Citation: RFS Pharma, LLC. (Re), 2023 CACP 10
Commissioner's Decision #1643
Décision du commissaire nº1643
Date: 2023-03-17

TOPIC:	G00	Utility
	C00	Ambiguity or indefiniteness
SUJET:	G00	Utilité
	C00	Caractère ambigu ou indéfini

Application No. 2,722,308
Demande nº 2 722 308

IN THE CANADIAN PATENT OFFICE

DECISION OF THE COMMISSIONER OF PATENTS

Patent application number 2,722,308, having been rejected under subsection 30(3) of the *Patent Rules* (SOR/96–423) as they read immediately before October 30, 2019, has consequently been reviewed in accordance with paragraph 199(3)(c) of the *Patent Rules* (SOR/2019-251). The recommendation of the Patent Appeal Board and the decision of the Commissioner are to refuse the application if the necessary amendments are not made.

Agent for the Applicant:

RIDOUT & MAYBEE LLP
250 University Ave
5th floor
Toronto, Ontario
M5H 3E5

INTRODUCTION

[1] This recommendation concerns the review of rejected Canadian application number 2,722,308, which is entitled “Nucleoside derivatives for treatment of *Caliciviridae* infections, including Norovirus infections” and is owned by RFS Pharma, LLC (the Applicant).

[2] A review of the rejected application has been conducted by the Patent Appeal Board (the Board) pursuant to paragraph 199(3)(c) of the *Patent Rules* (SOR/2019-251) (the *Patent Rules*). As explained in more detail below, our recommendation is that the Commissioner of Patents refuse the application if the necessary amendments are not made.

BACKGROUND

The application

[3] The application has a filing date of April 9, 2009 and was laid open to public inspection on October 22, 2009.

[4] The application relates to the new use of compositions comprising a class of nucleoside analogs, that were known in the field for treating other viruses by inhibiting viral replication, for the treatment or prevention of infections caused by a *Caliciviridae* virus, such as Norovirus.

[5] The claims under review are claims 1 to 17 on file, dated April 24, 2019 (the claims on file).

Prosecution history

[6] On October 11, 2019, a Final Action (FA) rejecting the claims on file was issued pursuant to subsection 30(4) of the *Patent Rules* (SOR/96–423) as they read immediately before October 30, 2019. The FA stated that claims 1-13 and 15-17 were rejected for not complying with section 2 of the *Patent Act* and that claims 1-17 were rejected for not complying with subsection 27(4) of the *Patent Act*.

[7] On April 2, 2020, a response to the FA (RFA) was filed by the Applicant. In the RFA, the Applicant proposed claim amendments and provided a number of arguments in support of their patentability.

[8] The Examiner was not persuaded by the proposed amendments and arguments provided in the RFA and so the application was forwarded to the Board, along with a Summary of Reasons (SOR) on February 16, 2021.

[9] The SOR was forwarded to the Applicant on February 18, 2021. In a letter dated May 17, 2021, the Applicant expressed continued interest in having the application reviewed by the Board.

[10] This Panel was formed to review the rejected application and make a recommendation to the Commissioner as to its disposition.

[11] During the review an additional question arose in relation to whether claims 3, 4, 14 and 16 contain clarity defects that introduce further indefiniteness or ambiguity not identified in the FA and so the Applicant was notified of these issues pursuant to subsection 86(9) of the *Patent Act*.

[12] In a preliminary review letter dated December 7, 2022, we set out our preliminary views that claims 1-13 and 15-17 on file do not comply with section 2 of the *Patent Act* and that claims 1-17 on file do not comply with subsection 27(4) of the *Patent Act*. We further expressed our view that the proposed claim amendments would not address the utility defect or the newly identified indefiniteness or ambiguity defects. Finally, we provided the Applicant with an opportunity to make oral and/or written submissions in response to our preliminary review letter.

[13] In a response dated February 7, 2023, the Applicant did not provide any arguments, opting instead to submit a new set of proposed claims 1-15 (the proposed claims) to address the outstanding issues set out in our letter. Further, the Applicant indicated that an oral hearing was not required.

[14] We have completed our review and have set out our conclusions below.

ISSUES

[15] This review will consider whether the subject-matter of claims 1-13 and 15-17 on file at the time of the FA lacks the utility that is required by section 2 of the *Patent Act* and further whether the subject-matter of claims 1-17 is indefinite or ambiguous contrary to subsection 27(4) of the *Patent Act*.

LEGAL PRINCIPLES AND OFFICE PRACTICE

Purposive construction

[16] In accordance with *Free World Trust v Électro Santé Inc*, 2000 SCC 66 and *Whirlpool Corp v Camco Inc*, 2000 SCC 67, purposive construction is performed from the point of view of the person skilled in the art in light of the relevant common general knowledge (CGK), considering the whole of the disclosure including 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 skilled person that a variant has a material effect upon the way the invention works.

[17] We consider that 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.

Utility

[18] 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

[19] 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).

[20] 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).

[21] 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).

[22] 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):

- there must be a factual basis for the prediction;
- the inventor must have, at the date of patent, an articulable and sound line of reasoning from which the desired result can be inferred from the factual basis; and
- there must be a proper disclosure of the factual basis and line of reasoning.

