelves of the Patent Office. On the other hand, common general knowledge is a different concept derived from a common sense approach to the practical question of what would in fact be

known to an appropriately skilled addressee—the sort of man, good at his job, that could be found in real life.

The two classes of documents which call for consideration in relation to common general knowledge in the instant case were individual patent specifications and “widely read publications”.

As to the former, it is clear that individual patent specifications and their contents do not normally form part of the relevant common general knowledge, though there may be specifications which are so well known amongst those versed in the art that upon evidence of that state of affairs they form part of such knowledge, and also there may occasionally be particular industries (such as that of colour photography) in which the evidence may show that all specifications form part of the relevant knowledge.

As regards scientific papers generally, it was said by Luxmoore, J. in British Acoustic Films (53 R.P.C. 221, at 250):

“In my judgment it is not sufficient to prove common general knowledge that a particular disclosure is made in an article, or series of articles, in a scientific journal, no matter how wide the circulation of that journal may be, in the absence of any evidence that the disclosure is accepted generally by those who are engaged in the art to which the disclosure relates. A piece of particular knowledge as disclosed in a scientific paper does not become common general knowledge merely because it is widely read, and still less because it is widely circulated. Such a piece of knowledge only becomes general knowledge when it is generally known and accepted without question by the bulk of those who are engaged in the particular art; in other words, when it becomes part of their common stock of knowledge relating to the art.” And a little later, distinguishing between what has been written and what has been used, he said:

“It is certainly difficult to appreciate how the use of something which has in fact never been used in a particular art can ever be held to be common general knowledge in the art.”

> Those passages have often been quoted, and there has not been cited to us any case in which they have been criticised. We accept them as correctly stating in general the law on this point, though reserving for further consideration whether the words “accepted without question” may not be putting the position rather high: for the purposes of this case we are disposed, without wishing to put forward any full definition, to substitute the words “generally considered as a good basis for further action”.

Having in mind the principles above, it is our preliminary view that the relevant question in the instant context is whether a given piece of knowledge was generally known and accepted without question by the bulk of those who are engaged in the particular fields of swine virology, cell biology, immunology, molecular biology and transgenic animal production techniques at the relevant time or otherwise generally considered as a good basis for further action.

To answer this question, established reference works (such as textbooks, review articles, handbooks, etc.) or demonstrated commonality of certain knowledge in a number of disclosures in the field are relevant to the inquiry: see the Manual of Patent Office Practice (CIPO) at 12.02.02c, revised October 2019.

Furthermore, it is our preliminary view that information in the instant specification may be evidence of the CGK as it could be reasonable to consider general or broadly worded assertions of conventional practice or knowledge as CGK (see Corning Cable Systems LLC v Canada (Attorney General), 2019 FC 1065 and Newco Tank Corp v Canada (Attorney General), 2015 FCA 47).

Having considered the CGK listed in the Final Action, and having reviewed the specification as a whole as well as the scientific literature pertinent to the claimed subject-matter, it is our preliminary view that the following pieces of knowledge and methods were generally known and accepted without question by the bulk of those who are engaged in the particular

fields of swine virology, cell biology, immunology, molecular biology and, with respect to transgenic animal production techniques, commonly used in the art at the relevant time:

- The techniques for the production of genetically modified porcine cells and genetically modified animals (as evidenced by D7 and the instant description at paras [0053] to [0056], [0058], [0059] and [0067] to [0069]).
- Gene and protein structures of CD163 as well as the main biological functions of CD163, e.g., receptor for haemoglobin clearance (as evidenced by Van Gorp et al., Molecular Immunology, 47(7-8), pages 1650-1660, 2010 (D9), and the instant description at paras [0011]).
- The important role of CD163 and in PRRSV infectivity (as evidenced by D5, D9 and Van Breedam et al., Journal of General Virology, Vol 91, pages 1659-1667, 2010 (D10).

We note that both D9 and D10 are cited in the instant description at para [0011] (D9) and paras [0008] and [0009] (D10). Further, the Applicant is hereby notified pursuant to subsection 86(9) of the *Patent Rules* that we consider that the disclosure of these documents is relevant to the obviousness inquiry below.

[19] The Applicant did not contest or otherwise comment on the identity of the POSITA in the Response to the Preliminary Review letter or at the hearing and we therefore adopt the above characterization of the POSITA for our final analysis.

[20] With respect to the CGK, the Applicant submitted at the hearing that the CGK identified in the Preliminary Review letter cannot carry that much weight within the obviousness analysis and that the gap between the cited prior art and the claimed subject-matter is too wide to be bridged by said CGK.

[21] More specifically, the Applicant submitted that: i) methods of genetically modifying a swine cell with targeted genetic modifications were not CGK; and ii) methods to regenerate a genetically modified swine from a genetically modified swine cell were not CGK.

[22] According to the Applicant’s submissions, although the review article D7 reflects

that somatic cell nuclear transfer (SCNT) was an approach to obtain a genetically modified swine with targeted genetic modifications that was known to at least some in the art, very few instances had been successful and hence the approach had not been widely adopted, presumably because of serious technical challenges in making those methods work.

[23] Furthermore, the Applicant submits that D1 provides evidence that the production of a genetically modified swine with targeted genetic modifications was not part of the CGK as the methods described in D1 could not lead to the successful generation of genetically modified swine for reasons explained in a statement by Dr. Randall S. Prather (the inventor listed in the instant application) that was signed on September 2, 2015 and submitted to the European Patent Office.

[24] We respectfully disagree for the following reasons.

[25] The CGK listed in our Preliminary Review letter is not a general suggestion that such knowledge was something that “everybody knew” or a broad proposition that “everybody knew” how to do targeted genetic modifications in swine cells lines in order to arrive at viable pigs as suggested by the Applicant at the hearing. The CGK identified in the Preliminary Review letter is the CGK expected from the POSITA. The Supreme Court of Canada explained that although the POSITA is deemed to have no scintilla of inventiveness or imagination, a patent specification is addressed to “skilled individuals sufficiently versed in the art to which the patent relates to enable them on a technical level to appreciate the nature and description of the invention”: Whirlpool at para 53. Moreover, “in the case of patents of a highly technical and scientific nature, that person may be someone possessing a high degree of expert scientific knowledge and skill in the particular branch of the science to which the patent related”: Consolboard v MacMillan Bloedel (Sask) Ltd, [1981] 1 SCR 504 at page 525. Further, the POSITA can represent a composite of scientists—highly skilled and trained persons who conduct scientific research to advance knowledge in an area of interest—and researchers: Bayer Aktiengesellschaft v Apotex Inc [1995] 60 CPR (3d) 58 at page 79:

> The notional skilled technician can be a composite of scientists, researchers and technicians bringing their combined expertise to bear on the problem at hand. “This is particularly true where the invention relates to a science or art that transcends several scientific disciplines”, (*per* Wetston J. in *Mobil Oil*

Corp. v. Hercules Canada Inc. (unreported, September 21, 1994, F.C.T.D., at p. 5 [now reported 57 C.P.R. (3d) 488 at p. 494, 82 F.T.R. 211].)

[26] On the basis of these principles, the POSITA was defined in the Preliminary Review letter as a team comprising researchers in the fields of swine virology, cell biology and immunology and that also includes a molecular biologist that is familiar with transgenic animal production techniques and their applications. As mentioned above, the Applicant did not contest or otherwise comment on the identity of the POSITA in the Response to the Preliminary Review letter or at the hearing.

[27] We acknowledge that the disclosure of the instant application is of a highly technical and scientific nature and therefore we consider that the defined POSITA, in turn, possesses as CGK a high degree of expert scientific knowledge and skill in the particular branches of science to which the patent relates, including molecular biology, cellular transgenesis and transgenic animal production techniques. Accordingly, it is our view that it is not unreasonable that said POSITA would possess as CGK the current and most commonly used methods in the field of genetic modification of swine.

[28] In that regard, we are of the view that D7 constitutes a better representation than D1 as to what was the CGK of the POSITA relating to genetically modified swine with targeted genetic modifications. D7 is a review article that summarizes the current techniques, as of March 2010, for the genetic modification of swine. D7 teaches that SCNT is one of these techniques that was made available at least 10 years before D7's publication date and that SCNT was, at that point in time, the only route to introduce targeted mutations into the pig genome. In our opinion, the steps and techniques related to swine transgenesis by SCNT (e.g., genetic modifications by targeted homologous recombination in nuclear donor cells, recovery and enucleation of matured oocytes, nuclear transfer and activation, *in vitro* culture of the reconstructed embryos and transfer to synchronized recipients) were commonly known by the POSITA as swine transgenesis by SCNT was the most common technique in the field at the relevant time to introduce targeted mutations into the pig genome.

[29] With respect to the submission that since D7 discloses only a few instances of success using the SCNT approach to obtain a genetically modified swine with targeted genetic modifications, D7 is evidence that such techniques have not been widely adopted, presumably because of serious technical challenges in making

those methods work, we offer the following.

[30] We understand that D7, although a review article, does not disclose an exhaustive and complete list of all successful reported and unreported attempts at producing genetically modified swine with targeted genetic modifications as D7 provides an overview of “Transgenic pigs as models for translational biomedical research”. Further, the fact that SCNT was, at the time of publication, the only route to introduce targeted mutations into the pig genome suggests that the SCNT approach would have been generally known and widely adopted by the bulk of those who are engaged in creating genetically modified swine with targeted mutations or otherwise generally considered as one of the best if not the best approach available at the time.

[31] Further, a CGK method or technique is not necessarily straightforward or always successful when practiced and that information is also part of the CGK related to that particular method or technique. In that regard, we acknowledge that it was CGK that, using the SCNT approach, the efficiency of cloning in swine was still relatively low, ranging between 0.5% and 5% offspring per transferred SCNT embryos (as evidenced by D7 on page 656). This is a consideration relevant to our obviousness inquiry below and the obvious to try factors.

[32] As mentioned above, the Applicant also submitted that methods of genetically modifying a swine cell with targeted genetic modifications were not CGK but did not offer specific reasons or arguments as to why. We already expressed the view that the SCNT approach to generate transgenic swine with targeted mutations was CGK for the foregoing reasons and the targeted genetic modifications in nuclear donor cells is the first general step of the SCNT method (as evidenced by D7 on page 656). It is therefore our view that the techniques of homology-directed gene targeting for introducing specific mutations in somatic cells, including somatic swine cells, were CGK for a molecular biologist that is familiar with transgenic animal production techniques and their applications.

[33] As indicated in the Preliminary Review letter, different passages of the instant description independently support our findings regarding the CGK and we find the following portions the most relevant in that regard insofar as it relates to swine transgenesis by SCNT and techniques of homology-directed gene targeting for introducing specific mutations in somatic cells [emphasis in bold added]:

[0043] Gene targeting carried out to make the animals of the invention can result in gene inactivation by disruption, removal, modification, or replacement of target gene sequences. **Methods for gene inactivation are well known in the art.** For example, a target gene can be inactivated by the insertion of a heterologous sequence (such as a selectable marker and/or a stop codon) into a target gene, deletion of a part of a gene or the entire gene, modification of a gene (e.g., by frame shift mutation, nonsense mutation, missense mutation, point mutation, replacement of a part or a whole gene with another nucleic acid sequence), or a combination of any of the above.

[0054] The transgenic animals of the invention can be made using the following general somatic cell nuclear transfer procedure. Briefly, the genome of a somatic porcine cell (e.g., a fetal fibroblast) is genetically modified by gene targeting as described above, to create a donor cell. The nucleus of such a genetically modified donor cell (or the entire donor cell, including the nucleus) is then transferred into a recipient cell, for example, an enucleated oocyte. The donor cell can be fused with a enucleated oocyte, or donor nucleus or the donor cell itself can be injected into the recipient cell or injected into the perivitelline space, adjacent to the oocyte membrane.

