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PATENTS ACT 1977

APPLICANT	Sun Pharmaceutical Industries Australia PTY Limited
ISSUE	Whether patent application GB 1600631.4 complies with Section 1(1)(b)
HEARING OFFICER	Dr C L Davies

DECISION

Introduction

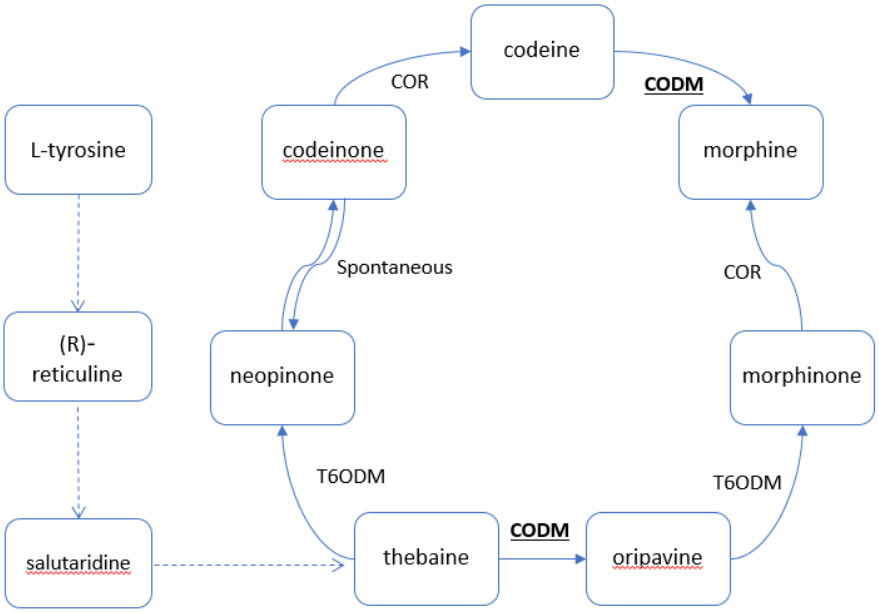
1 Patent application GB 1600631.4 ("the application") entitled "Modified Plant", was filed on 13 January 2016 in the name of "Sun Pharmaceutical Industries Australia PTY Limited" ("the applicants"). It was published as GB 2546285 A on 19 July 2017.

2 There have been a number of rounds of correspondence between the examiner and the applicants' attorney, throughout where the examiner has maintained that the claimed invention does not involve the inventive step required by Section 1(1)(b) of the Patents Act 1977 ("the Act").

3 With the position unresolved, the applicant requested to be heard, and the matter came before me at a hearing conducted by telephone on 23 March 2020. The issue of inventive step before me was set out in the examiner's pre-hearing report of 28 February 2020. The applicant was represented at the hearing by attorney Dr Robert Docherty of Symbiosis IP Limited, and I was assisted by Dr Rowena Dinham.

The invention

4 The invention relates to *Papaver somniferum* plants which are modified in their morphine biosynthetic pathways. *P. somniferum*, also known as the opium poppy, is a source of clinically useful opiate alkaloids including morphine, codeine and thebaine, which are all produced in the same biosynthetic pathway. As discussed in the description of the present application, the levels of codeine in wild type *P. somniferum* are typically less than 5% of the levels of morphine. Therefore codeine, which is one of the most commonly consumed opiates, is not efficiently extracted from wild plants and instead is usually made by a semi-synthetic process from morphine. The morphine biosynthetic pathway is illustrated below:



5 The examples in the application demonstrate how the *P. somniferum* plants contain more than one copy of the codeine 3-O-demethylase gene (CODM; in bold above), and how in order to achieve a complete reduction in the biosynthesis of morphine, all copies of the CODM gene need to be knocked out. This is achieved by the use of fast neutron mutagenesis (FNM) treatment of the seeds of high noscapine cultivars of *P. somniferum* (FNM is a well-known method for randomly mutating plant genes). The plants of the invention, produced by this method, lack all of the CODM genes and therefore CODM activity is completely absent. Therefore, the morphine pathway does not proceed beyond thebaine or codeine and the plants produce higher amounts of the clinically important codeine than the wild type plants, with no detectable morphine or oripavine. Given that this mutagenesis occurs in the high noscapine cultivars, the claimed plants also produce noscapine (albeit through a separate pathway to codeine).

6 The latest set of claims, filed on 5 December 2019, consists of six claims, with two independent claims, 1 and 5, which are set out below:

> *1. A Papaver somniferum plant wherein the plant is deleted for three linked codeine 3-O demethylases genes, wherein the deleted genes comprise the nucleotide sequence set forth in SEQ ID NO: 7, or genes comprising a nucleotide sequence which are 99% identical to the nucleotide sequence set forth in SEQ ID NO: 7, wherein the plant has undetectable codeine 3-O demethylase activity when compared to a wild-type Papaver somniferum plant and wherein the total alkaloid content of latex or dried straw extracted from said modified plant comprises codeine and noscapine with no detectable morphine or oripavine.*
>
> *5. A process for the extraction of codeine and/or related codeine alkaloids from a Papaver plant comprising the steps:*

i) harvesting a plant or plant material prepared from a plant according to any one of claims 1 to 4;

ii) forming a reaction mixture of particulate plant material;

iii) solvent extraction of the reaction mixture to provide an alkaloid enriched fraction; and

iv) concentrating said alkaloid enriched fraction to provide a codeine enriched fraction

7 I note here that the process of claim 5 is a known method of extracting alkaloids, and during the examination process this method in itself has not been disputed. As such, it is the plant material of claims 1-4 that is used in this process that relates back to the invention, and therefore any decision that I reach in relation to the inventive step of the plants of the invention will apply *mutatis mutandis* to the process claim of claim 5.