[23] These elements are assessed from the perspective of the skilled person 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 [*Bell Helicopter*]).

[24] Although a prediction does not need to amount to a certainty to be sound, there must be a prima facie reasonable inference of utility (*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).

Indefiniteness and ambiguity

[25] 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.

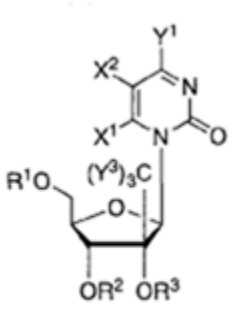
[26] In *Minerals Separation North American Corp v Noranda Mines Ltd*, [1947] Ex CR 306 at 352, 12 CPR 99, the Court emphasized the obligation of an Applicant to make clear in the claims the scope of the monopoly sought, as well as the requirement that the terms used in the claims be clear and precise:

> 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

Purposive construction

[27] The claims set on file contains claims 1-17. Claims 1-5 are the only independent claims. Claim 1 is illustrative:

> 1. A composition for use in treating or preventing infections caused by a *Caliciviridae* virus, comprising an effective treatment or preventative amount of a compound of Formulae (II):
>
> 
>
> (II)
>
> or a pharmaceutically acceptable salt thereof,
>
> wherein:
>
> R^1, R^2 and R^3 are independently H; phosphate; straight chained, branched or cyclic alkyl; acyl; CO-alkyl, CO-aryl, CO-alkoxyalkyl, CO-aryloxyalkyl, CO-substituted aryl, sulfonate ester; benzyl, wherein the phenyl group is optionally substituted with one or more substituents; alkylsulfonyl; arylsulfonyl; aralkylsulfonyl; a lipid; an amino acid; an amino acid residue; a carbohydrate; a peptide; or cholesterol; wherein at least one of R^2 and R^3 is not hydrogen; and
>
> wherein at least one of R^2 and R^3 is not hydrogen [*sic*]; and
>
> wherein:
>
> Y^1 is hydrogen, bromo, chloro, fluoro, iodo, CN, OH, OR^4, NH_2, NHR^4, NR^4R^5, SH or SR^4;

> X^1 is H, a straight chained, branched, or cyclic optionally substituted alkyl, CH_3, CF_3, $C(Y^3)_3$, 2-Br-ethyl, CH_2F, CH_2Cl, CH_2CF_3, CF_2CF_3, $C(Y^3)_2C(Y^3)_3$, CH_2OH, optionally substituted alkenyl, optionally substituted alkynyl, COOH, $COOR^4$, COO-alkyl, COO-aryl, CO-O-alkoxyalkyl, $CONH_2$, $CONHR^4$, $CON(R^4)_2$, chloro, bromo, fluoro, iodo, CN, N_3, OH, OR^4, NH_2, NHR^4, NR^4R^5, SH, or SR^5; and
>
> X^2 is H, a straight chained, branched or cyclic optionally substituted alkyl, CH_3, CF_3, $C(Y^3)_3$, 2-Br-ethyl, CH_2F, CH_2Cl, CH_2CF_3, CF_2CF_3, $C(Y^3)_2C(Y^3)_3$, CH_2OH, optionally substituted alkenyl, optionally substituted alkynyl, COOH, $COOR^4$, COO-alkyl, COO-aryl, CO-Oalkoxyalkyl, $CONH_2$, $CONHR^4$, $CON(R^4)_2$, chloro, bromo, fluoro, iodo, CN, N_3, OH, OR^4, NH_2, NHR^4, NR^4R^5, SH or SR^5; and
>
> wherein each Y^3 is independently H, F, Cl, Br, or I; and
>
> each R^4 and R^5 is independently hydrogen, acyl, alkyl, lower alkyl, alkenyl, alkynyl, or cycloalkyl.

[28] In contrast to claim 1, independent claims 2-5 define the 5-membered sugar ring more broadly than ribose and the pyrimidine base more broadly than cytosine (or derivatives of cytosine). Likewise, they do not limit the β-substituent (i.e., the substituent above the plane of the ring) at position 2' on the ribose ring to methyl or halo-substituted methyl (as in $C(Y^3)_3$ above wherein each Y^3 is independently H, F, Cl, Br or I), and claims 3-5 do not limit the α-substituent (i.e., below the plane of the ring) at position 3' to hydroxy or $-OR^2$.

[29] Dependent claims 6-17 define further limitations relating to combination therapy (claims 6-8), dosage (claims 9, 10, 12, 13), enantiomeric purity (claim 11) and Formula II from claim 1 (claims 14-17).

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

[30] In our preliminary review letter we said the following on pages 6-9:

> The FA and RFA did not formally characterize the skilled person. Based on the specification as a whole, our preliminary view is that the skilled person would be a person or team with knowledge and expertise relating to the chemistry, biology and pharmacology involved in the development of anti-viral agents.

In order to understand the CGK, the Handbook of Experimental Pharmacology and the following review articles were consulted:

De Clercq, E & Neyts, “Antiviral agents acting as DNA or RNA chain terminators” (Feb 2009) 189 Handb Exp Pharmacol pages 54-84.