[0055] Thus, upon obtaining somatic cells in which a target gene has been targeted (one or both alleles, as described above), nuclear transfer can be carried out. Optionally, the genetically modified donor cells can be cryopreserved prior to nuclear transfer. Recipient cells that can be used include oocytes, fertilized zygotes, or the cells of two-cell embryos, all of which may or may not have been enucleated.

[0056] Recipient oocytes can be obtained using methods that are known in the art or can be purchased from commercial sources (e.g., BoMed Inc., Madison, Wis.). The oocyte can be obtained from a “gilt,” a female pig that has never had offspring or from a “sow,” a female pig that has previously produced offspring.

[0058] Methods for enucleating swine oocytes are known in the art, and enucleation can be achieved by any of the standard methods. For example, enucleating a oocyte can be achieved with a micropipette in a micromanipulation medium.

…

[0059] Introduction of a membrane-bound nucleus from a donor swine cell into an enucleated recipient swine oocyte to form an oocyte containing the donor nucleus can be performed by fusing together the membrane of the membrane-bound nucleus from the donor mammalian cell with the membrane of the enucleated recipient mammalian oocyte to form an oocyte containing the nucleus from the donor mammalian cell. Alternatively, such introduction can be performed by microinjecting the membrane-bounded nucleus from the mammalian donor cell into the enucleated recipient mammalian oocyte to form an oocyte containing the nucleus from the donor mammalian cell. For example, one can introduce a donor cell (or nucleus) into the space under the zona pellucida or into the perivitelline space of the enucleated, recipient oocyte, and subsequently carry out membrane fusion to produce an oocyte containing within its cytoplasm the donor nucleus. **All means of introducing donor nuclear material into an enucleated recipient mammalian oocyte known to those of ordinary skill in the art are useful in the methods disclosed herein**.

…

[0067] After activation, the oocyte is typically cultured for a brief period *in vitro.* The resulting embryo is then transferred into a surrogate female, and development of the embryo proceeds in the surrogate. For example, the embryos can be cultured for about a week, and then transferred surgically or non-surgically to the reproductive tract of a surrogate. The embryos can be transferred into an oviduct through an ovarian fimbria of the surrogate. Alternatively, the

> embryos can be transferred into an oviduct of a surrogate by using a catheter that penetrates the wall of the oviduct. Another way of transferring embryos involves culturing them until the blastocyst stage followed by introduction into the reproductive tract of a surrogate swine. **These methods are well known in the art, and can readily be applied in producing the genetically modified swine of the present invention**.

[34] Therefore, for the reasons stated in the Preliminary Review Letter and the further reasons detailed above, it is our view that the following pieces of knowledge and methods were CGK to the defined POSITA:

- Gene and protein structures of CD163 as well as the main biological functions of CD163, e.g., receptor for haemoglobin clearance;
- The important role of CD163 and in PRRSV infectivity; and
- The techniques for the production of genetically modified porcine cells and genetically modified animals, more specifically the steps and techniques related to swine transgenesis by SCNT (e.g., genetic modifications by targeted homologous recombination in nuclear donor cells, recovery and enucleation of matured oocytes, nuclear transfer and activation, *in vitro* culture of the reconstructed embryos and transfer to synchronized recipients) as well as the techniques of homology-directed gene targeting for introducing specific mutations in somatic cells, including somatic swine cells.

The claims on file

[35] There are 70 claims on file. Independent claims 1, 15, 30, 33, 46, 52, 59 to 61 and 66 read as follows:

> 1. A genetically modified swine cell comprising inactivating mutations in both alleles of a *CD163* gene, wherein swine comprising said genetically modified swine cells exhibit increased resistance to a porcine reproductive and respiratory syndrome virus (PRRSV).

15. A genetically modified swine cell comprising inactivating mutations in both alleles of a *CD163* gene, wherein swine comprising said genetically modified swine cells exhibit increased resistance to a porcine reproductive and respiratory syndrome virus (PRRSV) and wherein the cell is produced by a method comprising:

    (a) enucleating a swine oocyte;

    (b) fusing the oocyte with a donor swine somatic cell, the genome of the somatic cell comprising at least one mutated *CD163* allele;

    (c) activating the oocyte to produce an embryo comprising the cell;

    (d) transferring the embryo into a reproductive tract of a surrogate swine, wherein the surrogate swine has initiated estrus but has not yet completed ovulation; and wherein gestation and term delivery produces a genetically modified swine cell whose genome comprises the mutations in both alleles of the *CD163* gene;

    (e) mating a male genetically modified swine produced by the method of steps (a) through (d) with a female genetically modified swine produced by the method of steps (a) through (d) to produce F1 progeny; and

    (f) screening the F1 progeny to identify genetically modified swine wherein both alleles of the *CD163* gene have been mutated in the cell.

30. A method for producing a genetically modified swine comprising a mutation in at least one allele of a *CD163* gene, the method comprising:

    enucleating a swine oocyte;

    fusing the oocyte with a donor swine somatic cell, the genome of the somatic cell comprising at least one mutated *CD163* allele; and

activating the oocyte to produce an embryo.

33. A method for producing a genetically modified swine comprising mutations in both alleles of a *CD163* gene, the method comprising:

mating a female genetically modified swine produced by the method of any one of claims 30-32 with a male genetically modified swine produced by the method of any one of claims 30- 32 to produce F1 progeny; and,

screening the F1 progeny to identify genetically modified swine wherein both alleles of the *CD163* gene have been mutated.

46. A method for producing a genetically modified swine comprising a mutation in an allele of a *CD163* gene, the method comprising:

editing the genetic content of a porcine cell to create a modification which alters the expression or activity of CD163; and

generating an animal from the cell.

52. A method for producing a genetically modified swine comprising a mutation in an allele of a *CD163* gene, the method comprising:

introducing a site-specific nuclease into a porcine cell, the nuclease being adapted to bind to a target sequence in a nucleic acid in an allele of the *CD163* gene; and

incubating the cell under conditions that permit the nuclease to act upon the DNA at or near the target sequence and thereby induce recombination, homology-directed repair, or non-homologous end joining at or near the target sequence in the nucleic acid.

59. A genetically modified swine cell produced by procreation of the swine as defined in any one of claims 30-58, comprising mutations in at both alleles of a *CD163* gene.

60. Use of swine comprising the genetically modified swine cell of any one of claims 1-24, for producing progeny.

61. A genetically modified swine cell comprising one or more alterations in a *CD163* gene sequence, wherein the one or more alterations are in a non-coding sequence of the *CD163* gene and inactivate the *CD163* gene, and wherein swine comprising said genetically modified swine cells exhibit increased resistance to porcine reproductive and respiratory syndrome virus (PRRSV).

66. A method for producing a genetically modified swine cell of any one of claims 61-65, the method comprising:

    introducing a site-specific nuclease into a porcine cell, the nuclease being adapted to bind to a target sequence in a nucleic acid in an allele of the *CD163* gene; and

    incubating the cell under conditions that permit the nuclease to act upon the DNA at or near the target sequence and thereby induce recombination, homology-directed repair, or non-homologous end joining at or near the target sequence in the nucleic acid.

[36] The dependent claims define further limitations regarding the absence of mutation in the *SIGLEC1* gene (claims 2, 16, 34 and 65), the contemplated mutations in the *CD163* gene (claims 3 to 6, 8 to 14, 17 to 20, 22, 35 to 38, 40, 48, 49, 54, 55, 62 to 64 and 68), the system or specific method used for mutating the *CD163* gene (claims 7, 21, 39, 47, 53 and 67) and the method or a step used to produce the contemplated genetically modified swine cell or swine (claims 23 to 29, 31, 32, 41 to 45, 50, 51, 56 to 58, 69 and 70).

Essential elements

[37] As stated above, all of the elements set out in a claim are presumed essential unless it is established otherwise or where such a presumption is contrary to the claim language. Further, a claim element is essential when it would have been obvious to the person skilled in the art that its omission or substitution would have a material effect on the way the invention works: Free World Trust at para 55.

[38] The Preliminary Review letter, on page 11, states the following with regard to the elements in the claims that the person skilled in the art would consider to be essential:

> With respect to claim language, our preliminary view is that the POSITA reading claims 1 to 70 in the context of the specification as a whole and in view of their CGK would understand that there is no use of language in any of the claims indicating that any of the elements are optional, preferred or were otherwise intended as being non-essential. Therefore, our preliminary view is that the POSITA would consider all of the elements in the claims to be essential.

[39] The Applicant did not contest or otherwise comment on our preliminary view regarding the essential elements of the claims on file and we therefore adopt it for the purposes of this final review.

UTILITY

Legal background

[40] Utility is required by section 2 of the *Patent Act*:

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

[41] In AstraZeneca Canada Inc v Apotex Inc, 2017 SCC 36 at para 53 [AstraZeneca], the Supreme Court of Canada stated that the "[u]tility will differ based on the subject-matter of the invention as identified by claims construction" and outlined the approach that should be undertaken to determine whether a patent discloses an invention with sufficient utility under section 2 of the *Patent Act*:

> [54] To determine whether a patent discloses an invention with sufficient utility under s. 2, courts should undertake the following analysis. First, courts must identify the subject-matter of the invention as claimed in

> the patent. Second, courts must ask whether that subject-matter is useful—is it capable of a practical purpose (i.e. an actual result)?
>
> [55] The Act does not prescribe the degree or quantum of usefulness required, or that every potential use be realized—a scintilla of utility will do. A single use related to the nature of the subject-matter is sufficient, and the utility must be established by either demonstration or sound prediction as of the filing date (AZT, at para 56).

[42] Therefore, utility must be established either by demonstration or sound prediction as of the Canadian filing date. Utility cannot be supported by evidence and knowledge that only became available after this date (see also Apotex Inc v Wellcome Foundation Ltd, 2002 SCC 77 at para 56 [AZT], cited in the passage above).

[43] The doctrine of sound prediction allows the establishment of asserted utility even where that utility had not been fully verified as of the filing date. However, a patent application must provide a “solid teaching” of the claimed invention as opposed to “mere speculation” (AZT at para 69).

[44] The soundness of a prediction is a question of fact (AZT at para 71). Analysis of that soundness should consider three elements (AZT at para 70): i) there must be a factual basis for the prediction; ii) the inventor must have, at the date of the patent, an articulable and sound line of reasoning from which the desired result can be inferred from the factual basis; and iii) there must be proper disclosure of the factual basis and line of reasoning.

[45] These elements are assessed from the perspective of the POSITA to whom the patent is directed, taking into account their CGK. Further, with the exception of the CGK, the factual basis and line of reasoning must be included in the patent application (See Bell Helicopter Textron Canada Ltée v Eurocopter SAS, 2013 FCA 219 at paras 152–153).

[46] Although a prediction does not need to amount to a certainty to be sound, there must be a *prima facie* reasonable inference of utility (Eli Lilly Canada Inc v Novopharm Limited, 2010 FCA 197, at para 85 [Eli Lilly]; Gilead Sciences Inc v Idenix Pharmaceuticals Inc, 2015 FC 1156 at para 251; Mylan Pharmaceuticals ULC v Eli Lilly Canada Inc, 2016 FCA 119 at para 55).