Third party observations

8 In addition to the rounds of correspondence between the examiner and the applicant, there has been an extensive number of observations filed under Section 21 of the Act. Whilst these observations are considered by the examiner, the third party themselves do not form part of the proceedings. Observations were also filed on 19 March, immediately prior to the hearing.

9 For the most part, these third party observations provide documents demonstrating what would have been known to the skilled person, and allege that there is a lack of inventive step in relation to at least some of these. There is also an argument that the claims are insufficient (and I note that the applicants provided additional evidence in relation to this with their voluntary amendments of 29 March 2018). As required by section 21 of the Act, the examiner would have considered the observations (and any subsequent amendments) submitted prior to his pre-hearing report as part of his examination process, and therefore I do not need to consider them further. On the other hand, the observations filed on 19th of March 2020 would not have been considered during the examination process. These observations do not provide any additional arguments, but do support the arguments previously made by the third party in relation to the lack of inventive step of the claims, and particularly what was the state of the art at the filing date. In light of this, I will consider these in coming to my decision.

The issues to be decided

10 The issue for me to decide is whether the invention involves an inventive step as required by section 1(1)(b) of the Act.

The law

11 The relevant provisions of the Act are reproduced below:

Section 1(1)

A patent may be granted only for an invention in respect of which the following conditions are satisfied, that is to say –

(a) the invention is new;

(b) it involves an inventive step;

(c) it is capable of industrial application;

(d) the grant of a patent for it is not excluded by subsections (2) and (3) or section 4A below;

and references in this Act to a patentable invention shall be construed accordingly.

and

Section 3

An invention shall be taken to involve an inventive step if it is not obvious to a person skilled in the art, having regard to any matter which forms part of the state of the art by virtue only of section 2(2) above (and disregarding section 2(3) above).

12 The examiner and applicants both agree that the structured approach for assessing inventive step, set out in *Windsurfing International Inc. v Tabur Marine (Great Britain) Ltd, [1985] RPC 59* and reformulated as the "Windsurfing/Pozzoli" test in *Pozzoli SPA v BDMA SA [2007] EWCA Civ 588*. The Windsurfing/Pozzoli test is as follows:

(1)(a) Identify the notional "person skilled in the art"

(1)(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?

13 According to section 125(1) of the Act, the claims are interpreted as they would be understood by the skilled person in light of the description and any drawings in the application as filed:

For the purposes of this Act an invention for a patent for which an application has been made or for which a patent has been granted shall, unless the

context otherwise requires, be taken to be that specified in a claim of the specification of the application or patent, as the case may be, as interpreted by the description and any drawings contained in that specification, and the extent of the protection conferred by a patent or application for a patent shall be determined accordingly.

Arguments and analysis

14 The examiner maintains that claims 1-6 are obvious in view of:

D1: WO 2013/163668 (TPI ENTERPRISES LTD)

D2: *Plant J*.; Vol 69 (2012), Wijekoon, C.P. & Facchini, P.J. "*Systematic knockdown of morphine…."*

D3: WO 2009/143574 (TASMANIAN ALKALOIDS PTY LTD)

I will now consider whether independent claim 1 is inventive over the above documents using the Windsurfing/Pozzoli test.

Step 1(a) and 1(b): identify the "person skilled in the art" and their relevant common general knowledge

15 Both the examiner and the applicants agree that the skilled person would be a plant molecular biologist experienced in the manipulation of plant metabolic pathways, aware of the many ways in which genes may be silenced. I see no reason to disagree with this.

16 In their agent's letter dated 5 December 2019 the applicants go on to explain that the skilled person would be aware that the different approaches to mutagenesis yield different results, for example with VIGS being gene specific and mutagenic agents (including the FNM used in the present application) being random. The examiner goes further into what would be common general knowledge. In his pre-hearing report dated 28 February 2020, he adds that the skilled person would be aware of the phenomenon of gene families in plants, and refers to Wikipedia as well as a couple of journal articles. The third party observations of 15 November 2017 also make this point. From reading the prior art cited by the examiner as well as that referred to by the third party observers, I am minded to accept that the skilled person would be aware that plants may contain multiple copies of a single gene, and in particular that *P. somniferum* has been shown to contain for copies of another enzyme in the morphine biosynthesis pathway, codeinone reductase (COR) (see *Plant J.;* Vol. 18, (1999), Unterlinner *et al*, "*Molecular cloning and functional expression of codeinone reductase: the penultimate enzyme in morphine biosynthesis in the opium poppy* Papaver somniferum", pp 465-475). Therefore, the skilled person working on metabolic pathways in plants, and particularly in *P. somniferum* would know that there was a strong possibility of more than one copy of a particular gene being present.

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

17 There appears to be a general agreement between the examiner and the applicants that the broad inventive concept relates to the modification of genes to modulate the alkaloid composition in *P. somniferum*. The applicants don't go any further into the inventive concept of claim 1, but I agree with the examiner in his pre-hearing report that the concept of the claim is a *P. somniferum* plant eliminated for the expression of three genes encoding CODM, resulting in a plant extract containing codeine and no detectable morphine or oripavine. The genes to be deleted are identical in sequence (i.e. as depicted by SEQ ID No 7). The claim also requires that the extract contain noscapine, although this is not associated with the modifications to the CODM gene as it is produced by a separate metabolic pathway.