Carroll, S S & Olsen, D B, “Nucleoside analog inhibitors of Hepatitis C virus replication” (2006) 6:1 Infect Disord Drug Targets pages 17-29.

Furman P A et al, “Nucleoside analog inhibitors of hepatitis C viral replication: recent advances, challenges and trends” (2009) 1:8 Future Med Chem pages 1429-1452.

Ahlquist, P et al, “Host factors in positive-strand RNA virus genome replication” (2003) 77:15 J Virol pages 8181-8186.

Our preliminary view is that the CGK of the skilled person or team would include the following:

…

● Norovirus is a single-stranded positive sense RNA virus (ssRNA+) from the family *Caliciviridae* which is one of a number of ssRNA+ virus superfamilies, other such superfamilies including *Flaviridae* (which includes Hepatitis C virus or “HCV”, West Nile and Bovine Viral Diarrhea Virus “BVDV”) and *Coronaviridae* (which includes SARS virus) to name a few (Description page 1; Ahlquist pages 8181, 8185; Carroll page 17; Furman pages 1429, 1433)

● The various (+)ssRNA virus superfamilies are defined by different RNA replication genes and features that are unique to each family, but they all share a similar mechanism of RNA replication (Alhquist page 8181)

● as of 2003, all known (+)ssRNA viruses had genes encoding an RNA-directed RNA polymerase (RDRP) enzyme that is used in genome replication (Alhquist page 8181)

…

● As of 2006, 15 of the 30 antivirals on the market were nucleoside analogs, i.e., analogs of the natural nucleosides (or deoxynucleotides) containing a ribose ring substituted with 2’, 3’ and 5’-hydroxy group in the α-configuration (or

3’- and 5’-hydroxy only for deoxynucleotides) linked to a purine or pyrimidine base, that are used by viruses as building blocks to synthesize viral RNA (or DNA) during replication (Carroll page 17)

● The 3’- and 5’-hydroxy groups possessed by all natural nucleosides are the reactive groups that ultimately polymerize to form the RNA chains (De Clercq pages 53-54; Carroll page 17)

● Because of their structural similarity to the natural nucleosides, some analogs can be phosphorylated in the cell to generate the active 5’-triphosphate nucleotide form that competes with the natural 5’-triphosphate nucleotides by inhibiting polymerase and posing as alternative monomers that can be used in RNA synthesis (De Clercq pages 53-54; Carroll page 19; Furman page 1431)

● Analogs that inhibit viral replication act as “chain terminators” that, once incorporated into the growing chain, prevent the polymerase from adding further nucleotides by either blocking access to the 3’-hydroxy group (virtual chain terminators) or by not having a 3’-hydroxy group to react with the 5’-triphosphate of the incoming nucleotide (obligate chain terminators) (De Clercq pages 54-55, 77; Furman page 1432-1433; Carroll page 19)

● In the absence of a mechanism for removing the chain terminator, the truncated viral genome is unable to support further rounds of RNA synthesis (Carroll page 19)

● As of 2009, the nucleoside analogs known to inhibit HCV replication were all virtual chain terminators and the majority of the published information concerned the class containing a 2’-*C*-methyl substituent in the β-configuration (De Clercq pages 66-67 and 76-78; Carroll page 19; Furman pages 1434-1436)

● The 2’-*C*-methyl class, and 2’-*C*-methylcytidine (herein 2’-CMeC), 2’-*C*-methyladenosine (2’-CMeA) and 2’-*C*-methylguanosine (2’-CMeG) specifically, were identified as potent inhibitors of BVDV and HCV replication (replicon) and their 5’-triphosphates were shown to inhibit catalytic activity of both BVDV RDRP and HCV RDRP in vitro (Carroll page 19; Furman page 1434)

● 2’-*C*-methyluridine (2’-CMeU) is also in this class and inhibits HCV replication, albeit to a lesser extent (Furman page 1435)

● The activity of this class is attributed to the 2'-*C*-methyl entity which, following incorporation into the growing chain, provides a steric clash with respect to the neighbouring 3'-α-hydroxy group that was believed to either block RDRP from adding the next incoming nucleotide 5'-triphosphate or prevent the optimal alignment needed for the two groups to react, thus preventing further chain extension (De Clercq pages 53-55; Carroll pages 19, 22; Furman page 1431)

● 2'-CMeC in its oral prodrug form acceded to phase II clinical trials in chronic HCV-infected patients, and phase I/II data showed that HCV-infected patients had significant reductions in viral load (De Clercq page 76; Furman page 1437)

● 2'-CMeC also demonstrated broad spectrum viral replication inhibitory activity in vitro against other *Flaviridae* viruses, including West Nile virus, yellow fever virus and the dengue-2 virus (DeClercq page 78; Furman page 1437)

● Although the pyrimidine/purine base of the 2'-*C*-methyl-ribonucleoside core is less critical to inhibition, very few modifications can be made at ribose position 2' and 3' before HCV RDRP inhibitory activity is completely lost: the size, location and stereoelectronic nature of the 2'-β-methyl substituent are all critical to activity, and a 3'-hydroxy (or a prodrug group that can metabolically convert to a hydroxy) is required (Carroll page 20; Furman pages 1433-1435)

● It was well known to replace the 3'- or 5'-hydroxy group hydrogen with a prodrug group to improve the bioavailability of 2'-CMeC and its derivatives, or with a monophosphate prodrug to improve the efficiency of intracellular conversion to the triphosphate form (Furman pages 1433-1437; De Clercq pages 76-77; Carroll page 20).