Analysis

[47] The Preliminary Review letter, on pages 13 to 18, explains that in our preliminary view claims 1, 2, 4 to 7, 15, 16, 18 to 21, 23 to 34, 36 to 39, 41 to 47, 49 to 53 and 55 to 70 on file contravene section 2 of the *Patent Act* because the utility of the claimed subject-matter has not been established by demonstration or a sound prediction across the entire scope:

> *What is the subject-matter of the invention as claimed?*
>
> In our preliminary view the subject-matter of the invention as recited in claims 1 to 29 and 60 that must be useful is directed to genetically modified swine cells comprising inactivating mutations in both alleles of a *CD163* gene, wherein swine comprising said genetically modified swine cells exhibit increased resistance to PRRSV (claims 1 to 29), and use thereof (claim 60). We consider that the utility of the subject-matter of claims 1 to 29 and 60 hinges on the production of a genetically modified swine comprising genetically modified swine cells with inactivating mutations in both alleles of a *CD163* gene and that exhibit increased resistance to PRRSV.
>
> With regard to claims 30 to 32, 46 to 49, 52 to 56 and 58, it is our preliminary view that the subject-matter of the invention as recited in these claims that must be useful is directed to a method for producing a genetically modified swine comprising a mutation in at least one allele of a *CD163* gene. We consider that the utility of the subject-matter of claims 30 to 32, 46 to 49, 52 to 56 and 58 hinges on the production of a genetically modified swine comprising at least one mutated *CD163* allele.
>
> With regard to claims 33 to 45, 50, 51 and 57 to 59, it is our preliminary view that the subject-matter of the invention as recited in these claims that must be useful is directed to a method for producing a genetically modified swine comprising mutations in both alleles of a *CD163* gene. We consider that the utility of the subject-matter of claims 33 to 45, 50, 51 and 57 to 59 hinges on the production of a genetically modified swine comprising mutations in both alleles of a *CD163* gene.
>
> With regard to claims 61 to 70, it is our preliminary view that the subject-matter of the invention as recited in these claims that must be useful is directed to genetically modified swine cells comprising one or more

alterations in a *CD163* gene sequence, wherein the one or more alterations are in a non-coding sequence of the *CD163* gene and inactivate the *CD163* gene in one or both alleles, and wherein swine comprising said genetically modified swine cells exhibit increased resistance to PRRSV (claims 61 to 65) as well as related production methods thereof (claims 66 to 70). We consider that the utility of the subject-matter of claims 61 to 70 hinges on the production of a genetically modified swine comprising genetically modified swine cells with one or more alterations in a non-coding sequence of the *CD163* gene that inactivate the *CD163* gene in one or both *CD163* alleles and that exhibit increased resistance to PRRSV.

Because of the phrases “comprising inactivating mutations in both alleles of a *CD163* gene” (independent claims 1 and 15), “comprising a mutation in at least one allele of a *CD163* gene” (independent claim 30), “comprising mutations in both alleles of a *CD163* gene” (independent claim 33), “comprising a mutation in an allele of a *CD163* gene” (independent claims 46 and 52), “comprising mutations in at both alleles of a *CD163* gene” (independent claim 59), “comprising one or more alterations in a *CD163* gene sequence, wherein the one or more alterations are in a non-coding sequence of the *CD163* gene” (independent claim 61), the scope of claims 1, 2, 4 to 7, 15, 16, 18 to 21, 23 to 34, 36 to 39, 41 to 47, 49 to 53 and 55 to 70 encompasses swine comprising genetically modified swine cells with complete deletion of both alleles of a *CD163* gene or comprising genetically modified swine cells that do not express CD163.

Is the utility of the claimed subject-matter established by demonstration as of the filing date?

Swine comprising genetically modified swine cells with complete deletion of both alleles of a CD163 gene or comprising genetically modified swine cells that do not express CD163, including swine that exhibit increased resistance to PRRSV

There is no indication in the record before us of a demonstrated production of swine that exhibit increased resistance to PRRSV and that comprise genetically modified swine cells with complete deletion of both alleles of a *CD163* gene or comprising genetically modified swine cells that do not express CD163.

Swine comprising genetically modified swine cells with inactivating mutations or a partial deletion in a portion of the *CD163* gene sequence in one or both alleles of a *CD163* gene, including swine that exhibit increased resistance to PRRSV

There is no indication in the record before us of a demonstrated production of swine comprising genetically modified swine cells comprising inactivating mutations or a partial deletion in one or both alleles of a *CD163* gene, including swine that exhibit increased resistance to PRRSV.

Genetically modified swine cells with one or more alterations in a *CD163* gene sequence, wherein the one or more alterations are in a non-coding sequence of the *CD163* gene and inactivate the *CD163* gene in one or both alleles and methods related thereto to generate a swine that exhibit increased resistance to PRRSV

There is no indication in the record before us of a demonstrated production of genetically modified swine cells comprising one or more alterations in a *CD163* gene sequence, wherein the one or more alterations are in a non-coding sequence of the *CD163* gene and inactivate the *CD163* gene in one or both alleles and methods related thereto to generate swine that exhibit increased resistance to PRRSV.

In view of the foregoing, it is our preliminary view that the utility of embodiments encompassed by the scope of claims 1 to 70 was not established on the basis of a demonstration as of the filing date.

Is the utility of the claimed subject-matter established by sound prediction as of the filing date?

Swine comprising genetically modified swine cells with complete deletion of both alleles of a *CD163* gene or comprising genetically modified swine cells that do not express CD163, including swine that exhibit increased resistance to PRRSV

The factual basis, the line of reasoning and the level of disclosure required for a sound prediction are to be assessed as a function of the knowledge that the POSITA would have to base that prediction on, and as a function of what that POSITA would understand from the

specification as a logical line of reasoning leading to the utility of the invention.

With regard to a factual basis supporting the prediction of utility and from which the desired result can be inferred, it is our preliminary view that the factual basis found in the instant specification or the CGK is lacking with regard to the production of swine comprising genetically modified swine cells with complete deletion of both alleles of a *CD163* gene or comprising genetically modified swine cells that do not express CD163 as the specification does not disclose representative embodiments or any other factual evidence relevant to predicting the viability of a genetically modified swine that does not express CD163.

Furthermore, it is our preliminary view that it would be apparent to the POSITA having read the specification that the line of reasoning according to which genetically modified swine cells with complete deletion of both alleles of a *CD163* gene or that do not express CD163 would be capable of giving rise to genetically modified swine that exhibit increased resistance to PRRSV is absent from the instant specification. To the contrary, the description at para [0045] expresses a line of reasoning that is the opposite of the required sound line of reasoning [emphasis added]:

> In the case of CD163, it is desirable to only inactivate its function related to PRRSV binding and/or uncoating while leaving the other functions of CD163 minimally affected or unaffected. While not being bound to any particular theory, it is believed that a complete CD163 knock-out may not be viable or could be seriously compromised due to the role of CD163 in binding and internalization of haemoglobin-haptoglobin complexes. Accordingly, CD163 can be inactivated by disrupting the fifth N-terminal scavenger receptor cysteine-rich (SRCR) domain of CD163, which was previously shown to play a leading role in PRRSV infection (Van Gorp et al., 2010), while leaving the other domains unaffected. SRCR domain 5 can be genetically modified by, e.g., introducing point mutations which alter the structure of this domain or by swapping this domain with another one. For example, SRCR domain 5 can be replaced with SRCR domain 8 from CD163 Ligand (CD163L) since this domain “swap” has been shown to reduce relative PRRSV infectivity to 0% in cultured cells (Van Gorp et al 2010).

Another passage of the description at para [0121] also does not support the soundness of producing genetically engineered swine with complete deletion of both alleles of a *CD163* gene or that do not express CD163 [emphasis added]:

> As already established, deletion of the cytoplasmic domain of CD163 eliminates infectivity of PRRSV, as does the deletion or modification of SRCR domain 5. Since some of the SRCR domains of CD163 have important functions for survival of the animal, e.g. hemoglobin removal, modification of the gene such that these other functions remain intact represents a solid strategy to create pigs that are resistant to PRRSV. Prior research has also suggested that the replacement of SRCR5 domain with CD163L domain 8 also blocks infectivity (Van Gorp et al. 2010b).

Swine comprising genetically modified swine cells with an alteration or a partial deletion in a portion of the *CD163* gene sequence in one or both alleles of a *CD163* gene and that exhibit increased resistance to PRRSV

In contrast to our preliminary views regarding genetically modified swine that do not express CD163, we consider that it would be apparent to the POSITA having read the specification that para [0045] cited above contains a sound line of reasoning according to which genetically modified swine cells with an alteration or a partial deletion in a portion of the *CD163* gene sequence in one or both alleles of a *CD163* gene would be capable of giving rise to genetically modified swine that exhibit increased resistance to PRRSV, namely the use of genetically modified swine cells comprising mutations in one or both alleles of a *CD163* gene that inactivate the CD163 functions related to PRRSV binding and/or uncoating while leaving the other functions of CD163 minimally affected or unaffected. We also consider that the results from the relevant literature reported in the same passage constitute a proper factual basis supporting the prediction of utility and from which the desired result can be inferred.

Genetically modified swine cells with one or more alterations in a *CD163* gene sequence, wherein the one or more alterations are in a non-coding sequence of the *CD163* gene and inactivate the *CD163* gene in one or both alleles and methods related thereto to generate a swine that exhibit increased resistance to PRRSV

> We consider that it would be apparent to the POSITA having read the specification that there is no factual basis to support a sound line of reasoning that genetically modified swine cells with one or more alterations in a non-coding sequence in one allele of a *CD163* gene would exhibit increased resistance to PRRSV.
>
> Further, and with respect to embodiments wherein the one or more alterations are in a non-coding sequence of the *CD163* gene in both alleles and result in the non-expression of CD163, it is our preliminary view that their utility was not established on the basis of a sound prediction as of the filing date for the same reasons expressed above with regards to swine comprising genetically modified swine cells with complete deletion of both alleles of a CD163 gene or comprising genetically modified swine cells that do not express CD163.
>
> **Conclusion on utility**
>
> In view of the foregoing, it is therefore our preliminary view that the utility of the claimed subject-matter has not been established by demonstration or a sound prediction across the entire scope of claims 1, 2, 4 to 7, 15, 16, 18 to 21, 23 to 34, 36 to 39, 41 to 47, 49 to 53 and 55 to 70 and thus these claims contravene section 2 of the *Patent Act*.

[48] At the hearing and in the Response to the Preliminary Review letter on pages 1 to 3, it was submitted that the present application establishes the utility of the subject-matter of claims 1, 2, 4 to 7, 15, 16, 18 to 21, 23 to 34, 36 to 39, 41 to 47, 49 to 53 and 55 to 70, including swine cells with complete deletion of both alleles of a *CD163* gene or with single allele alterations.

[49] With regard to PRRSV resistant swine comprising genetically modified swine cells with complete deletion of both alleles of a *CD163* gene, the Applicant first submits in the Response to the Preliminary Review letter that it would be clear to one of ordinary skill in the art reading notably paragraph [0045] of the description that a complete knock out of CD163 is not desirable *in all embodiments* as the specification teaches alternatives such as inactivating CD163 function related to PRRSV binding and/or uncoating while leaving the other functions of CD163 minimally affected or unaffected.

[50] As mentioned in the Preliminary Review letter, the utility of the claimed subject-matter must be established for the entire scope of the claims, in an independent

manner for each claimed embodiment. If a claim is broad enough to encompasses both useful and non-useful subject-matter, it still contravenes section 2 of the *Patent Act*.

[51] The Applicant also respectfully disagrees with the Panel's assertion that the statements in the application about the potentially deleterious effects of double allele inactivation in paragraphs [0045] and [0121] amount to statements that such embodiments of the claimed invention definitively lack any utility or that there is no scintilla of utility. In particular, the Applicant notes that the application specifically contemplates double allele inactivation embodiments, teaching that even in the circumstance that this approach may have deleterious effects, it may be useful in some other contexts, supporting the Applicant's arguments that there is a sound prediction of a scintilla of utility. When specifically asked at the hearing about the nature of such other contexts and where in the specification such contexts are disclosed, the Applicant submitted that it could be a very wide variety of kinds of pigs that are of technological interest and wherein these modifications, the CD163 knockouts, are understood to have potential use in all of those possible contexts and for all of those different genetic backgrounds. The Applicant presented pigs for human organ transplantation or for meat production as examples.