Step 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;

18 At the hearing, Dr Docherty spent some time discussing how the prior art was to be understood in the context of the invention. In particular he contended that there were factual errors in how the examiner was interpreting the prior art, and that this was fundamental to the assessment of inventive step.

19 Dr Docherty explained that **D1** relates to a different type of poppy than that of the present invention, *Papaver bracteatum*, and that this poppy is genetically and phenotypically different to *P. somniferum*. In particular, *P. bracteatum* doesn't have the CODM or the T6ODM genes (although it does have the COR gene), and therefore whilst the plant can make thebaine, it does not produce oripavine, codeine or morphine. However, the inventors in D1 modify the *P. bracteatum* such that it encodes one or both of CODM and T6ODM so that it can produce codeine, oripavine and morphine. In other words, in Dr Docherty's opinion, D1 is attempting to convert *P. bracteatum* into *P. somniferum* by effectively introducing the genes required to continue the morphine biosynthesis pathway beyond thebaine (i.e. CODM and T6ODM); this is the opposite of the present application, where the genes of the pathway are deleted in order to modify which opioids are produced by *P. somniferum*. He specifically referred to Table 6 (at page 46 of D1), which discloses what genes need to be *introduced* into *P. bracteatum* in order to make morphine, codeine and oripavine, i.e. CODM and T6ODM. Therefore, Dr Docherty points out that contrary to the present application, D1 doesn't delete CODM from *P. bracteatum* as CODM is not present in the first place.

20 On the other hand, the examiner focussed on the passage at paragraph [0172] which states that in order to make *P. bracteatum* plants with a higher yield or purity of codeine, any residual CODM activity in the plants may be reduced using suitable known methods of mutagenesis. The difference therefore, in the examiner's opinion, is that the deletion of CODM occurs in *P. bracteatum* rather than *P. somniferum*.

21 Upon reading D1, it is clear that both Dr Docherty and the examiner are *prima facie* correct in their interpretation of what is disclosed. It is evident from the examples (and particularly Example 2 and its corresponding Figure 2), that levels of CODM and T6ODM are undetectable in the *P. bracteatum* genome with the primers used,

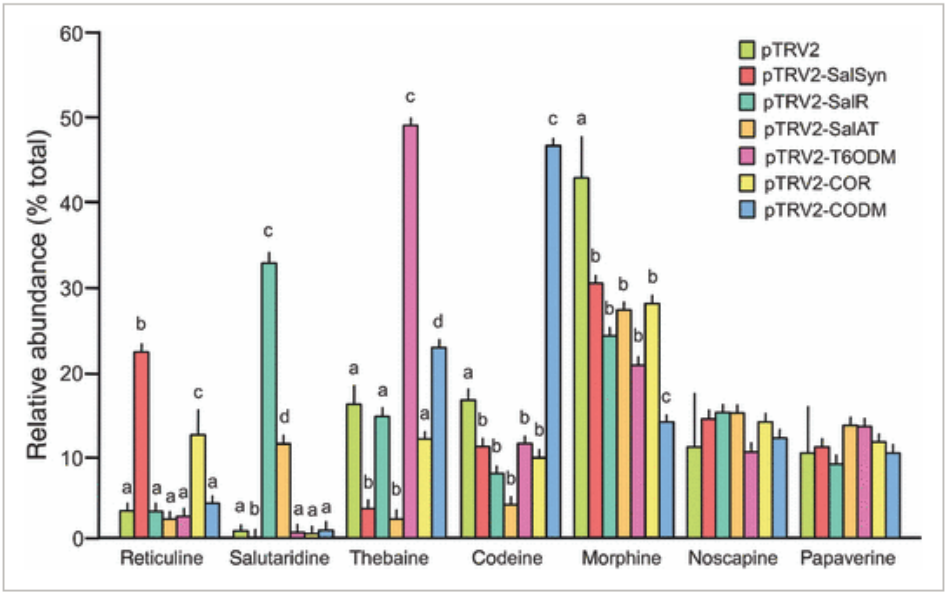
although COR is present and used as a positive control. The passage at para [0178] also concludes that the *P. bracteatum* genome does not comprise a detectable (my emphasis) level of the CODM and T6ODM genes in the samples tested. However, para [0061] does point out that the inventors have identified some *P. bracteatum* cultivars where low levels of oripavine may accumulate, and conclude that CODM may in fact be active, at least at a low level, and therefore it may only be necessary to introduce T6ODM into these plants in order to produce morphine or codeine. I assume that it is for this reason that Example 1, at paragraph [0172], suggests that residual CODM activity may be reduced in order to further reduce the level of morphine production and thus make plants with a higher yield or purity of codeine.

22 It appears to me that both Dr Docherty and the examiner are (not unsurprisingly) referencing parts of D1 that advance their arguments for and against an inventive step, respectively. However, when taken as a whole, it is clear that D1 discloses that the morphine biosynthesis pathway can be manipulated in *P. bracteatum* in order to modify the yields of individual opioids within that pathway, and the absence of any *apparent* inherent CODM and T6ODM in *P. bracteatum* allows for a simpler manipulation of the pathway than in the alternative poppy species *P. somniferum*, as these genes can simply be added to the plants rather than deleted. The addition of one or both of CODM and T6ODM will result in the production of different opioids in the pathway; of particular relevance here is that a pathway without the presence of CODM (but where T6ODM has been added and COR is present naturally) will produce both thebaine and codeine with no detectable morphine or oripavine (see Table 6 therein).