Subject to any comments or clarifications the Applicant wishes to make, the Panel intends to adopt the above characterizations for the purposes of our analysis.

[31] In the response to our letter the Applicant did not dispute, contest or comment on our characterization of the skilled person or their CGK as set out above. We therefore adopt these characterizations for the purposes of our analysis.

Essential elements

[32] In our preliminary review letter we said the following on pages 9-10:

> As mentioned above, we consider that all of the elements set out in a claim are presumed essential unless it is established otherwise or such presumption is contrary to the claim language. In our view, the skilled person reading claims 1-17 in the context of the specification as a whole and the CGK would understand that there is no use of language in the claims indicating that any of the elements are optional, preferred or were otherwise intended as being non-essential. Our preliminary view is therefore that all of the elements of claims 1-17 are essential.

[33] The Applicant did not contest or comment on this view in its response to our preliminary review letter. We therefore adopt all of the elements set out in the claims as essential elements for the reasons set out above.

The utility of claims 1-13 and 15-17 was not soundly predicted as of the filing date

[34] In our preliminary review letter we said the following on pages 10-11:

> On page 2, the FA contends that the subject-matter of claims 1-13 and 15-17 on file does not comply with section 2 of the *Patent Act* because the factual basis disclosed in the application is not sufficient to soundly predict utility and there is no articulable and sound line of reasoning to connect the factual basis to the utility of the subject-matter as claimed.
>
> Importantly, there appears to be agreement that the utility was not demonstrated for any of claims 1-17 on file and that the utility of claim 14 was soundly predicted as of the claim date.
>
> The position in the FA is that a single test result demonstrating in vitro activity for only one compound is not sufficient to reasonably extend that activity to the millions of compounds encompassed by the claims on file …
>
> > (S)ince antiviral activity was only measured for 2'-*C*-methylcytidine, this is the only compound that can represent a factual basis for the prediction. This single compound is not a sufficient representative of the entire

> genera of compounds of the aforementioned Formulae, since it doesn't reflect the variation within the genera.
>
> …
>
> There is no articulable and sound line of reasoning for the utility of all the claims compounds in "treating or preventing infections cause by a *Caliciviridae* virus", based on extrapolation of this utility from the tested compound…Without a sound line of reasoning, the (skilled person) would have no way of knowing what is a soundly predictable variation of 2'-*C*-methylcytidine that could still retain antiviral activity against *Caliciviridae* viruses.
>
> …

It is important to note that the SOR conceded that utility could have been predicted at the filing date for some of the compounds within the scope of the claims, namely derivatives of 2'-*C*-methylcytidine ribosides, but not for those lacking a 2'-*C*-methyl group, those with a sugar ring other than ribose or those with a base other than cytosine (pages 2-3). In this view, it appears that there was agreement that utility could be soundly predicted for compounds other than just 2'-CMeC even though that was the only compound tested. The disagreement was with the extent of how far out that activity could reasonably be extrapolated while maintaining a prediction that is sound.

The RFA did not agree with the position in the FA with respect to the claims on file, however all of the arguments in favour of utility were directed to the proposed claims. The Applicant's earlier letter of April 24, 2019 made the following three arguments supporting a sound prediction of utility for the compounds of claims 1-13 and 15-17 on file (page 8):

> First, with respect to the factual basis, the Applicant has demonstrated in example 10, a compound within the scope of the claims was tested in a replicon system that is predictive of efficacy against Norovirus infection. The tested compound was shown to be effective at a low micromolar EC_{50}.
>
> Second, similarly to *AZT*, *Monsanto* and *Burton Parsons*, where the line of reasoning was grounded in the known "architecture of chemical compounds", Applicant submits that there are clear structural

> similarities between the compounds covered by the amended claims and the compound in example 10.
>
> Third, there has been a proper disclosure where the factual basis and the articulable line of reasoning are set out in the description as discussed above.

> The first steps of a utility analysis are to identify the subject-matter of the invention as claimed in the patent application and to ask whether that subject-matter is useful—if it is capable of a practical purpose, i.e. an actual result (*AstraZeneca*, at paras 54-55). On page 2, the FA identifies the utility of the claimed subject-matter as the utility that is asserted in the claims, namely "for treating or preventing infections caused by a *Caliciviridae* virus". The RFA did not dispute this. Since this utility is explicitly asserted in all of the independent claims, we agree that this is the actual result that had to be established as of the filing date.

[35] The Applicant did not dispute, contest or comment on our preliminary view that there was agreement that the utility was not demonstrated for any of claims 1-17 on file and that the utility of claim 14 was soundly predicted as of the claim date. Further, the Applicant did not dispute, contest or comment on our preliminary view that "treating or preventing infections caused by a *Caliciviridae* virus" was the utility that had to be established. We therefore adopt this as the utility that had to be established by sound prediction as of the filing date.