[52] The fact that a double allele inactivation embodiment may or may not be useful in other contexts is not the relevant consideration before us. What is relevant is the context of the instant claimed subject-matter. In AstraZeneca at para 53, the Supreme Court stated:

> Utility will differ based on the subject-matter of the invention as identified by claims construction. Thus, the scope of potentially acceptable uses to meet the s. 2 requirement is limited—not *any* use will do. By requiring the usefulness of the proposed invention to be related to the nature of the subject-matter, a proposed invention cannot be saved by an entirely unrelated use. It is not sufficient for an inventor seeking a patent for a machine to assert it is useful as a paperweight.

[53] Therefore, a single use is sufficient but it must be related to the nature of the identified claimed subject-matter. We first identified in the Preliminary Review letter on pages 13 and 14 the subject-matter of the claimed invention as recited in claims 1 to 70 that must be useful, as instructed by AstraZeneca. Importantly, the

Applicant did not contest or otherwise comment on those identifications and statements. Encompassed by the scope of claims 1, 2, 4 to 7, 15, 16, 18 to 21, 23 to 34, 36 to 39, 41 to 47, 49 to 53 and 55 to 70 are genetically modified swine cells comprising inactivating mutations in both alleles of a *CD163* gene, wherein swine comprising said genetically modified swine cells exhibit increased resistance to PRRSV. Hence the usefulness of the claimed subject-matter hinges on the production of a viable genetically modified swine comprising genetically modified swine cells with inactivating mutations in both alleles of a *CD163* gene and that exhibit increased resistance to PRRSV.

[54] If it cannot be established, by demonstration or sound prediction, that genetically modified swine cells comprising inactivating mutations in both alleles of a *CD163* gene can lead to the successful generation of genetically modified swine that exhibit increased resistance to PRRSV, then the claimed-subject matter lacks utility insofar as it relates to this claimed embodiment.

[55] With regard to a demonstration of utility, we stated in the Preliminary Review letter that there is no indication in the record before us of a demonstrated production of swine that exhibit increased resistance to PRRSV and that comprise genetically modified swine cells with complete deletion of both alleles of a *CD163* gene or comprising genetically modified swine cells that do not express CD163 as of the filing date.

[56] The Applicant did not contest or otherwise comment on that preliminary finding or any other finding concerning a lack of demonstrated utility for the entirety of the claimed subject-matter as of the filing date and we therefore adopt those findings here for the purposes of this final review.

[57] It was with regard to a sound prediction of utility, and more specifically whether the specification contains a sound line of reasoning that genetically modified swine cells with complete deletion of both alleles of a *CD163* gene or that do not express CD163 would be capable of giving rise to genetically modified swine that exhibit increased resistance to PRRSV, that statements contained in paras [0045] and [0121] were considered and referred to in the Preliminary Review letter.

[58] We acknowledge that the application specifically contemplates double allele inactivation embodiments and prophetically describes how to make those desired embodiments but we consider that this disclosure instead amounts to the predicted

and desired useful result of the AZT analysis—the starting point of the inquiry rather than serving as a factual basis and/or a line of reasoning as suggested by the Applicant. Our inquiry is whether the inventor has an articulable and sound line of reasoning from which the prediction that genetically modified swine cells with complete deletion of both alleles of a *CD163* gene or that do not express CD163 would be capable of giving rise to genetically modified swine that exhibit increased resistance to PRRSV can be inferred from the factual basis.

[59] Regarding the factual basis, the specification does not disclose representative embodiments or any other factual evidence supporting the prediction that a genetically modified swine that does not express CD163 would be viable. We consider that relevant factual evidence is also absent from the CGK.

[60] Further, we are of the view that taken as a whole the specification does not disclose an articulable and sound line of reasoning supporting the prediction that genetically modified swine cells with complete deletion of both alleles of a *CD163* gene or that do not express CD163 would be capable of giving rise to genetically modified swine that exhibit increased resistance to PRRSV. As indicated in the Preliminary Review letter, paras [0045] and [0121] contain statements that do not support the soundness of producing genetically engineered swine with complete deletion of both alleles of a *CD163* gene or that do not express CD163. Thus, we consider that there is no *prima facie* reasonable inference of utility insofar as genetically modified swine cells with complete deletion of both alleles of a *CD163* gene or that do not express CD163 would be capable of giving rise to genetically modified swine that exhibit increased resistance to PRRSV.

[61] At the hearing, the Applicant drew a parallel between the instant case and the case before the Supreme Court in AZT. It was submitted that, like AZT, the instant case deals with a similarly prophetic sound prediction of utility under circumstances in which there were reasons to qualify the prediction to the extent of suggesting other embodiments might be better but there is no suggestion that they could not work at all, or that they would be useless either in the application itself or in the art.

[62] In AZT, the patent involved the use of a drug in the treatment of HIV/AIDS. The Supreme Court of Canada upheld the patent under the doctrine of sound prediction. In that case, the inventors had both a factual basis (positive *in vitro* tests) for their prediction that AZT would work in human patients and a sound line of reasoning linking those facts to the desired outcome. At para 75, it was found

that in that case “the inventors possessed and disclosed in the patent both the factual data on which to base a prediction, and a line of reasoning (chain terminator effect) to enable them to make a sound prediction at the time they applied for the patent”. It was sufficient that at that time the inventors disclosed in the patent a rational basis for making a sound prediction that AZT would prove useful in the treatment and prophylaxis of AIDS (see para 3).

[63] That is not the situation before us. While the instant application contains some information about producing hypothetical swine that exhibit increased resistance to PRRSV comprising genetically engineered swine cells with complete deletion of both alleles of a *CD163* gene or that do not express CD163, it neither discloses a factual basis nor sets out a sound line of reasoning to support the prediction that genetically modified swine cells with complete deletion of both alleles of a *CD163* gene or that do not express CD163 would be capable of giving rise to genetically modified swine that exhibit increased resistance to PRRSV.

[64] In AZT, the inventors disclosed a factual basis in the form of positive *in vitro* tests. In contrast, while the instant specification discloses factual evidence as to why genetically modified swine with an alteration or a partial deletion in a portion of the *CD163* gene sequence of both alleles of a *CD163* gene would be resistant to PRRSV, the specification does not disclose any factual evidence relevant to predicting that the genetically modified swine cells with complete deletion of both alleles of a *CD163* gene or that do not express CD163 would be capable of giving rise to a viable swine resistant to PRRSV.

[65] In AZT, the inventors disclosed a line of reasoning (chain terminator effect) to enable them to make a sound prediction. The instant application does not set out a sound line of reasoning as to why genetically modified swine cells with complete deletion of both alleles of a *CD163* gene or that do not express CD163 would be capable of giving rise to a viable genetically modified swine that exhibits increased resistance to PRRSV. To the contrary and as explained above, the specification taken as a whole and notably paras [0045] and [0121] indicates to the POSITA that genetically modified swine that do not express CD163 would not be viable and thus directly undermines the prediction that genetically modified swine cells with complete deletion of both alleles of a *CD163* gene would be capable of giving rise to genetically modified swine that exhibit increased resistance to PRRSV.

[66] At the hearing, the Applicant also alluded to the relatively low bar for substantiating

a sound prediction of utility and submitted that if mere speculation is not enough, a scintilla of utility is sufficient.

[67] We first note that the correct threshold for a sound prediction is a "*prima facie* reasonable inference of utility", not a "scintilla of utility" (see Legal Background section above, and notably Eli Lilly at para 85). We expressed our views regarding the soundness of the prediction that genetically modified swine cells with complete deletion of both alleles of a *CD163* gene or that do not express CD163 would be capable of giving rise to genetically modified swine that exhibit increased resistance to PRRSV having this threshold in mind.

[68] On the other hand, the "scintilla of utility" threshold relates to the degree or quantum of usefulness required (see AstraZeneca at para 55). In other words, "[a] valid patent requires utility, though a mere scintilla of utility is sufficient" (Apotex Inc. v. Janssen Inc., 2021 FCA 45, at para 37). Although a "scintilla of utility" will suffice, that scintilla must relate to the nature of the claimed subject-matter: AstraZeneca at para 55.

[69] As mentioned above, we identified in the Preliminary Review letter on pages 13 and 14 the subject-matter of the claimed invention as recited in claims 1 to 70 that must be useful and the associated utility. In view of the claimed subject-matter, we found that the alleged utility of swine cells with complete deletion of both alleles of a *CD163* gene or that do not express CD163 must relate to the production of viable genetically modified swine that exhibit increased resistance to PRRSV. If it could be established by demonstration or a sound prediction that genetically modified swine cells with complete deletion of both alleles of a *CD163* gene or that do not express CD163 were capable of giving rise to viable genetically modified swine that exhibit increased resistance to PRRSV, it would be useful subject-matter. Having considered the entire record before us, we are of the view that it was not the case for the reasons found in the Preliminary Review letter and for the further reasons detailed above.

[70] With regard to single allele alterations embodiments such as the ones encompassed by independent claim 61 on file and claims depending thereon, the Response to the Preliminary Review letter submits on page 3 that "it was apparent as of the *filing date* to an *inventive person* of skill in the art that single allele alterations could be useful".

[71] Firstly, our preliminary view expressed in the Preliminary Review letter on page 17 concerning single allele alteration embodiments was not regarding whether single allele alterations could be useful at all in any context but was rather directed to whether genetically modified swine cells with one or more alterations in a non-coding sequence in only one allele of a *CD163* gene and that inactivate the *CD163* gene would be capable of giving rise to genetically modified swine that exhibit increased resistance to PRRSV as this was the identified claimed subject-matter for which the utility had to be established.

[72] Secondly, our preliminary view was based on the fact that the single allele alterations embodiments encompassed by independent claim 61 on file and claims depending thereon still express unaltered CD163 and hence, such heterozygous embodiments should still be susceptible to PRRSV infection. Therefore, we consider that it would be apparent to the POSITA having read the specification that there is no factual basis or a sound line of reasoning to support a prediction that the encompassed genetically modified heterozygous swine that still express unaltered CD163 would exhibit increased resistance to PRRSV.

Conclusion on utility

[73] In view of the foregoing, it is therefore our view that the utility of the claimed subject-matter has not been established by demonstration or a sound prediction across the entire scope of claims 1, 2, 4 to 7, 15, 16, 18 to 21, 23 to 34, 36 to 39, 41 to 47, 49 to 53 and 55 to 70 and thus these claims contravene section 2 of the *Patent Act*.

OBVIOUSNESS

Legal background

[74] Section 28.3 of the *Patent Act* requires that the subject-matter of a claim not be obvious to the POSITA:

> 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 before the one-year period immediately preceding the filing date or, if the claim date is before that period, before the claim 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.

[75] In Sanofi at para 67, the Supreme Court of Canada states 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?

[76] In the context of the fourth step, the Court in Sanofi states that it may be appropriate in some cases to consider an “obvious to try” analysis.

[77] The Court in Sanofi identifies the following non-exhaustive factors to be considered

in an obvious to try analysis [defined terms added]:

> Is it more or less self-evident that what is being tried ought to work? Are there a finite number of identifiable predictable solutions known to persons skilled in the art? [the Self-Evident Factor]
>
> What is the extent, nature and amount of effort required to achieve the invention? Are routine trials carried out or is the experimentation prolonged and arduous, such that the trials would not be considered routine? [the Extent and Effort Factor]
>
> Is there a motive provided in the prior art to find the solution the patent addresses? [the Motive Factor]

Analysis

[78] The Preliminary Review letter, on pages 19 to 27, explains that in our preliminary view swine comprising genetically modified swine cells with complete deletion of one or both alleles of a CD163 gene or comprising genetically modified swine cells that do not express CD163 as well as methods related thereto would not have been obvious to the POSITA in view of the cited prior art and the CGK. However, we expressed the preliminary view that claims 1 to 3, 5 to 17, 19 to 35, 37 to 48, 50 to 54 and 56 to 70 on file encompass subject-matter that would have been obvious to the POSITA in view of the cited prior art and the relevant CGK.