23 Both D1 and the present invention are concerned with the manipulation of the morphine biosynthesis pathways in poppy species in order to produce different opioids. Aside from the obvious difference of utilising different poppy species, the main difference between D1 and the present invention is how the morphine biosynthesis pathway is modified in order to produce the desired opioids. Given that no (or very little) CODM is present naturally, it is not necessary to delete these genes in *P. bracteatum* in order to obtain codeine with no morphine or oripavine, as long as the T6ODM and COR genes are present. Conversely, in the present invention, three CODM genes need to be deleted in *P. somniferum* in order to obtain codeine with no morphine or oripavine, again as long as the T6ODM and COR genes are present. I also note that *P. bracteatum* extracts are not disclosed to contain noscapine.

24 **D2** discloses the manipulation of the pathway in *P. somniferum*, and at the hearing Dr Docherty went to lengths to discuss the difference between the knock-down of the genes using virus-induced gene silencing (VIGS) as opposed to the knock-out of genes. In this regard he considered that the examiner was contradicting himself with his references to ‘knock-down’ and ‘knock-out’. Having read the examiner’s correspondence, I am not clear where this confusion arises, as the pre hearing report appears to only refer to ‘knock-down’ and silencing of the CODM gene, with the only difference being that there is no mention of more than one CODM gene needing to be silenced in order to preferentially produce codeine. Regardless of how the examiner intends D2 to be read, I accept Dr Docherty’s interpretation that D2 discloses the knock-down and not the knock-out of the CODM gene, and this is consistent with how VIGS works, in general.

25 At the hearing, Dr Docherty pointed out that the knock-down method used in D2 doesn't reduce the morphine or oripavine to undetectable levels because it doesn't delete the CODM genes, as is required by claim 1. In particular he referred to Figure 5 of D2, which I have reproduced below:



26 According to Dr Docherty, the alkaloid content of the plant where the CODM has been knocked down (pTRV2-CODM, blue bar) differs from that of the present invention in that morphine is still detectable (and oripavine is likely to be also). I agree with this, the knock-down method used in D2 doesn't appear to reduce all of the CODM activity because morphine is still produced, albeit at around 25% of the level that it is produced in the wild type/ control plant (pTRV2). However, it is clear that the amount of codeine has increased almost three-fold in the CODM knock-down plants compared to the wild type/control. Therefore, whilst this document doesn't demonstrate that the CODM activity has been deleted, as required by claim 1, it has been greatly reduced, and this has resulted in an increase in codeine production with a decrease in morphine and oripavine production. Noscapine is also produced. Therefore, the difference between D2 and the present invention is that the three CODM genes have not been deleted or indeed completely silenced, and instead some expression remains, and therefore whilst there is an increase in codeine production, there is still some morphine and oripavine produced.

27 **D3**, in Dr Docherty's opinion, is the closest prior art, as it discloses a *P. somniferum* plant with an increase in codeine production, but where morphine and oripavine are detectable, which indicates that some CODM activity is retained. However, there is no genetic basis given for the changes in opioid production in this document. In his skeleton arguments, Dr Docherty considers that taking the whole document into consideration, it would be understood that there is a decrease in CODM activity, and not to the undetectable levels required of present claim 1. He also points out that there is no suggestion that there are three linked CODM genes that are deleted. At the hearing, Dr Docherty referred to Table 22, where selected "ideal" plants were grown in fields and then their opioid contents tested. In these plants, there is a clear increase in codeine but there is also some detectable morphine and oripavine, which in his opinion indicates that there is some CODM activity.

28 Dr Docherty acknowledged that the authors of D3 were also the source of the numerous third party observations in relation to this application. He referred to the observations submitted on 5 December 2019, and particularly the declaration provided by Dr Corey Hudson ("the Hudson declaration"), dated 15 October 2019. In these observations, the plants PH08-0002 from D3 (which produce codeine but not morphine or oripavine) were screened for the presence of the CODM genes using the primers of Table 5 of the present application. It is clear in the samples tested, none of the primer pairs amplified amplicons of the expected size, although there were some 'off target' amplicons present in both the PF08-0002 plants and the original parental plants, and Dr Docherty considers that the fact that 'off target' amplicons are present suggests that the plants may have some CODM genes present.

29 Therefore, in Dr Docherty's opinion, the plants of D3 differ from those of the present invention in that not all of the CODM activity has been shown to be deleted (i.e. the plants have not been deleted for all three CODM genes), there is still some residual morphine and oripavine, and additionally the *P. somniferum* cultivars used do not contain noscapine.

30 In his pre-hearing report, the examiner sets out that D3 provides a *P. somniferum* having a high codeine content with substantially no morphine or oripavine, and that whilst there is no genetic basis given, the document indicates that the reason that the plants accumulate codeine is that the step between codeine and morphine has been blocked. He refers to tables 12, 14, 17, 19 and 20-22 which provide details of plants having high levels of codeine but no, or essentially no, morphine or oripavine. In the examiner's opinion, the difference between D3 and the present invention is that there is no mention of more than one CODM needing to be silenced. The examiner does not discuss the absence of noscapine in the cultivars of D3.

31 I agree with Dr Docherty that D3 does appear to be the closest prior art. The intention of this document was to produce a *P. somniferum* plant with a high concentration of codeine. This document was published before the enzymatic pathway involved in morphine biosynthesis in *P. somniferum* had been fully characterised, although it was clear that it was known that there were two pathways for the conversion of thebaine to morphine, and which opioids where biosynthesised in turn along these pathways. I will not go into great detail regarding the methods used to produce the plants in D3 at this point, but I do note that the initial mutagenesis was performed using the same FNM as used in the present application, and then the plants were crossed with a different phenotype/genotype of *P. somniferum* to arrive at plants that produce a high amount of codeine.

