Patents Act 1977 **Opinion Number** **19/24**

OPINION UNDER SECTION 74A

Patent	EP 2782559 B1
Proprietor(s)	LO. LI. Pharma SRL
Exclusive Licensee	
Requester	Dr A Hersi
Observer(s)	
Date Opinion issued	21 November 2024

The request

1. The Comptroller has received a request from Dr A Hersi of Polybiotics (the requester) to issue an opinion on the validity of EP 2782559 B1 (the patent).

2. The patent has a filing date of 21 November 2012 and a claim to an earlier priority date of 22 November 2011. It was originally published as PCT application WO 2013/076121 before entering the European regional phase. The patent was granted on 6 June 2018 and it remains in force. The proprietor is LO. LI. Pharma SRL.

3. No observations were received.

Preliminary matters

4. A request for an opinion on this patent has previously been made by the requester (see Opinion 07/24). That request sought an opinion on both the validity and infringement of the patent. However, the validity part of that opinion was not considered because the examiner considered that the documents referred to in the request had either already been considered during post-grant opposition proceedings at the EPO, or they were substantially similar to those documents. In view of the superiority afforded to decisions of the EPO opposition division, it was considered inappropriate to reconsider those documents for the purpose of forming an opinion on validity.

5. The requester now makes a new opinion request regarding the validity of the patent, and has supplied a substantial number of new documents.

6. Given the large number (39) of documents referred to, I consider that it is

appropriate to proceed with the opinion and issue an opinion on the validity of the patent as requested. The documents referred to in the request are listed in Appendix 1. They are identified in the request as O1-O39 and I have used the same references in the opinion.

7. I note that a number of the documents were published after the priority date of the patent. These documents will not be considered further. Although the requester has suggested that I could infer certain information was known at the priority date if it was published soon after, that is not a step I can take. The evidence must have been in the public domain before the priority date, otherwise it is just speculation. The late published documents are: O9 (2016), O10 (2012) and O11 (2012).

The patent

8. The patent describes a medicinal composition comprising both myo-inositol and d-chiro-inositol. The patent specifies that it is a treatment for polycystic ovary syndrome (PCOS).

9. Claims 1 and 7 of the patent read:

> *1. A pharmaceutical composition containing myo-inositol and D-chiro-inositol in a weight ratio between 10:1 to 100:1.*
>
> *7. A pharmaceutical composition according to claims 1-6 for use in a method of treating polycystic ovary syndrome (PCOS).*

10. On the face of it, the claimed priority date is valid for at least these claims, with the priority application appearing to contain equivalent claims (1 and 6 – in Italian).

Claim construction

11. As a first step in determining infringement I must correctly construe the claims. This means interpreting them in the light of the description and drawings as instructed by Section 125(1). In doing so I must interpret the claims in context through the eyes of the person skilled in the art. Ultimately the question is what the person skilled in the art would have understood the patentee to be using the language of the claims to mean. This approach has been confirmed in the decisions of the High Court in *Mylan v Yeda*[1] and the Court of Appeal in *Actavis v ICOS*[2].

12. Claim construction was considered in the previous opinion. I agree with the construction adopted therein. Furthermore, the requester has not made any arguments to suggest that there were any errors in that construction.

13. Claim 1 was construed as:

> *"a composition suitable for use as a pharmaceutical wherein the*

[1] *Generics UK Ltd (t/a Mylan) v Yeda Research and Dev. Co. Ltd & Anor* [2017] EWHC 2629 (Pat)
[2] *Actavis Group & Ors v ICOS Corp & Eli Lilly & Co.* [2017] EWCA Civ 1671

composition comprises both myo-inositol and D-chiro-inositol in a ratio, by weight, of 10:1 to 100:1.

14. It was noted that, in line with IPO guidance at paragraph 31 of "Examining patent applications relating to chemical inventions"[3], a claim to 'a pharmaceutical composition comprising X' is construed as a composition comprising X that is *suitable for* such use.

15. As in the request, the abbreviations MYO and DCI will be used to refer to myo-inositol and d-chiro-inositol respectively.