The POSITA and the relevant CGK

[79] The POSITA and the relevant CGK have been identified as part of the purposive construction of the claims above wherein the Applicant's arguments regarding the CGK have been considered. Although in that context the information forming the relevant CGK is identified using the publication date, this information is also considered CGK at the claim date and is therefore relevant for assessing obviousness.

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

[80] The Preliminary Review Letter on page 20 states the following with regard to the inventive concepts of the claims on file:

> As mentioned above, our preliminary view is that the POSITA would consider all of the elements in the claims to be essential, and so they should be reflected in the inventive concepts of the claims. Therefore, for the purposes of this assessment we take into account all of the essential elements of the claims. In our preliminary view, the combination of essential elements of independent claims 1, 15, 30, 33, 46, 52, 59 to 61 and 66 represents their inventive concepts as well.
>
> It is also our preliminary view is also that the elements of the dependent claims relating to the absence of mutation in the SIGLEC1 gene, the contemplated mutations in the CD163 gene, the system or specific method used for mutating the CD163 gene and the method or a step used to produce the contemplated genetically modified swine cell or swine, as set out above, are part of the respective inventive concepts of the dependent claims.

[81] The Applicant did not contest or otherwise comment on the identification of the inventive concepts of the claims on file and we therefore consider that the combination of essential elements of independent claims 1, 15, 30, 33, 46, 52, 59 to 61 and 66 represents their inventive concepts and that the additional elements of the dependent claims are part of their respective inventive concepts.

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

[82] The Preliminary Review Letter on pages 20 and 21 states the following with regard to the differences that exist between the matter cited as forming part of the "state of the art" and the inventive concepts of the claims:

In addition to D3, D4, D5 and D7 introduced above, the Final Action cites the following documents as relevant art:

D1:	US20110016546 A1	Bedell et al.	20 January 2011

D6: Oetke et al., Molecular and Cellular Biology, 26(4), pages 1549-1557, 2006

D8: Lunney and Chen, Virus Research, 154, pages 161-169, 2010

D1 discloses the use of zinc finger nucleases to introduce mutations within porcine chromosomal sequences encoding the CD163 protein, wherein the edited chromosomal sequences comprise a mutation such that CD163 protein is not produced. Genetically modified porcine animals and cells thereof comprising said edited chromosomal sequence coding for CD163 may be heterozygous or homozygous for the introduced mutation. D1 teaches that these animals will have increased disease resistance, such as to PRRSV infection. D1 teaches that the animals may be crossbred to create animals comprising more than one edited chromosomal sequence, or to create animals that are homozygous for one or more edited chromosomal sequences.

D6 discloses the generation of sialoadhesin -/- mice. The mice were viable and fertile, and showed no developmental abnormalities. D6 teaches that sialoadhesin orthologues share an amino acid identity from 69-78% between mouse, pig and human, and that the cellular expression pattern is well-conserved among mammalian species. This suggests that the specific functions of sialoadhesin may also be conserved. D6 teaches that the sialoadhesin -/- mice are an ideal model to investigate the role of sialoadhesin in modulating the immune and inflammatory responses.

D8 reviews advances made using genomic approaches to identify biomarkers that are correlated with swine resistance to infection with PRRSV. D8 teaches that there is no evidence of receptor null individuals for PRRSV likely because there are multiple receptors, sialoadhesin and CD163. D8 teaches that many viral receptors are likely essential cell surface proteins and thus deletion would not likely result in viable pigs. D8 teaches

> that genetic selection for disease resistance must consider potential negative effects on other commercially important traits.
>
> In our preliminary view the main difference between the inventive concepts of claims 1 to 70 on file and either D1, D3, D4, D5, D9 or D10 lies in the production of a genetically modified swine that exhibits increased resistance to PRRSV and that comprises genetically modified swine cells with an alteration, a partial deletion or a complete deletion of the *CD163* gene sequence in both alleles of a *CD163* gene or in a non-coding sequence of the *CD163* gene.

[83] The Applicant did not contest or otherwise comment on our characterization of the differences that exist between the matter cited as forming part of the "state of the art" and the inventive concepts of the claims and we therefore adopt the above characterization for our final analysis.

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?

[84] The Preliminary Review Letter on pages 22 to 26 explains why it was our preliminary view that claims 1 to 3, 5 to 17, 19 to 35, 37 to 48, 50 to 54 and 56 to 70 on file encompass subject-matter that was obvious to try and thus would not have required any degree of invention from the POSITA in view of the cited prior art and the relevant CGK with regard to the differences that exist between the matter cited as forming part of the "state of the art" and the inventive concepts of the claims:

> Although the Court in Sanofi provides a four-step approach for addressing the issue of obviousness, it is important to remember that the obviousness analysis is concerned with whether bridging the difference between the prior art and a second point constitutes steps that require any degree of invention: Bristol-Myers Squibb Canada Co v Teva Canada Limited, 2017 FCA 76 at para 65

> It may be helpful to keep in mind that the obviousness analysis asks whether the distance between two points in the development of the art can be bridged by the Skilled Person using only the common general knowledge available to such a person. If so, it is obvious. The first of those points is the state of the prior art at the relevant date. References in the jurisprudence to “the inventive concept”, “the solution taught by the patent”, “what is claimed” or simply “the invention” are attempts to define the second point.

Given that the subject-matter of the present claims relates to the production of genetically modified swine cells and swine with increased resistance to a swine virus, a field which we consider an area of endeavor “where advances are often won by experimentation” (Sanofi at para 68), we therefore have considered an “obvious to try” analysis.

For a finding that an invention was “obvious to try”, it must have been “more or less self-evident to try to obtain the invention. Mere possibility that something might turn up is not enough” (Sanofi at para 66).

Before considering the facts of the present case, it is worth noting that a finding that it would have been more or less self-evident that what is being tried “ought to work” does not mean that certainty of success is required, otherwise there would be no point in describing it as something “to try”. Indeed, an “obvious to try” analysis is used precisely in areas where advances are won by experiment, so that success cannot be guaranteed before trying (Les Laboratoires Servier v Apotex Inc, 2019 FC 616 at para 269). Rather, what must be considered is whether it is more or less self-evident that the “try” ought to work in view of the CGK and the prior art; a mere possibility will not suffice but an amount of uncertainty is allowed in the obvious to try analysis: See Janssen Inc v Apotex Inc, 2021 FC 7 at para 135:

> As to “ought to work”, it is clear that certainty of success is not required otherwise there would be no point in describing it as something “to try”. “Trying” implies the possibility of failure but with the expectation of success. While never easy to define on a

> spectrum of likely success, it is neither a Boston College Doug Flutie “Hail Mary” pass nor a Wayne Gretsky “open net shot”. Some limited experimentation is permitted in the context of the second factor. It is not to be arduous, inventive or unusual.

In view of the foregoing and within the context of the claimed subject-matter, we consider that the relevant questions are whether it would have been more or less self-evident to the POSITA, based on the disclosures of D1, D3, D4, D5, D9 and/or D10, and the relevant CGK, that: 1) swine comprising genetically modified swine cells with complete deletion of both alleles of a CD163 gene or comprising genetically modified swine cells that do not express CD163 ought to exhibit increased resistance to PRRSV; and 2) swine comprising genetically modified swine cells with an alteration or a partial deletion in a portion of the CD163 gene sequence in one or both alleles of a CD163 gene ought to exhibit increased resistance to PRRSV.

Swine comprising genetically modified swine cells with complete deletion of one or both alleles of a *CD163* gene or comprising genetically modified swine cells that do not express CD163

Although the POSITA would have been taught by D1 to introduce mutations within porcine chromosomal sequences encoding the CD163 protein, wherein the edited chromosomal sequences comprise a mutation such that CD163 protein is not produced, we are of the preliminary view that it would not have been more or less self-evident to the POSITA, given the relevant CGK regarding the main biological functions of CD163 and particularly the homeostatic role of CD163 to prevent haemoglobin toxicity, that a genetically modified swine that does not express CD163 would be viable in advance of routine testing.

We consider that the above assessment is determinative of the “obvious to try” inquiry for claims 1, 2, 4 to 7, 15, 16, 18 to 21, 23 to 34, 36 to 39, 41 to 47, 49 to 53, 55 to 60, 69 and 70, insofar as they encompass swine comprising genetically modified swine cells with complete deletion of one or

both alleles of a CD163 gene or comprising genetically modified swine cells that do not express CD163 as well as methods related thereto.

However, this is not the end of the inquiry as the scope of several of these claims also encompasses subject-matter related to swine comprising genetically modified swine cells with an alteration or a partial deletion in a portion of the *CD163* gene sequence in one or both alleles of a *CD163* gene.

Swine comprising genetically modified swine cells with an alteration or a partial deletion in a portion of the *CD163* gene sequence in one or both alleles of a *CD163* gene

D1, D3, D4, D5, D9 and D10 all disclose that CD163 is an important receptor for PRRSV infectivity.

D1, D4, D5, D9 and D10 further disclose that the SRCR domains of CD163 that are essential to PRRSV infectivity are more centrally located with a key role for SRCR domain 5, while the first four SRCR domains and cytoplasmic tail are not required. Otherwise, D9 also teaches that the haemoglobin-haptoglobin complexes have high affinity with SRCR domain 3.

Given the above teachings and the CGK identified above, we are of the preliminary view that it would have been more or less self-evident to the POSITA that swine comprising modified swine cells having an alteration, a partial deletion, or a SRCR domain swap in a portion of both allelic *CD163* gene sequences that is known to influence PRRSV infectivity (e.g., SRCR domain 5) while leaving the other domains intact, ought to be viable and exhibit increased resistance to PRRSV.

Furthermore, it would have been more or less self-evident to the POSITA that mating female and male animals generated from genetically modified swine cells with an alteration, a partial deletion, or a SRCR domain swap in a portion of one allele of the *CD163* gene that is known to influence PRRSV infectivity (e.g., SRCR domain 5) while leaving the other domains intact, ought to produce swine comprising modified swine cells having said

alteration, a partial deletion, or a SRCR domain swap in both alleles of the *CD163* gene and exhibiting increased resistance to PRRSV.

Although we considered that the above assessment is largely determinative of the “obvious to try” inquiry in this case, we make the following observations with regard to other non-exhaustive factors to be considered.

Regarding the Motivation Factor, which includes considerations provided in the prior art to find the solution the patent addresses and the motivation to combine the teachings of the cited prior art, we offer the following preliminary views.

We consider that there was general motivation in the prior art to address PRRSV infections in swine herds and specific motivation in the prior art to do so by preventing the CD163 receptor to play its pivotal role in PRRSV infectivity.

We further consider that each of D1, D4, D5 and D10 independently provides a strong motive to produce genetically modified swine comprising alterations in the SRCR domains of CD163 that are essential to PRRSV infectivity and also consider that D9 and/or the CGK provide a strong motive to leave the other portions of CD163 unaltered, including domains necessary for haemoglobin clearance functions of CD163.

Therefore, it is our preliminary view that the POSITA would have been motivated by D1 and the results disclosed in each of D4, D5, D9 and D10 to produce swine comprising genetically modified swine cells with an alteration or a partial deletion in a portion of the *CD163* gene sequence in both alleles of a *CD163* gene by mating female and male animals generated from genetically modified swine cells with an alteration or a partial deletion in a portion of the *CD163* gene sequence in one allele of a *CD163* gene.