32 D3 then goes on to produce several generations of the high codeine-producing plant. Table 19 discloses *P. somniferum* selections from the F3 generation grown in a greenhouse with high levels of codeine, no morphine and minimal oripavine; PH08-0002 is one such example line. The next generation of plants (F4) are grown from the seeds of the F3 generation, depicted in Example 11, and are what Dr Docherty referred to as their "ideal" plants at the hearing, grown in fields. Their alkaloid yield *in kilograms alkaloid per hectare* depicted in Table 22 is something that Dr Docherty considers distinguishes these plants from those of the present invention. It is clear from Table 22 that whilst these plants do have a very high yield of codeine there is a small amount of morphine and oripavine present.

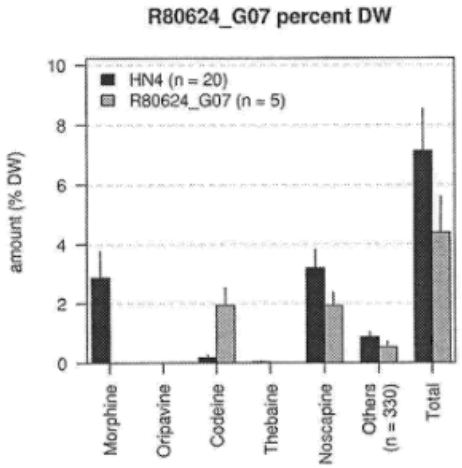
33 Example 12 goes on to sow another trial of F4 generation crops in different sites, where Table 24 depicts the mean alkaloid content of these plants on a dry weight basis, and the passage at page 75 line 20- page 76 line 5 discusses the alkaloid content of these plants as comprising codeine and low (if any) morphine or oripavine. This goes on to discuss the higher morphine content in Table 21/22 being consistent with there being a small number of volunteer plants growing at the trial site, whereas the locations used in Example 12 were chosen as they had never grown poppies, or had done so many years earlier and so were free from volunteer poppy plants.

34 From reading D3, it is clear the *P. somniferum* produced therein, and grown in Examples 10-12 do indeed produce a high level of codeine. To what extent morphine is not produced isn't quite as clear cut as the possibility of contamination from volunteer plants is not unrealistic, but what is clear is that the plants depicted in Tables 19, 21, 22 and 24 produce, at most, substantially no morphine or oripavine. Of particular interest is Table 24, which measures the mean alkaloid content in the poppy straw, and depicts the morphine and oripavine to be 0% of the mean alkaloid content, with codeine ranging between 3-4% on a dry weight basis (DWB). This table is reproduced below:

Table 24. Straw and seed weights hand-harvested and alkaloid content in the poppy straw grown in trial crops.

Line sown	Poppy straw wt (Kg)	Seed weight (Kg)	Mean Alkaloid content (% DWB)				c/cmot
			Morphine	Codeine	Oripavine	Thebaine	
PH08-0026	9.7	14.6	0.00	3.97	0.00	0.39	0.910
PH08-0043	8.6	11.4	0.01	3.14	0.00	0.06	0.978
PH08-0046	10.0	12.5	0.00	4.19	0.00	0.21	0.952
PH08-0065	8.5	7.7	0.00	2.98	0.00	0.98	0.752
PH08-0067	8.1	9.5	0.00	3.01	0.00	0.38	0.888

This is probably the most comparable measurement to the levels of alkaloids in the plants claimed in the present application, where the only measurement the codeine, morphine and oripavine content is provided by Figure 3, depicted below also as a percentage of the dry weight:



35 Therefore, using a like for like comparison in the means for measuring the alkaloid content of the *P. somniferum* produced in D3 and claimed in the present invention, it appears to me that both Table 24 of D3 and Figure 3 of the present invention both disclose 0% dry weight basis as an indication of the morphine and oripavine content of the plants. Consequently, I see no difference here in the amounts of morphine and oripavine in the plants of D3 and the plants of the present invention.

36 However, whether the plants of D3 are deleted for three linked codeine 3-O-demethylase genes, as required by claim 1 of the present invention cannot be determined from this document alone, not least because the genetic basis for the modification of the morphine biosynthesis pathway was not known at the time this document was published. However, there is the possibility that this deletion has occurred as part of the FNM treatment in Example 1 of D3, and therefore the plants cultivated in Examples 10-13, which show 0% morphine on a dry weight basis, may inherently lack all three CODM genes.

37 At this point I refer back to the Hudson declaration. From this declaration (and the accompanying ATCC genotyping report that accompanied it with the third party observations dated 5 December 2019), the use of the primers used in the present application to amplify the CODM genes in the PH08-0002 *P. somniferum* line of D3 did not produce a fragment of the size expected if CODM had been present. I have considered Dr Docherty's assertion that off-target amplicons mean that there is residual CODM activity, but I cannot accept this. Non-specific bands are common problems during PCR reactions, and are usually due to the primers binding to non-specific sequences in the target DNA. Moreover, genomic analysis is not necessarily a clear indication of the absence of the activity of the gene, as mutations can occur that retain the overall size of the gene but impact upon transcription or translation. Neither the present application, D3 or the Hudson declaration have looked at the transcriptional product, and other than the observed lack of CODM activity as determined by the lack of oripavine and morphine production, there are no investigations into the translational products either.