Factual basis and sound line of reasoning

[36] On pages 11-15 of our letter, we expressed our preliminary view that there was no line of reasoning that would support extending the activity of 2'-CMeC against Norovirus replication to compounds with position 2'-β as CF_3, H or a group larger than methyl or substituted methyl or 3'-α other than -OH or a group -OR that could be metabolically converted to -OH:

> The FA considers the factual basis as consisting of the one experimental test result demonstrating replication inhibitory activity of 2'-CMeC against Norovirus in a replicon system. This was not disputed in the Applicant's letter of April 24, 2019 or the RFA. We agree that this test result is the extent of the factual basis that is disclosed in the application. However, facts or elements from the CGK

that are relevant to the factual basis and line of reasoning can also be considered even if they were not included in the application: *Bell Helicopter* at paras 152–153.

As we set out above under CGK, a significant amount of information was known to the skilled person about the class of 2'-methyl nucleoside analogs and 2'-CMeC specifically. They were well known viral replication inhibitors with in vitro efficacy against other (+)ssRNA viruses and a 2'-CMeC prodrug had been shown to work in human patients infected with chronic HCV. The mechanism of action of 2'-CMeC as a virtual chain terminator that inhibits the HCV RDRP enzyme was also well known and that activity was generally attributed to the 2'-methyl group. In our view, this information from the CGK would also have been relevant to the factual basis and line of reasoning at the filing date. In this view, we do not agree with the FA that there is no articulable and sound line of reasoning connecting the factual basis to utility for at least some of the claimed analogs.

With respect to the line of reasoning specifically, the FA stated that Norovirus is one genus of the family *Caliciviridae*, and that due to "similarities across the family (e.g. all are (+)ssRNA viruses), it is predictable that antiviral activity against *Norovirus* could be extended to all members of the *Caliciviridae* family" (page 2).

We agree that there is a sound line of reasoning for extending the antiviral activity against Norovirus to the other members of the *Caliciviridae* family since it was well known that viruses within a family share similar RNA replication genes, features and mechanisms. However, to the extent that this saying that the activity could be extended to all (+)ssRNA viruses, we would not agree. As stated above, it was CGK that the various (+)ssRNA superfamilies have distinct RNA replication genes and features that are unique to each family. This is why the well known activity of 2'-CMeC against HCV (from the family *Flaviridae*), for example, is not predictive on its own of activity against viruses outside of the family *Flaviridae*, such as Norovirus.

However, since 2'-CMeC was shown to inhibit replication of Norovirus as well, our view is that this would have suggested to the skilled person that 2'-CMeC may be operating in the same way that it does for HCV. This implies a level of homology within the active sites of the HCV and Norovirus RDRP enzymes insofar as the 2'-C-methyl group is concerned. Further, while the description

states on page 3 that the Applicant did not wish to be bound to a particular theory, the reader's attention is repeatedly drawn to parallels between Norovirus and HCV in respect of their replication enzymes, mentioning "viral polymerase" specifically (see pages 2, 3, 49, 51 and 55). Our preliminary view is that these disclosures, when read in the context of the CGK, would have formed the basis for a line of reasoning that 2'-CMeC may be inhibiting Norovirus and HCV by the same mechanism of action: RDRP incorporates it into the growing chain, the 2'-methyl blocks access to the 3'-hydroxy group and that terminates RNA synthesis and viral replication.

As stated above, the Applicant submitted that the line of reasoning is grounded in the known architecture of chemical compounds, pointing out that there are clear structural similarities between the claimed compounds and 2'-CMeC. We agree there that are clear structural similarities, however not all of the compounds defined in the claims have the 2'-methyl or substituted-methyl entity that was known to be responsible for RDRP inhibition and the chain terminator effect in HCV.

…It was CGK that while modifying some of the substituents at positions 2' and 3' on the ribose ring completely abolishes activity, the identity of the base is less critical to inhibition. As such, our preliminary view is that there is a sound line of reasoning for extending the activity that was demonstrated for 2'-CMeC to analogs containing a substituted pyrimidine or six-membered heteroaryl ring, as set out in independent claims 1-5 on file…

Importantly, the RFA submitted that while the substituents in this position are defined more broadly than methyl, the skilled person would understand that the list of substituents in the independent claims represent a reasonable extrapolation from methyl. This submission was made in the context of the proposed independent claims 1-4 (page 10), but we consider it as being relevant to the claims on file as well. For the reasons that follow, we are unable to agree with this submission because it was CGK that some of the specific modifications defined in the claims cause 2'-C-methyl nucleosides to lose activity altogether.

Claim 1 defines the 2'-β group as methyl (-$C(Y^3)_3$ wherein each Y^3 is H) or substituted methyl (wherein each Y^3 is independently H, F, Cl, Br or I). However, it was well known that increasing the size and stereoelectronic effects of the 2'-methyl group negatively impacts activity. To this end, it had

been shown that replacing all three methyl hydrogens with fluorines (i.e., β-CF_3) abolishes the activity of 2'-CMeA altogether (Carroll page 20). Consequently, our preliminary view is that there is no sound line of reasoning that would support extending the activity of 2'-CMeC to analogs with β-CF_3 at position 2'.