Finally and with respect to the Extent and Effort Factor, we consider that the extent, nature, and amount of effort required to use CGK techniques for the production of genetically modified swine cells and genetically modified

animals would have been within the POSITA's capabilities as of the claim date.

Therefore, and taking into account the foregoing considerations of the relevant factors pertaining to an "obvious to try" analysis, we are of the preliminary view that it was obvious to try to obtain a genetically modified swine comprising modified swine cells having an alteration, a partial deletion, or a SRCR domain swap in a portion of both allelic *CD163* gene sequences that is known to influence PRRSV infectivity (e.g., SRCR domain 5) while leaving the other domains intact such that the other functions of CD163 remain intact. It also follows that we are of the preliminary view that it was obvious to try to obtain said genetically modified swine by mating female and male animals generated from genetically modified swine cells with an alteration or a partial deletion in a portion of the *CD163* gene sequence in one allele of a *CD163* gene.

Genetically modified swine cells with one or more alterations in a *CD163* gene sequence, wherein the one or more alterations are in a non-coding sequence of the *CD163* gene and inactivate the *CD163* gene

Turning now to claims 61 to 70, insofar as the scope of these claims encompasses genetically modified swine comprising modified swine cells having one or more alterations in a non-coding sequence of the *CD163* gene that inactivate one or more of the SRCR domains of CD163 that are essential to PRRSV infectivity and related methods of production, it is our preliminary view that it would have been more or less self-evident to the POSITA to try to obtain such genetically modified swine cells and genetically modified swine in view of the teachings of D1, D9, the results disclosed in either of D4, D5, or D10 and the relevant CGK for the same reasons expressed above with respect to swine comprising genetically modified swine cells with an alteration or a partial deletion in a portion of the *CD163* gene sequence in both alleles of a *CD163* gene as targeting the non-coding sequence portions instead or the coding ones in order to inactivate the SRCR domains of CD163 that are essential to PRRSV infectivity while leaving the other domains intact does not require any degree of invention.

[85] As stated in the Preliminary Review letter on page 22, it was our preliminary view that given that the subject-matter of the present claims relates to the production of genetically modified swine cells and swine with increased resistance to a swine virus, a field which we consider an area of endeavor “where advances are often won by experimentation” (Sanofi at para 68), an “obvious to try” analysis was warranted.

[86] The Applicant did not contest or otherwise comment on the relevance of an “obvious to try” analysis and has presented arguments in response to our analysis that are aligned with the obvious to try approach taken. We therefore adopt the “obvious to try” analytical framework for our final analysis.

[87] In the Preliminary Review letter on page 23 and with regard to the Self-Evident Factor and swine comprising genetically modified swine cells with an alteration or a partial deletion in a portion of the *CD163* gene sequence in one or both alleles of a *CD163* gene, we stated that the relevant question was whether it would have been more or less self-evident to the POSITA, based on the disclosures of D1, D3, D4, D5, D9 and/or D10, and the relevant CGK, that swine comprising genetically modified swine cells with an alteration or a partial deletion in a portion of the *CD163* gene sequence in one or both alleles of a *CD163* gene ought to exhibit increased resistance to PRRSV.

[88] The Applicant did not contest or otherwise comment on the relevance of that question to the Self-Evident Factor and we will therefore also consider said question for our final analysis.

[89] With respect to the cited prior art and any indication that genetically editing *CD163* alone can produce swine harboring resistance to PRRSV infection, the Response to the Preliminary Review letter submits that:

- D1 does not describe or provide any information specifically directed to genome editing the *CD163* chromosomal sequence, and that D1 names *CD163* among a list of other genes and merely speculates that *CD163* can be edited using a nuclease such that CD163 is not produced and that this may produce increased disease resistance in pigs;

- D3, D4 and D5 merely provide *in vitro* data;

- D4 teaches co-transfection of SIGLEC1 in combination with different CD163 constructs in a human hepatic cell line and that expression of both entry mediators offers a model for virus entry and infection (i.e., SIGLEC1 and CD163);

- On the basis of D8 and D4, the POSITA could not reasonably expect that making any of the edits solely to CD163 could result in conferring resistance to PRRSV infection; and

- In sum, the cited prior art does not provide any indication that genetically editing CD163 alone can produce swine harboring resistance to PRRSV infection. Rather, it would be entirely unpredictable whether making an edit within CD163 would confer resistance to PRRSV.

[90] When the cited prior art is considered in its entirety, it is our view that the cited prior art points the POSITA in the direction of altering the *CD163* gene sequence in pig cells to confer resistance to PRRSV infection in pigs comprising said modified pig cells.

[91] Each of D1, D4, D5, D9 and D10 discloses that CD163 is an important receptor for PRRSV infectivity and teaches that the SRCR domains of CD163 that are essential to PRRSV infectivity are more centrally located with a key role for SRCR domain 5 [emphasis added]:

> (**D1 at para [0027]**) Further, scavenger receptor CD163 is a key entry mediator for PRRSV. In one study, CD163 protein domains involved in PRRSV infection were identified through the creation of deletion mutants and chimeric mutants. Infection experiments revealed that scavenger receptor cysteine-rich (SRCR) domain 5 (SRCR 5) is essential for PRRSV infection, while the four N-terminal SRCR domains and the cytoplasmic tail are not required. The remaining CD163 protein domains need to be present but can be replaced by corresponding SRCR domains from CD163-L1, resulting in reduced (SRCR 6 and interdomain regions) or unchanged (SRCR 7 to SRCR 9) infection efficiency. In addition, CD163-specific antibodies recognizing SRCR 5 are able to reduce PRRSV infection.

(**D4 on page 3102 and 3104**) Simultaneous replacement of CD163 SRCR 4, 5, and 6 with the corresponding domains of CD163-L1 resulted in a loss of infectivity (mutant L). To evaluate the contribution of each of the three domains, all three were replaced separately. Substitution of CD163 SRCR 4 had no influence on infection (mutant P), while swapping CD163 SRCR 5 completely inhibited infection (mutant Q). Replacing CD163 SRCR 6 resulted in reduced infection efficiency (mutant R). Like SRCR 6, both PST I and II seemed not to be essential, but the presence of the corresponding domains of CD163-L1 reduced infection (mutants M and O). Interestingly, CD163 SRCR domains 7, 8, and 9, closest to the plasma membrane, could be replaced by the corresponding domains from CD163-L1 without significantly influencing PRRSV infection (mutant N).

…

However, in the case of the PAb incubated on cells expressing mutant Q, all antibodies except the ones recognizing CD163 SRCR 5 were depleted, and the remaining antibodies were still able to reduce PRRSV infection to the same level as the original PAb, confirming that the antibodies recognizing SRCR 5 are responsible for the observed blocking effect.

In conclusion, the CD163 cytoplasmic tail is dispensable for PRRSV infection, as are the four N-terminal extracellular SRCR domains. The essential domains are more centrally located, with SRCR 5 as a key component. So far, only SRCR 2 and SRCR 3 have been found involved in biological processes. Hemoglobin-haptoglobin (HbHp) complexes are internalized upon binding to SRCR 3 of CD163 (11, 14). Previously, it was shown that HbHp complexes are not able to reduce PRRSV infection (30), which is in agreement with the results obtained with the mutants described here, showing that the four N-terminal SRCR domains are not involved. In addition, a 13- amino-acid motif within SRCR 2 has been identified as a putative interaction site that mediates erythroblast binding (8) and interaction with both Gram-positive and -negative bacteria (9).

(**D5 on page 100 and 102**) Although CD169 binds and internalizes PRRSV particles, this is an incomplete process and does not lead to the initiation of virus replication (Vanderheijden et al., 2003). In contrast, transient transfection of the CD163 gene into PRRSV non-permissive cell lines (CHO-K1, BHK-21 and PK-15) caused these cells to become susceptible to PRRSV infection (Van Gorp et al., 2008). Higher PRRSV titers were attained in cells transiently co-expressing both CD169 and CD163 than in cells expressing CD163 alone. However, in our labs, we were unable to demonstrate enhancement of PRRSV production by stably transfecting CD169 into a cell line that already stably expressed CD163, using PRRS viruses that have been previously adapted to grow on cells expressing CD163 alone (unpublished data). (See D5 on page 100)

4. CD163 domains involving in PRRSV infectivity

The CD163 domains involved in PRRSV infection were dissected in detail (Van Gorp et al., 2010b). Various deletion mutants of porcine CD163, and porcine CD163 chimeric constructs with human CD163-L1, were generated and tested for PRRSV receptor activity. CD163-L1 is a gene duplication of the human CD163 gene. The CD163-L1 gene is structurally similar to CD163, but expressed CD163-L1 protein did not confer the PRRSV permissive phenotype (Van Gorp et al., 2010b). SRCR domain deletion and replacement experiments revealed that SRCR 5 of porcine CD163 is essential for infection, while the first four N-terminal repeats and cytoplasmic tail are not required. The remaining four C-terminal repeats can be replaced with corresponding CD163-L1 repeats, but deletion of these four repeats or the PST II domain (proline–serine–threonine rich domain II or second inter-domain segment) abolished infection. Deletion of the PST I domain (first inter-domain segment) reduced infectivity. From these results it seems that the distance between SRCR 5 and the cellular membrane may be critical for receptor function. The identification of SRCR 5 as the critical domain for PRRSV infection is consistent with the finding of others that SRCR 1–2 and 9 are not involved (Calvert et al., 2007; Das et al., 2010).

…

Several studies in recent years have confirmed a pivotal role for CD163 in the initiation of PRRSV infection. Molecular interactions between CD163 domains and specific viral proteins are being discovered. New stable cell lines are being constructed to examine early events leading viral entry and productive PRRSV infection, and some of these may have utility in the manufacturing of novel vaccines.

(**D9 on page 1654**) Analysis of the interaction between PRRSV and CD163 revealed that the cytoplasmic tail containing the internalization motif is dispensable for PRRSV infection, as are the 4 N-terminal SRCR domains. The essential domains are more centrally located with a key role for SRCR domain 5, but also other SRCR domains and the 2 PST domains are required (Van Gorp et al., 2010). So far, no biological role has been attributed to these domains as other ligands were shown to interact with SRCR domain 2 or 3 (Fabriek et al., 2007b, 2009; Madsen et al., 2004).

(**D10 on page 1663**) The exact mechanism of action of CD163 is not yet known. Recently however, CD163 domains crucial for PRRSV infection were identified. Different mutant forms of CD163 were evaluated for their capacity to confer a PRRSV-permissive phenotype to non-permissive cells. In one approach, mutants of CD163 were obtained by deleting specific domains of the protein. In another approach, chimaeric proteins were obtained by swapping specific domains of CD163 with the corresponding regions of human CD163-L1, a paralogue of human CD163 that does not allow PRRSV infection, or vice versa. The results of this study indicate that the four N-terminal scavenger receptor cysteine-rich (SRCR) domains of CD163 are not involved, while the fifth SRCR domain has a leading role in PRRSV infection. In addition, the presence of the sixth SRCR domain and of the two proline–serine–threonine (PST)-rich interdomains of CD163 has a positive influence on the infection efficiency. The presence of the SRCR domains 7, 8 and 9 seems important for a correct overall structure and presentation of the CD163 domains that are critical for infection. The cytoplasmic tail of CD163, which contains a YxxΦ-motif that directs the constitutive endocytosis of this molecule, is dispensable, arguing against a

role for CD163 as an internalization receptor for PRRSV (Van Gorp et al., 2010).

[92] The lack of evidence for PRRSV receptor null individuals as reported by D8 does not reveal anything regarding the actual role of CD163 in PRRSV infection and thus D8 is not evidence that CD163 does not play a critical role in PRRSV infection or that edits solely to CD163 could not result in conferring resistance to PRRSV infection. We consider that the POSITA would appreciate that, unlike D8, the relevant teachings of D1, D4, D5, D9 and D10 squarely address the role of CD163 and SRCR domains of CD163 in PRRSV infectivity.