38 In my opinion, from looking at the evidence provided in the present application and the evidence provided with the Hudson declaration, the absence of fragments of the expected size in both sets of amplification reactions, using the same primers, demonstrates the same result: the CODM genes in the mutant plant R80624_G07 of the present application, and the mutant plant PH08-0002 in D3 have not been amplified in the PCR reaction. It would therefore appear to me that the plants of Table 24 of D3, which display 0% DWB morphine and oripavine and between 3-5% codeine, are inherently deleted for the three linked CODM genes in the same way as the plants of the present invention, which also display 0% DWB morphine and oripavine and 2% codeine. Therefore, from the evidence in front of me, I conclude that the only difference between the plants of D3 and those of the present invention is that the *P. somniferum* of D3 do not produce noscapine.

Step 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?

39 In the pre-hearing report the examiner considers that there was a lack of inventive step in light of **D1** because the skilled person would apply the same methods to *P.*

somniferum as they do to *P. bracteatum* in order to silence the CODM genes. At the hearing Dr Docherty points out that *P. bracteatum* does not comprise the CODM genes, and so the skilled person would not insert the CODM genes only to delete them again. I agree with Dr Docherty here. The skilled person would not consider deleting the CODM genes from *P. bracteatum,* because these genes are not present in that poppy species. However, the skilled person would learn that selective activation of the enzymes in the morphine biosynthesis pathway allows for the manipulation of the opioids produced, and in particular that the presence of T6ODM and COR, but the absence of CODM allows for the accumulation of codeine at the expense of morphine and oripavine, as indicated in Table 6. Therefore would the skilled person consider investigating whether CODM activity from *P. somniferum* could be deleted in order to increase the codeine yield in this plant?

40 Methods of mutagenesis, such as FNM, were readily available to the skilled person at the priority date, but D1 doesn't disclose mutating any of the morphine biosynthetic pathway genes in *P.* somniferum. Whilst I acknowledge that it would appear to be obvious to investigate the pathway in view of D1, it would be equally as likely that the skilled person wishing to produce a high yield of codeine would in fact continue to modify *P. bracteatum* by the addition of genes. This is a far easier method than the use of random mutagenesis to delete genes, as this would require extensive screening of the progeny in order to identify those which would have the CODM deletions. Therefore, on balance I agree with the applicants that the claims are inventive in view of **D1**.

41 Similar to D1, **D2** does not disclose the presence of three CODM genes in *P. somniferum*, and in his skeleton arguments Dr Docherty asserts that given that there is some residual CODM activity, the skilled person would consider that there was a different pathway or mechanism that leads to the low levels of morphine and oripavine. In his opinion this is because the skilled person would understand that VIGS reduces gene expression to undetectable levels. I disagree with this, knock-down methods can be highly efficient but are not guaranteed to reduce gene expression levels 100%, and D2 also acknowledges this. Figures 2 and 3 respectively demonstrate mRNA transcript abundance and protein expression, and it is clear that VIGS has not removed all CODM expression. In addition, from reading the supplemental information that accompanies D2, it is clear that the VIGS construct targets the same sequence as that depicted by SEQ ID No 7 of the present application, and that the RNA transcript depicted in Figure 2 also corresponds to that which would be produced by SEQ ID No 7. Therefore, the skilled person reading this document would understand that there is residual morphine and oripavine production because there was still some residual CODM activity. The question that I must ask, therefore, is whether the skilled person reading D2 would consider removing all of the CODM activity in order to obtain an even higher yield of codeine, and in doing so would they delete three CODM genes?

42 As I discussed above, and as pointed out by Dr Docherty at the hearing, the skilled person would know that VIGS is a knock-down method of gene suppression, and not a knock-out method. They would also appreciate that in order to remove all activity they would need to knock-out CODM expression. Methods of knocking out genes in plants were well known at the filing date of the present application, and amongst these methods is FNM, which was used by the present application to delete the

CODM genes. Therefore, the means to delete the genes from the plants of D2 was available to the skilled person, as well as the means to screen for plants that contained the deletion. In his pre-hearing report the examiner refers to the decision of the Court of Appeal in *Genentech Inc's Patent* [1989] RPC 147. Here, Mustill LJ considered (at page 276 line 1-16) that in in assessing inventive step the court should consider the obstacles the skilled man would face along the various routes to the goal, and enquire how he could have overcome these obstacles, either in the same way as the inventor overcame these obstacles, by circumventing them or by choosing another route towards the goal. He went on to state that "….*the court must finally ask whether [the obstacles] could have been overcome by pertinacity, sound technique or trial and error, with no more, or whether there would have been required a spark of imagination beyond the imagination properly attributable to the man skilled in the art. Only if the question is answered in the latter sense are the requirements of section 1(1)(b) fulfilled."*