This 2'-β group is labelled as "R^6" in claims 2 and 3, "R^{12}" in claim 4 and "A" in claim 5. These claims define this group more broadly than just methyl or substituted methyl and include further groups known to abolish activity, such as hydrogen and groups larger than methyl. It was CGK that having a methyl group in place of the natural 2'-β-hydrogen group is responsible for the activity of the 2'-C-methyl nucleoside as chain terminators. It had also been shown that activity is lost altogether even if the methyl group is moved by one position to 3'-β with a hydrogen at 2'-β (Carroll page 20). Accordingly, our preliminary view is that there is no sound line of reasoning that would support extending the activity of 2'CMeC to analogs with a hydrogen in the 2'-β position.

Further, it was CGK that the activity is lost when the size of the group at position 2' is increased over that of methyl (Furman page 1433). This had been shown for 2'-CMeA when the size was increased by only one carbon in going from methyl (-CH_3) to ethyl (-CH_2CH_3) (Carroll page 20). Computer modelling indicated that the increased bulk was sufficient to prevent the analog from interacting with the active site in RDRP which in turn prevents the enzyme from being able to add the analog to the growing nucleotide chain (Carroll page 20). Consequently, our preliminary view is that there is no line of reasoning that would support extending the activity demonstrated for 2'-CMeC to analogs that have a 2'-β group that is larger than methyl or substituted methyl.

By contrast, our preliminary view is that there is a sound line of reasoning for extending the activity to analogs with the remaining groups from claims 2-5 with methyl or the following substituted methyl groups in the 2'-β position: CH_2-CN, CH_2NH_2, CH_2OH, $C(Y^3)_3$ (excluding CF_3), CH_2F and CH_2Cl.

With regard to the 3'-α-hydroxy group, it was well known that the presence of this group was required for inhibitory activity. Though HCV RDRP does not make use of the 3'-hydroxy of the 2'-methyl nucleotides as a nucleophile during chain extension, that group was thought to serve as an important binding determinant for the initial incorporation of the analog by RDRP to the growing chain (Carroll page 20). It was also well known that the activity of 2'-CMeC is

> retained when the hydrogen of the 3'-α-hydroxy group (-OH) is replaced with a prodrug group (-OR), such as valyl ester, that can be metabolically converted back to the hydroxy group (De Clercq page 76, Furman pages 1434, 1435, 1437). Consequently, our preliminary view is that there is no sound line of reasoning that would support extending activity of 2'CMeC to analogs defining the 3'-α group (i.e., "R^9" in claim 3, 4 and "X" in claim 5) as hydrogen or a group other than -OH or -OR (i.e., OH, OR^2, -O(acyl), -O(lower acyl), -O(R^4), -O(alkyl), -O(lower alkyl), -O(alkenyl), -O(alkynyl), -O(aralkyl), -O(cycloalkyl) and -O-aryl).
>
> Based on the CGK, our preliminary view is that there is no reason why the skilled person would think that modifying 2'-CMeC at the 1', 2'-α or 4' position would negatively impact activity.…
>
> With respect to the 5' position, which is defined as -OR^1 (claims 1-4) or -OR^3 (claim 5), it was CGK that modifying the natural -OH hydrogen to a prodrug group would increase bioavailability and that modifying to a monophosphate prodrug group would improve the efficiency of the intracellular conversion to the triphosphate form. Further, it had been shown that the activity is retained for 2'-*C*-methyl analogs having a prodrug or monophosphate prodrug group at position 5' (Furman pages 1435, 1441-1443). As such, our preliminary view is that there is a line of reasoning that would support extending the activity demonstrated for 2'-CMeC to the -OR^1 and -OR^3 analogs defined in the claims.

[37] The Applicant did not dispute, contest or comment on any of the above views in the response to our letter. Instead, the Applicant proposed claim amendments that would limit the substituents at 2'-β and 3'-α in a manner consistent with those identified in our letter as having a sound line of reasoning for extending the demonstrated activity.

[38] For the same reasons provided above, our conclusion is that there is no line of reasoning that would support extending the activity demonstrated against Norovirus to all of the compounds falling within the scope of independent claims 1-5 on file.

Proper disclosure

[39] We expressed the following preliminary views on page 15 of our letter:

> As stated above, the activity of 2'-CMeC against Norovirus was disclosed in the application in Example 10 and the parallels drawn between Norovirus and HCV were disclosed on pages 2, 3, 49, 51 and 55. The remainder of the above information was CGK and so there was no obligation to disclose it as part of the application.

[40] The Applicant did not contest or comment on this. We therefore adopt this position for the analysis.

Conclusions on utility

[41] For the reasons set out above, our conclusion is that the skilled person would have known at the filing date that some of the groups at position 2'-β and 3'-α on the ribose ring encompass substituents known to abolish the inhibitory activity of 2'-*C*-methyl nucleosides against HCV, and so there would not have been a sound line of reasoning to support a prediction of utility for those compounds against Norovirus or *Caliciviridae* viruses in general. Specifically, there would not have been a sound prediction of utility for the compounds in claims 1-5 defining the 2'-β group as CF_3, H or a group larger than methyl or substituted methyl or the 3'-α other than -OH or a group that can be metabolically converted to -OH.