[93] Further, we are of the view that the POSITA would understand from D1, D5, D9 and D10 that their teachings about the critical role of CD163, and more particularly the SRCR domain 5 of CD163, regarding PRRSV infectivity are mainly based on the disclosure of D4. As the Applicant correctly pointed out in the Response to the Preliminary Review letter on page 5, D4 describes modified regions of CD163 that had little to no effect on PRRSV infectivity. However, D4 also reports that no infection was observed in cells co-expressing SIGLEC1 and a CD163 mutant having the SRCR domain 5 replaced with SRCR domain 8. It is our view that the POSITA would understand from those results that altering CD163 *alone*, rather than both SIGLEC1 and CD163, is sufficient to confer resistance to PRRSV infection and that mutations targeting SRCR domain 5 of CD163 are more likely to confer resistance to PRRSV infection than mutations targeting other portions of CD163.

[94] The Response to the Preliminary Review letter further submits on page 5 that the POSITA is well aware that modifying the genomic DNA can affect the transcription and translation of the edited genomic DNA and that edits can affect protein folding and transport of the protein within the cell.

[95] We acknowledge that the POSITA would be aware that modifying the genomic DNA may or may not affect the transcription and translation of the edited genomic DNA and that edits may or may not affect protein folding and transport of the protein within the cell. However, as mentioned in the Preliminary Review letter, it is worth noting that a finding that it would have been more or less self-evident that what is being tried “ought to work” does not mean that certainty of success is required, otherwise there would be no point in describing it as something “to try”. Indeed, an “obvious to try” analysis is used precisely in areas where advances are

won by experiment, so that success cannot be guaranteed before trying (Les Laboratoires Servier v Apotex Inc, 2019 FC 616 at para 269). Rather, what must be considered is whether it is more or less self-evident that the "try" ought to work in view of the CGK and the prior art; a mere possibility will not suffice but an amount of uncertainty is allowed in the obvious to try analysis: See Janssen Inc v Apotex Inc, 2021 FC 7 [Janssen] at para 135:

> As to "ought to work", it is clear that certainty of success is not required otherwise there would be no point in describing it as something "to try". "Trying" implies the possibility of failure but with the expectation of success. While never easy to define on a spectrum of likely success, it is neither a Boston College Doug Flutie "Hail Mary" pass nor a Wayne Gretsky "open net shot". Some limited experimentation is permitted in the context of the second factor. It is not to be arduous, inventive or unusual.

[96] On the basis of the disclosures of D1, D4, D5, D9 and D10, and the relevant CGK, it is our view that the likely success of making an edit in a portion of both allelic *CD163* gene sequences that is known to influence PRRSV infectivity to confer resistance to PRRSV (e.g., SRCR domain 5) while leaving the other portions of CD163 unaltered, including domains necessary for haemoglobin clearance functions of CD163, is less than a certainty but more than a mere possibility.

[97] It follows that we are of the view that it would have been more or less self-evident to the POSITA that swine comprising modified swine cells having an alteration, a partial deletion, or a SRCR domain swap in a portion of both allelic *CD163* gene sequences that is known to influence PRRSV infectivity (e.g., SRCR domain 5) while leaving the other domains intact, ought to be viable and exhibit increased resistance to PRRSV.

[98] Furthermore and for the same reasons, it would have been more or less self-evident to the POSITA that mating female and male animals generated from genetically modified swine cells with an alteration, a partial deletion, or a SRCR domain swap in a portion of one allele of the *CD163* gene *that is known to influence PRRSV infectivity* (e.g., SRCR domain 5) while leaving the other domains intact, ought to produce swine comprising modified swine cells having said alteration, a partial deletion, or a SRCR domain swap in both alleles of the *CD163* gene and exhibiting increased resistance to PRRSV.

[99] With respect to claims 61 to 70, insofar as the scope of these claims encompasses genetically modified swine comprising modified swine cells having one or more alterations in a non-coding sequence of the CD163 gene that inactivate one or more of the SRCR domains of CD163 that are essential to PRRSV infectivity (e.g., SRCR domain 5) and related methods of production, we offer the following views. We consider that it would have been more or less self-evident to the POSITA to try to obtain such genetically modified swine cells and genetically modified swine in view of the teachings of D1, D9, the results disclosed in either of D4, D5, or D10 and the relevant CGK for the same reasons expressed above with respect to swine comprising genetically modified swine cells with an alteration or a partial deletion in a portion of the CD163 gene sequence in both alleles of a CD163 gene as targeting the non-coding sequence portions instead or the coding ones in order to inactivate the SRCR domains of CD163 that are essential to PRRSV infectivity (e.g., SRCR domain 5) while leaving the other domains intact does not require any degree of invention.

[100] Although we consider that the above assessment is largely determinative of the "obvious to try" inquiry in this case, we make the following observations with regard to the other non-exhaustive factors to be considered and corresponding arguments presented by the Applicant, starting with the Motivation Factor.

[101] The Response to the Preliminary Review letter addresses the Motivation factor on pages 4 to 5 when it disagrees that the cited prior art provides specific motivation to address PRRSV infection in swine by preventing the CD163 receptor to play a "pivotal role" in PRRSV infectivity.

[102] The Response to the Preliminary Review letter more specifically submits that D1 does not describe or provide any information specifically directed to genome editing the CD163 chromosomal sequence, and that D1 names CD163 among a list of other genes and merely speculates that CD163 can be edited using a nuclease such that CD163 is not produced and that this may produce increased disease resistance in pigs.

[103] With respect to D3, D4 and D5, the Response to the Preliminary Review letter submits that these documents would not provide the POSITA with any motivation regarding inactivating CD163 alone because D3, D4 and D5 merely provide *in vitro* data and because D4 teaches the expression of both entry mediators (i.e., SIGLEC1 and CD163) in a model for virus entry and infection.

[104] We respectfully disagree. We consider that the POSITA would understand from each of D1, D4, D5, D9 and D10, or otherwise would know from the CGK, that PRRSV is one of the most significant viral pathogens in the swine industry and would also understand, for reasons explained above, that each of D1, D4, D5, D9 and D10 discloses that CD163 is an important receptor for PRRSV infectivity and teaches that the SRCR domains of CD163 that are essential to PRRSV infectivity are more centrally located with a key role for SRCR domain 5.

[105] We therefore consider that there was a general motivation in the prior art to address PRRSV infections in swine herds and specific motivation in the cited prior art to do so by preventing the CD163 receptor to play its pivotal role in PRRSV infectivity.

[106] In that regard, we consider: i) that D1 provides a strong motive to produce genetically modified swine comprising alterations in CD163, notably at paras [0027] and [0028]; ii) that each of D4, D5 and D10 independently provides a strong motive to focus the alterations in the SRCR domains of CD163 that are essential to PRRSV infectivity (e.g. SRCR domain 5); and iii) that D9 and/or the CGK provides a strong motive to leave the other portions of CD163 unaltered, including domains necessary for haemoglobin clearance functions of CD163.

[107] With respect to the Extent and Effort Factor, we consider that the extent, nature, and amount of effort required to use CGK techniques for the production of genetically modified swine cells and genetically modified animals would have been within the POSITA's capabilities as of the claim date.

[108] We have considered the Applicant's arguments regarding CGK in the "The POSITA and the relevant CGK" section above and we stated that a CGK method or technique is not necessarily straightforward or always successful when practiced and we acknowledged the fact that, using the SCNT approach, the expected efficiency of cloning in swine was relatively low, ranging between 0.5% and 5% offspring per transferred SCNT embryos (as evidenced by D7 on page 656). That being said, some limited experimentation is permitted in the context of this factor but it is not to be arduous, inventive or unusual (see Janssen at para 135).

[109] As indicated above, we have already determined that the SCNT approach was not inventive or unusual as the SCNT approach was a technique that was made available at least 10 years before the claim date, was the only route to introduce

targeted mutations into the pig genome and otherwise deemed CGK. We are of the same general view regarding the techniques of homology-directed gene targeting for introducing specific mutations in somatic cells.

[110] Although the techniques for the production of genetically modified porcine cells and genetically modified swine are objectively not simple and/or straightforward, we consider that the SCNT approach was nonetheless the most routinely carried out technique by a molecular biologist that is familiar with transgenic swine production techniques for introducing specific mutations.

[111] Also relevant to the effort required is the actual course of conduct that culminated in the making of the invention (Sanofi at para 70). As mentioned above, there is no indication in the record before us of a demonstrated production of swine comprising genetically modified swine cells comprising inactivating mutations or a partial deletion in one or both alleles of a *CD163* gene, including swine that exhibit increased resistance to PRRSV. The closest embodiment is found in Example 1 that describes on pages 21 to 27 of the description the actual production of swine comprising genetically modified swine cells with both *SIGLEC1* alleles deleted. We consider that Example 1 applies CGK techniques for the production of genetically modified porcine cells and genetically modified swine, more specifically the steps and techniques related to swine transgenesis by SCNT as well as the techniques of homology-directed gene targeting for introducing specific mutations in somatic cells. Example 1 and the different passages of the instant description that are quoted above at para [33] independently support our findings that swine transgenesis by SCNT and techniques of homology-directed gene targeting for introducing specific mutations in somatic cells were not arduous, inventive or unusual.

[112] Under the heading “Commercial Success”, the Response to the Preliminary Review letter notes on page 7 that:

> [T]he present application is part of a global patent application portfolio that has been licensed to Genus PLC. In partnership with Genus PLC, Applicant has filed 38 patent applications globally with 12 having been granted.
>
> The present application focuses on preventing PRRSV, a highly challenging and costly disease in the global pig industry. However, current therapies,

> such as vaccines, often fail to provide satisfactory protection due to strain variation and inadequate immune system stimulation. The present application aims to offer an alternative approach through the use of genetically modified pigs exhibiting increased resistance to PRRSV. Therefore, the present application has been licensed to Genus PLC to develop PRRS-resistant pigs for combating PRRS".

[113] Commercial success of the claimed invention may be a relevant, though not conclusive, secondary consideration in assessing obviousness, mainly in borderline cases (Pollard Banknote Limited v BABN Technologies Corp, 2016 FC 883, at para 221). That being said, commercial success cannot save an invention that is obvious, and there must be a causal relationship between the alleged invention and any commercial success as it may be that commercial success is due to other factors (see Teva Canada Limited v Janssen Inc, 2018 FC 754 at paras 91 and 92).

[114] It is not clear to us how the fact that a given application is part of a broader licensed portfolio or how the fact that 12 patents directed to unspecified subject-matter were granted is specifically relevant to the commercial success of the instant *claimed invention*. "A patent, as has been said many times, is not intended as an accolade or civic award for ingenuity" (AZT at para 37).

[115] Further, we consider that the instant case is not the type of borderline case in which an otherwise obvious invention might be saved by showing commercial success for the reasons detailed above.

[116] Finally, we consider that the Applicant has not presented evidence as it regards commercial success of the *claimed invention*, more specifically genetically modified swine cells with an alteration or a partial deletion in a portion of the *CD163* gene sequence in both alleles of a *CD163* gene which confer PRRSV resistance to genetically modified swine that comprise said cells. We are of the same view regarding genetically modified swine cells having one or more alterations in a non-coding sequence of the *CD163* gene that inactivate one or more of the SRCR domains of CD163 that are essential to PRRSV infectivity.