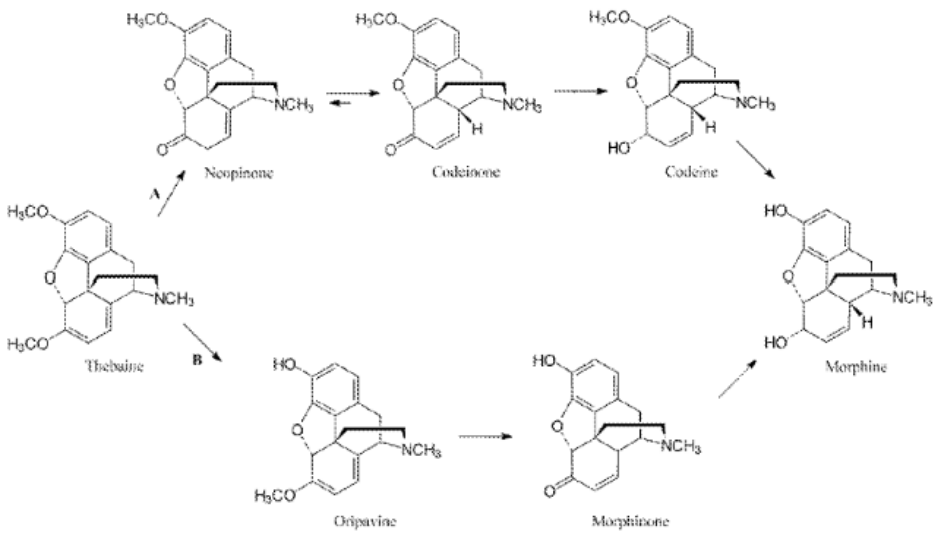
43 In the present case, means to knock out/ delete genes in *P. somniferum* were known, including FNM, and the skilled person seeking to knock out all CODM activity from the plants of D2 would have these techniques at their disposal. I admit that the FNM method is a random mutagenesis method that does not guarantee that the desired genes would be deleted, but D2 discloses means to detect the deletion of the CODM genes, both in terms of screening for opioid production, as well as in terms of methods for detecting mRNA and protein levels. This is comparable to the methods provided by the present application to delete the CODM genes and to detect the effectiveness of this deletion. Therefore, in my opinion the skilled person who was looking to improve the codeine production by complete knock-out of the CODM genes would consider the use of FNM to delete the CODM gene, and in doing so would be driven to screen for those plants that displayed increased codeine levels in combination with no morphine or oripavine production as a marker for the deletion of this gene. The number of copies of the CODM gene would appear to be irrelevant; either CODM was being expressed (and so there would be some morphine and oripavine production), or it wasn't, and the random mutagenesis methods that could be used, such as FNM, are likely to inherently knock out the three linked CODM genes. The methods used in the present application are no more than routine methods and the obstacles (deletion of CODM expression) can be overcome by mere pertinacity or trial and error; there is no spark of imagination involved. Therefore, the skilled person starting from D2 and wishing to produce *P. somniferum* plants that display high levels of codeine, no morphine/ oripavine, and which also produce noscapine, would routinely use FNM to generate the mutants, followed by screening to identify the desired plants. In doing so using the plants of D2 they would inherently arrive at a plant deleted for all three CODM genes and that also produced noscapine, and as such claim 1 does not involve an inventive step in view of **D2**.

44 As discussed above, the only difference between the plants of **D3** and the plants claimed in the present application is that the plants of D3 do not produce noscapine. The introduction of the ability of the plants to produce noscapine into claim 1 was made with the amendments filed on 5 December 2019. In the letter accompanying these amendments, the applicants point out that the ability of *P. somniferum* to produce noscapine is dependent on the presence of a cluster of genes, and that D3

does not disclose plants that are able to produce this drug. No reason for the specific choice of this plant is provided, other than its ability to produce noscapine.

45 *P. somniferum* is known to produce noscapine, and like other opioid products from poppies, it is a desired medicinal compound. I note that in the present application the applicants have not specifically produced a noscapine-producing *P. somniferum*, they simply chose one as the starting material prior to FNM. The resultant products of FNM are plants that lack CODM, and so accumulate codeine at the expense of morphine, and also continue to produce noscapine. The authors of D3, on the other hand, chose a starting material that did not produce noscapine, and then subjected this to FNM. They also were unaware of which genes were involved in the morphine biosynthetic pathway, as they had not yet been characterised. However, the pathway itself was known, as depicted by Scheme 1 of D3:

Scheme 1



Postulated biosynthetic pathways in *Papaver somniferum*
A; Parker et al., 1972
B; Brochmann-Hanssen, 1984

46 As Dr Docherty pointed out at the hearing, the mutagenesis method as a whole in D3 differed to that of the present invention, but that appears to be due to the starting material chosen- in D3 the inventors chose a *P. somniferum* cultivar that accumulated thebaine and oripavine (i.e. the pathway did not progress to neopinone or morphinone as it lacked T6ODM). FNM resulted in plants that accumulated thebaine only (and so inherently lacked CODM), followed by crossing of progeny with morphine-producing plants (which would contain the genes for the entire pathway), and by crossing progeny they arrived at a plant that had the ability progress the pathway beyond thebaine to neopinone (i.e. had restored T6ODM activity), yet could not progress beyond codeine or to oripavine (and so still inherently lacked CODM). Even without a knowledge of the exact genes involved, the skilled person would be able to deduce from the morphine biosynthetic pathway depicted in Scheme 1 that the plants characterised in Example 12 of D3 were essentially blocked at the point of conversion of codeine to morphine and thebaine to oripavine. They would also be able to deduce that the blocking of codeine to

morphine occurred as a result of a mutation introduced by FNM. The question therefore is whether the skilled person would consider applying FNM to other *P. somniferum* cultivars with the expectation that they could also block the conversion of codeine to morphine and thebaine to oripavine?

47 I have considered Dr Docherty's assertion at the hearing that poppies are unusual in that there are different species which produce different compounds depending on the presence or absence of genes, but from what I can see from the prior art *P. somniferum* is known to produce opioids such as morphine and codeine, as well as other alkaloids including noscapine, and there is nothing to suggest that the methods of D3 could not be applied to all variants of *P. somniferum*; indeed noscapine-producing poppies are contemplated as part of the invention of D3 (see, for example, page 5 line 9-11). Furthermore, the method used in the present invention to delete the CODM genes is the same as the method used to block the production of morphine and oripavine in D3, and it does not appear from the disclosure of the present application that any particular modification of this well-known method is required in order to achieve this mutagenesis.