[42] For the remaining compounds, our conclusion is that activity against Norovirus could have been soundly predicted as of the filing date. By extension, and in the same manner as claim 14, activity against Norovirus could also predictably extend to activity against all *Caliciviridae* viruses since, for (+)ssRNA viruses, the viruses within a family were known to share similar replication genes, features and replication mechanisms.

[43] To the extent that they include compounds that would not have soundly predicted utility within their scope, our conclusion is that the dependent claims 6-13 and 15-17 also lack a sound prediction of utility for the same reasons as the independent claims.

The subject-matter of claims 1-17 is indefinite or ambiguous

Claims 1-17

[44] We said the following on pages 16-17 of our preliminary review letter:

> On page 5, the FA explains that claims 1-17 are indefinite because the claims are directed to compositions but are defined in terms of only one single component: the nucleoside analog. The FA points to the *Manual of Patent Office Practice* (CIPO) at §11.04 (now §16.04), revised March 1998 [*MOPOP*] which indicates that claims to compositions must contain at least two components.
>
> In response, the RFA did not dispute, contest or comment on this defect from the FA, opting instead to propose amending each of the independent claims to add a second component, namely “a pharmaceutically-acceptable carrier or excipient”.
>
> The SOR confirms that the proposed amendments adding “a pharmaceutically-acceptable carrier or excipient” to the independent claims would address the issue and render the claims definite and compliant with subsection 27(4) of the *Patent Act*.
>
> §16.04 of the MOPOP explains that defining the invention distinctly and in explicit terms requires that sufficient elements be recited for operability and that, in the case of a composition “a claim must define a minimum of two ingredients, at least broadly”.
>
> With regard to operability, since the compositions comprising the nucleoside analogs are defined as being specifically for use in treating or preventing infections caused by a *Caliciviridae* virus, we agree that the compositions would, at a minimum, require a pharmaceutically acceptable carrier or formulating excipient to facilitate that use. That said, it is not presently clear that omitting such formulating agents would invalidate an issued claim on the basis that its boundaries would be unclear to the skilled person.
>
> Nevertheless, these are not issued claims yet and we agree that clarity would be improved by explicitly defining the second component that would in this

> case be required for operability. Our preliminary view is therefore that claims 1-17 do not comply with subsection 27(4) of the *Patent Act.*

[45] The Applicant did not dispute, contest or comment on our preliminary view in response to our letter. Instead, the Applicant proposed amending the independent claims to add “and a pharmaceutically acceptable carrier or excipient” in the same manner proposed in their response to the Final Action.

[46] Therefore, for the same reasons set out above our conclusion is that claims 1-17 on file do not comply with subsection 27(4) of the *Patent Act*.

Claims 3, 4, 14 and 16

[47] On page 2 of our preliminary review letter, we notified that Applicant that during the course of our review additional questions arose as to whether claims 3, 4, 14 and 16 contain clarity defects that introduce further indefiniteness or ambiguity to these claims. We said the following on page 17 in relation to these claims:

> Independent claims 3 and 4 define the 3-α group R^9 as including “OR^2” but no definition is provided for R^2. Our preliminary view is that this renders the scope of these claims indefinite.
>
> Claims 14 and 16 each depend on claim 1 but define limitations that contradict the subject-matter defined in that claim. Specifically, claim 1 explicitly limits formula (II) to exclude compounds where R^2 and R^3 are both hydrogen, and yet claim 14 defines a compound having hydrogens in both positions. Likewise, claim 1 defines the 2’-β substituent using the label $C(Y^3)_3$, but claim 16 refers to the group in that position using the label R^6, not $C(Y^3)_3$. Consequently, since claims 14 and 16 depend on claim 1, our preliminary view is that these definitions introduce avoidable ambiguity, contrary to subsection 27(4) of the *Patent Act*.

[48] Once again the Applicant did not dispute, contest or comment on our preliminary view in response to our letter. Instead, the Applicant proposed amendments to these claims to address our concerns from the preliminary review letter.

[49] Therefore, for the same reasons set out above our conclusion is that claims 3, 4, 14 and 16 on file do not comply with subsection 27(4) of the *Patent Act*.

PROPOSED CLAIMS

[50] As mentioned above, the Applicant submitted a new set of proposed claims in the response to our preliminary review letter dated February 7, 2023. Page 1 of that letter states that the amended claim set addresses the outstanding issues set out in our letter.