[117] With respect to dependent claims that define further limitations regarding the absence of mutation in the SIGLEC1 gene (claims 2, 16, 34 and 65), the

contemplated mutations in the CD163 gene (claims 3 to 6, 8 to 14, 17 to 20, 22, 35 to 38, 40, 48, 49, 54, 55, 62 to 64 and 68), the system or specific method used for mutating the CD163 gene (claims 7, 21, 39, 47 and 53) and the method or a step used to produce the contemplated genetically modified swine cell or swine (claims 23 to 29, 31, 32, 41 to 45, 50, 51, 56 to 58, 67, 69 and 70), the Preliminary Review letter stated that the recited additional features do not require any inventive ingenuity in view of the cited prior art and/or the identified CGK.

[118] The Applicant did not specifically contest or otherwise comment on the above preliminary views regarding the dependent claims and we therefore adopt these views here for the purposes of this final review.

Conclusion on obviousness

[119] It is therefore our view that claims 1 to 3, 5 to 17, 19 to 35, 37 to 48, 50 to 54 and 56 to 70 on file encompass subject-matter that would have been obvious to the POSITA, as of the relevant date, having regard to D1, D9 and either D4, D5, or D10 as well as the relevant CGK, contrary to section 28.3 of the *Patent Act*.

INDEFINITENESS

Legal background

[120] Subsection 27(4) of the *Patent Act* requires claims to distinctly and explicitly define the subject-matter of the invention:

> 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.

[121] In Minerals Separation North American Corp v Noranda Mines Ltd, [1947] Ex CR 306 at 352, 12 CPR 99, the Court emphasized the obligation of an Applicant to make clear in the claims the scope of the monopoly sought, as well as the requirement that the terms used in the claims be clear and precise:

> 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.

Analysis

[122] The Preliminary Review letter, on pages 27 and 28, explains why in our preliminary view claims 1 to 3 are indefinite:

> The Final Action, on page 6, indicates that claims 1, 8 to 13, 15, 30, 34, 52, 59 and 61 are indefinite and do not comply with subsection 27(4) of the *Patent Act*:
>
> > Claims 1, 15 and 61 are indefinite and do not comply with subsection 27(4) of the *Patent Act.* The claims are directed to a "swine cell" (singular form), but then refer to "swine cells" (plural form), causing ambiguity.
> >
> > Claims 8-13 are indefinite and do not comply with subsection 27(4) of the *Patent Act.* These dependent claims are directed to a "swine", rather than a "swine cell" as specified in the claims from which they depend.
> >
> > Claim 30 is indefinite and does not comply with subsection 27(4) of the *Patent Act.* The outcome of the method does not achieve its purpose as stated in the preamble. The purpose of the method is "producing a genetically modified swine", but the outcome is "activating the oocyte to produce an embryo". All of the steps required to carry out the claimed method must be specifically defined.
> >
> > Claim 34 is indefinite and does not comply with subsection 27(4) of the *Patent Act.* It is unclear whether the element "the swine" refers to the element ‘‘a genetically modified swine" (claims 30, 33), "a

> surrogate swine" (claim 31), "a female genetically modified swine" (claim 33), or "a male genetically modified swine" (claim 33).
>
> Claim 52 is indefinite and does not comply with subsection 27(4) of the *Patent Act.* The outcome of the method does not achieve its purpose as stated in the preamble. The purpose of the method is "producing a genetically modified swine", but the outcome is "incubating the cell".
>
> Claim 59 is indefinite and does not comply with subsection 27(4) of the *Patent Act.* The phrase "mutations in at both alleles" lacks clarity.

> The Response to the Final Action and the letter dated December 14, 2022 do not comment on or contest the above views and instead submits proposed claims with amendments addressing the identified issues.
>
> Having reviewed claims 1, 8 to 13, 15, 30, 34, 52, 59 and 61, we agree with the Final Action that these claims suffer from indefiniteness, ambiguity and/or lack clarity for the reasons reproduced above. Therefore, it is our preliminary view that claims 1, 8 to 13, 15, 30, 34, 52, 59 and 61 do not comply with subsection 27(4) of the *Patent Act*.

[123] The Applicant did not contest or otherwise comment on those preliminary findings and we therefore adopt the foregoing reasoning and conclude that claims 1, 8 to 13, 15, 30, 34, 52, 59 and 61 do not comply with subsection 27(4) of the *Patent Act*.

THE PROPOSED CLAIMS DO NOT REMEDY THE DEFECTS

[124] During the review, the Panel may consider proposed amendments.

[125] As mentioned above, the Applicant submitted proposed claims 1 to 69 (proposed claims set-1) on January 24, 2022 with the Response to the Final Action and further submitted a second set of proposed claims (proposed claims set-2) on December 14, 2022.

[126] In the Response to the Preliminary Review letter and at the hearing, the Applicant

did not specifically address the proposed claims sets 1 and 2 but indicated that the Panel should consider the presented submissions when addressing both proposed claims sets.

[127] A review of proposed claims set-1 indicates that claim 1 on file has been amended to incorporate the limitation of claim 6 and claim 6 on file has been cancelled. In addition, claim 7 is also amended for proper dependency to now depend from claims 1 to 5 in view of the cancellation of claim 6. Otherwise, it is submitted that proposed claims corresponding to claims 1, 8 to 13, 15, 30, 34, 52, 59 and 61 on file have been amended to address the indefiniteness, ambiguity and/or lack clarity issues of the claims on file.

[128] According to page 2 of the Summary of Reasons, the amendments found in proposed claims 1, 7 to 12, 14, 29, 32, 33, 51, 58 and 60 would overcome the defects identified under subsection 27(4) of the *Patent Act* in the Final Action with respect to claims 1, 8 to 13, 15, 30, 34, 52, 59 and 61 on file. We agree.

[129] However, given the lack of meaningful difference between the scope of claims 6 to 70 on file and proposed claims 1 to 69, it is our view that: 1) the utility of the claimed subject-matter has not been established by demonstration or a sound prediction across the entire scope of proposed claims 1, 2, 4 to 6, 14, 15, 17 to 20, 22 to 33, 35 to 38, 40 to 46, 48 to 52 and 54 to 69 for the same reasons provided above for corresponding claims on file; and 2) proposed claims 1 to 3, 5 to 16, 18 to 34, 36 to 47, 49 to 53 and 55 to 69 would not comply with section 28.3 of the *Patent Act* for the same reasons provided above for corresponding claims on file.

[130] Further, and as noted in the Summary of Reasons on page 2, proposed claim 49 does not comply with subsection 63(2) of the *Patent Rules* because it refers to itself. We also note that proposed claim 7 should not depend on proposed claim 4 as proposed claim 4 recites complete deletions. Moreover, proposed claim 47 refers to proposed claim 46 twice.

[131] In proposed claims set-2, proposed claims 1, 14, 29, 32, 45, and 51 incorporate the limitations of claims 2, 7, 15, and 33 of proposed claims set-1 to recite that "…the at least one mutated *CD163* allele comprises an alteration in a portion of the *CD163* gene sequence that encodes the SRCR5 domain of the CD163 protein..." and that "the swine cell does not comprise an inactivating mutation in either allele of a SIGLEC1 gene". The dependency of claim 49 of proposed claims set-1 was

also purportedly addressed.

[132] Given that the proposed claims set-2 comprises the amendments found in the proposed claims set-1 that were made to address the indefiniteness, ambiguity and/or lack of clarity issues of the claims on file, we are of the view that the amendments found in the proposed claims set-2 would also overcome the defects identified under subsection 27(4) of the *Patent Act* in the Final Action with respect to claims 1, 8 to 13, 15, 30, 34, 52, 59 and 61 on file.

[133] However, we already have considered the subject-matter of the independent claims of proposed claims set-2 within our obviousness analysis of the claims on file in light of the Applicant's arguments presented in the Response to the Preliminary Review letter and at the hearing, namely genetically modified swine cells with inactivating mutations comprising an alteration in a portion of the *CD163* gene sequence that encodes the SRCR5 domain of the CD163 protein and wherein the swine cell does not comprise an inactivating mutation in either allele of a *SIGLEC1* gene as well as swine comprising said genetically modified swine cells. It is therefore our view that the subject-matter of proposed claims set-2 would not comply with section 28.3 of the *Patent Act* for the same reasons provided above with respect to the claims on file.

[134] With regard to the utility of the subject-matter encompassed by the proposed claims set-2, we already have considered the subject-matter of proposed claims 60 to 69 within our utility analysis of the claims on file in light of the Applicant's arguments presented in the Response to the Preliminary Review letter and at the hearing. It is therefore our view that the utility of the subject-matter has not been established by demonstration or a sound prediction across the entire scope of proposed claims 60 to 69 for the same reasons provided above with respect to the corresponding claims on file.

[135] Further, the proposed claims set-2 is missing claims numbered 2, 7, 15 and 33 but the remaining claims haven't been renumbered accordingly. Finally, claim 49 of proposed claims set-2 still refers to itself.

Conclusion on proposed claims

[136] In view of the foregoing reasons, it is our view that the proposed amendments do not meet the requirements of a necessary amendment under subsection 86(11) of

the *Patent Rules*.

CONCLUSIONS

[137] We have determined that the utility of the claimed subject-matter has not been established by demonstration or a sound prediction across the entire scope of claims 1, 2, 4 to 7, 15, 16, 18 to 21, 23 to 34, 36 to 39, 41 to 47, 49 to 53 and 55 to 70 on file and thus these claims contravene section 2 of the *Patent Act*.

[138] We have further determined that claims 1 to 3, 5 to 17, 19 to 35, 37 to 48, 50 to 54 and 56 to 70 on file encompass subject-matter that would have been obvious to the POSITA, contrary to section 28.3 of the *Patent Act*.

[139] We have also determined that claims 1, 8 to 13, 15, 30, 34, 52, 59 and 61 on file do not comply with subsection 27(4) of the *Patent Act*.

[140] In our view, proposed claims set-1 and proposed claims set-2 would not overcome the identified defects with respect to the claims on file and otherwise contain additional defects. Therefore, the proposed amendments do not meet the requirements of a necessary amendment under subsection 86(11) of the *Patent Rules*.

RECOMMENDATION OF THE BOARD

[141] In view of the above, the Panel recommends that the application be refused on the grounds that:

- subject-matter encompassed by claims 1, 2, 4 to 7, 15, 16, 18 to 21, 23 to 34, 36 to 39, 41 to 47, 49 to 53 and 55 to 70 lacks utility, contrary to section 2 of the *Patent Act*;
- subject-matter encompassed by claims 1 to 3, 5 to 17, 19 to 35, 37 to 48, 50 to 54 and 56 to 70 on file is obvious, contrary to section 28.3 of the *Patent Act*; and
- claims 1, 8 to 13, 15, 30, 34, 52, 59 and 61 on file suffer from indefiniteness, ambiguity and/or lack clarity, contrary to subsection 27(4) of the *Patent Act*.

Marcel Brisebois	Robin Green	Christine Teixeira
Member	Member	Member

DECISION OF THE COMMISSIONER

[142] I concur with the findings of the Board and its recommendation to refuse the application on the grounds that:

- subject-matter encompassed by claims 1, 2, 4 to 7, 15, 16, 18 to 21, 23 to 34, 36 to 39, 41 to 47, 49 to 53 and 55 to 70 lacks utility, contrary to section 2 of the *Patent Act*;
- subject-matter encompassed by claims 1 to 3, 5 to 17, 19 to 35, 37 to 48, 50 to 54 and 56 to 70 on file is obvious, contrary to section 28.3 of the *Patent Act*; and
- claims 1, 8 to 13, 15, 30, 34, 52, 59 and 61 on file suffer from indefiniteness, ambiguity and/or lack clarity, contrary to subsection 27(4) of the *Patent Act*.

[143] Therefore, 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 to appeal my decision to the Federal Court of Canada.

Konstantinos Georgaras

Commissioner of Patents
Dated at Gatineau, Quebec
this 11th day of January, 2024.