48 Therefore, in my opinion, the skilled person reading D3 would understand that subjecting a *P. somniferum* plant that produces morphine to FNM would result in, amongst others, a modification that prevents progression of the pathway beyond codeine and thebaine, and they would then be able to screen for the modification by analysis of the opioids produced. Even if they were not able to identify the specific genes that were deleted, as I discussed above, the deletion of three linked CODM genes would be inherent in any plant screened that displayed a high level of codeine production and little or no morphine or oripavine, and D3 teaches the skilled person how to perform such a screening. There is nothing in the present application or in the prior art that suggests that applying FNM to a high noscapine producing plant would have any significant technical difficulty. Furthermore there is nothing in the present application that would suggest that the FNM is specifically targeted towards the CODM genes; indeed this is a well-known method of mutagenesis and therefore when applied to *P. somniferum* in both D3 and the present application it would appear to be capable of deleting all CODM activity, which would inherently be due to the deletion of the three linked CODM genes.

49 In their skeleton arguments, the applicants submitted that the skilled person aiming to solve the problem of providing a plant with high codeine and undetectable morphine and oripavine would have to do further research and apply thoughts beyond attributable to him to create the plant of claim 1. They refer to T 0441/93 (Cloning in Kluyveromyces/ GIST BROCADES), which confirmed that an inventive step could be acknowledged if residual research rather than routine work was needed to transfer technology from one field to another. However, in the present application the technology (FNM) was not transferred from one field to another, and instead was applied to the same plant species, and therefore I consider that the facts of this case are distinguishable from the facts of the case in T 0441/93. Therefore, in my opinion, the skilled person reading D3 would be minded to use FNM on other *P. somniferum* cultivars, including those that produced noscapine, in order to attempt to manipulate the morphine biosynthesis pathway and increase the yield of codeine. In doing so they would arrive at a *P. somniferum* plant which would inherently be deleted for the CODM genes, which they could detect by analysis of the opioids

produced, as per D3, or using primers specific for the CODM genes, as per the present invention. Therefore, I consider that claim 1 also lacks an inventive step over **D3**.

50 I should point out here that at the hearing I asked Dr Docherty whether a deposit had been made of the plants of the invention. Dr Docherty considered that a deposit is only required for enablement purposes. He is correct here: if the skilled person was not able to obtain the plant of the invention by following the disclosure of the application and in light of their common general knowledge, then a deposit would be required. Dr Docherty pointed out the specification discloses different types of mutagenesis, what plants you could use and how you would mutate them, and also provides the primers to identify whether you had obtained the desired plant. From this it appears that the ability of the skilled person to obtain the plants of the invention does not rely upon the skill involved in the actual mutagenesis; the only methodology disclosed of how these plants deleted for 3 linked CODM genes are obtained is provided in Example 4. There are no details of the FNM itself or how the plants were screened, other than by their ability to produce codeine at the expense of morphine and oripavine, as well as continuing to produce noscapine, and therefore I can assume that there are no special conditions required as part of the FNM or the opioid screening in order to arrive at the plants of the present invention. As there are no special conditions required, then I can also assume that the FNM methods applied in D3 would also be effective in deleting the three linked CODM genes in all *P. somniferum* cultivars. I acknowledge that the inventors provide primers that identify plants deleted for the CODM genes, however, these primers themselves do not alter the plants produced by the FNM; they merely provide an additional means of characterising plants that have previously been identified by their ability to produce high levels of codeine with no detectable morphine or oripavine. Any plants subjected to FNM and screened for increased codeine and no morphine/ oripavine will inherently have deletions in the three genes of SEQ ID No 7, as required by claim 1, and whether the deletion is detected using the primers provided or not does not alter the product itself.

51 Consequently, I cannot see anything in the teaching of **D2** or **D3**, particularly when combined with the common general knowledge surrounding FNM, that would discourage the skilled person from attempting to obtain high-codeine containing plants by subjecting different cultivars of *P. somniferum* to random mutagenesis by FNM and screening for the different opioids produced. Given that noscapine is also a desired drug produced by *P. somniferum*, plants that produce this would be an obvious, if not arbitrary choice for such a mutagenesis. However, if I am wrong in this assumption and the FNM methods required to obtain the plants of claim 1 are beyond what is disclosed in D3 (or the skilled persons common general knowledge), then in the absence of any technical detail in the application of the mutagenesis method used, I cannot see how the skilled person could obtain the plants of the invention. They would be faced with the undue burden of identifying the specific conditions that are beyond the routine and that would be required to obtain these plants. Furthermore, the lack of any deposit for plants produced by such undisclosed specific methods would likely render the application insufficient.

52 Therefore, claim 1 lacks an inventive step in light of both **D2** and **D3**. Claim 5, which merely refers to a routine method of extraction of codeine from these plants, also lacks an inventive step in view of these documents.

53 Dependent claims 2-4 merely relate to the alkaloid content of the plants of the claim, and there does not appear to be anything other than what would be routinely obtained from the plants of claim 1, and therefore these claims also lack an inventive step. Claim 6 refers to the plant material as comprising poppy straw or latex, which is disclosed in both D2 and D3.

Outstanding issues

54 Other than inventive step, I note that there are no further issues outstanding on this application.

Conclusion

55 I find that the claimed invention does not involve an inventive step according to section 1(1)(b). I therefore refuse the application under Section 18(3) of the Act.

Appeal

56 Any appeal must be lodged within 28 days after the date of this decision.

C. L. Davies

Deputy Director, acting for the Comptroller