[51] The proposed amendments would limit independent claims 1-3 on file to compounds with the 2'-α group as OH and the 2'-β group as CH_3 (claim 1) or CH_3, CH_2F or CH_2Cl (claims 2 and 3). The proposed amendments would further limit the R^9 group in claim 3 on file (position 3'-α) to OH, OR^2, -O(acyl), -O(lower acyl), -O(R^4), -O(alkyl), -O(lower alkyl), -O(alkenyl), -O(alkynyl), -O(aralkyl), -O(cycloalkyl) and -O-aryl, however the embodiment later in claim 3 that R^9 can come together with R^7 or R^{11} to form a bridge compound or it can form a spiro compound together with R^{10} remains. Further, the proposed amendments would delete independent claims 4 and 5 on file outright and renumber claims 6-17 accordingly. In addition, the proposed amendments would provide the missing definition of R^2 in claim 3, would make claim 14 on file (renumbered as claim 12) an independent claim that no longer refers to claim 1 and would replace the definition "R^6 is methyl" with "Y^3 is H" in claim 16 on file (renumbered as claim 14). Finally, the proposed amendments would add the embodiment "and a pharmaceutically acceptable carrier or excipient" to all of the independent claims.

[52] With respect to utility, the proposed amendments to independent claims 1, 2, 4 and 5 would limit the claims to subject-matter that we identified above as having soundly predicted utility. However, claim 3 would still contain the embodiments that R^9 can come together with R^7, R^{11} or R^{10} to form a bridged or spiro compound which is not within the list of groups identified in our letter that would have been expected to metabolically convert to the hydroxy group (De Clercq page 76, Furman pages 1434, 1435, 1437). As we explained in our letter, it was well known that the hydroxy group was required for inhibitory activity and so there is no line of reasoning that would support extending activity of 2'CMeC to compounds with these substituents at position 3'-α. The Applicant did not dispute, contest or comment on this point from our preliminary review letter in their response. For this reason, our conclusion is that the proposed amendments

would not render the subject-matter of claim 3 compliant with section 2 of the *Patent Act*.

[53] With regard to indefiniteness or ambiguity, since the proposed amendments would add the embodiment “and a pharmaceutically acceptable carrier or excipient” to all of the independent claims this would address that outstanding defect from our letter. Further, the amendments to add the missing definition of R^2 in claim 3 and delete claim 4 would address that outstanding defect from our letter. In addition, the proposed amendment to make claim 14 an independent claim would address that defect as well.

[54] With regard to the proposed amendment to claim 16 on file to replace the definition “R^6 is methyl” with “Y^3 is H”, we agree that this would remove the contradiction with claim 1 identified in our letter. However, it would also introduce confusion and redundancy since the proposed changes to claim 1 would already limit the definition of Y^3 to H. As a result, this proposed amendment would render the claim non-compliant with subsection 27(4) of the *Patent Act*.

[55] In view of the above, our conclusion is that the proposed amendments to the claims would not render the claims on file compliant with the *Patent Act* and *Patent Rules* unless further amendments are made, amendments wherein the embodiments that R^9 can form a bridged or spiro compound with neighbouring substituents are deleted from claim 3 and the claim corresponding to claim 16 on file is deleted outright.

CONCLUSIONS

[56] We have concluded that claims 1-13 and 15-17 on file do not comply with section 2 of the *Patent Act*, and further that claims 1-17 on file do not comply with subsection 27(4) of the *Patent Act*. Pursuant to subsection 86(11) of the *Patent Rules* we have further concluded that specific amendments to these claims are necessary in order to make the application allowable.

RECOMMENDATION OF THE BOARD

[57] In view of the above, the Panel recommends that the Applicant be notified, in accordance with subsection 86(11) of the *Patent Rules*, that the following specific amendments are "necessary" for compliance with the *Patent Act* and *Patent Rules*, and that you intend to refuse the application unless these amendments, and only these amendments, are made:

- delete claims 1 and 2 on file and replace them with claims 1 and 2 proposed in the Applicant's letter of February 7, 2023;
- delete claim 3 on file and replace it with claim 3 proposed in the Applicant's letter of February 7, 2023 with the following additional changes to that proposed claim: replace "R^7 and R^9, R^8 and R^7, or R^9 and R^{11}" with "or R^8 and R^7" and delete "or R^9 and R^{10}";
- delete claims 4-15 on file and replace them with claims 4-13 proposed in the Applicant's letter of February 7, 2023;
- delete claim 16 on file; and
- renumber claim 17 on file as claim 14.

Cara Weir	Marcel Brisebois	Owen Terreau
Member	Member	Member

DECISION OF THE COMMISSIONER

[58] I concur with the conclusions and recommendation of the Board. In accordance with subsection 86(11) of the *Patent Rules*, I hereby notify the Applicant that the following amendments, and only these amendments, must be made in accordance with paragraph 200(b) of the *Patent Rules* within (3) months of the date of this decision, failing which I intend to refuse the application:

- delete claims 1 and 2 on file and replace them with claims 1 and 2 proposed in the Applicant's letter of February 7, 2023;
- delete claim 3 on file and replace it with claim 3 proposed in the Applicant's letter of February 7, 2023 with the following additional changes to that proposed claim: replace "R^7 and R^9, R^8 and R^7, or R^9 and R^{11}" with "or R^8 and R^7" and delete "or R^9 and R^{10}";
- delete claims 4-15 on file and replace them with claims 4-13 proposed in the Applicant's letter of February 7, 2023;
- delete claim 16 on file; and
- renumber claim 17 on file as claim 14.

Konstantinos Georgaras

Commissioner of Patents

Dated at Gatineau, Quebec

This 17th, day of March, 2023