Prior art background

16. The requester provides the following background to MYO and DCI and their role in treating symptoms of PCOS:

> ***Background and Common General Knowledge in the Field:***
>
> *Inositols are sugar alcohols that exist as stereoisomers, sharing similar chemical structures but differing in their spatial orientation. Of the nine known stereoisomers, MYO and DCI are the most common in nature. The human body synthesizes MYO from glucose and converts some MYO into DCI via the enzyme epimerase (O1). Naturally, DCI is found in carob pods and certain legumes, while MYO is present in citrus fruits and specific pulses (O2, O3).*
>
> *Both MYO and DCI play crucial roles in insulin signalling pathways. Their deficiencies are associated with insulin resistance, a condition where the body improperly responds to insulin, leading to metabolic issues such as hyperglycaemia (high blood sugar) (O4, O5). Insulin resistance is a hallmark of conditions like Polycystic Ovarian Syndrome (PCOS) and diabetes (O5). PCOS is a prevalent hormonal disorder characterized by metabolic dysfunctions including hyperglycemia, abnormal cholesterol levels, hypertension, and insulin resistance (O5). This condition often leads to elevated androgens (male hormones like testosterone), fertility problems, and irregular menstrual cycles. Weight gain is also common in PCOS due to insulin resistance (O6).*
>
> *By the time of the patent filing, it was well established that MYO and DCI supplements could ameliorate insulin resistance and alleviate symptoms in individuals with PCOS (O7, O8). Both inositols were recognized as safe for human consumption, though the scope of the patent is not limited to human use but extends to any potential applications. This information is considered common knowledge to a professional skilled in the art, as supported by multiple studies and clinical observations.*

[3] Examining patent applications relating to chemical inventions, accessible at https://www.gov.uk/government/publications/examining-patent-applications-relating-to-chemical-inventions/examining-patent-applications-relating-to-chemical-inventions-may-2017

17. The skilled person is considered to be a pharmacologist specialising in supplements for alleviating conditions associated with PCOS.

18. I am prepared to accept that the statement above is an appropriate summary of the skilled person's common general knowledge and, in particular, as evidenced by the disclosures of the documents referred to, MYO and DCI were recognised individually as supplements that could be used to alleviate symptoms in individuals with PCOS.

19. The requester uses the prior art to establish a timeline in the skilled person's understanding of the role of MYO and DCI as supplements for PCOS, which is broken down into the following steps:

    i) Establishment of DCI as a supplement – prior art showing DCI's role as an insulin sensitiser and its effective doses.

    ii) Establishment of MYO as a supplement – prior art highlighting MYOs role in insulin sensitisation and its effective doses.

    iii) MYO to DCI conversion – studies and data showing the physiological conversion rates and the importance of maintaining specific ratios for effectiveness.

    iv) Deficiency in insulin resistance – studies and data showing the physiological conversion rates and the importance of maintaining specific ratios for effectiveness.

20. In general terms I am content to accept that this chronology forms part of the skilled person's common general knowledge.

21. The requester suggests that this chronology "*clearly demonstrates that the prior art provided the necessary foundation and impetus for combining MYO and DCI.*"

22. On the face of it the requester is not suggesting that the combination of MYO and DCI is part of the skilled person's common general knowledge. Rather that it would be obvious for the skilled person to combine them. Such a combination is any case disclosed in the prior art in O35 (JP 2006213684), but this is the only document referred to by the requester which explicitly discloses such a combination for treating insulin resistance or PCOS, and the ratio of MYO:DCI lies outside the scope of the range specified by claim 1 of the patent. O35 is the main prior art document considered by the EPO opposition division. They found the patent inventive based on this document and the skilled person's common general knowledge. Given that there is only the single document disclosing the combination of MYO and DCI, I do not consider that the combination is part of the skilled person's common general knowledge.

23. Although O35 is the only document which explicitly discloses a supplement comprised of both MYO and DCI for treating insulin resistance and/or PCOS, there are other documents which the requester has identified that nevertheless mention both compounds in the context of supplements. I shall consider these documents further and the requester's arguments based upon them. Subject to a couple of

exceptions, I shall not consider any further any of the documents which disclose only one of DCI or MYO. On the whole these are only evidence of the background and chronology set-out above and which I am prepared to accept is accurate.

24. O37 also discloses a supplement comprising both DCI and MYO, but the supplement is for body-building, and DCI and MYO are just a couple of the ingredients.

25. Looking at those documents which mention both MYO and DCI, O25 discusses a study of young women taking daily supplements in the form of 4000mg MYO and 400µg folic acid.

26. This paper identified the role of DCI as follows:

> *"DCI is known to have a role in activating enzymes that control glucose metabolism. Indeed a defect in tissue availability or altered metabolism of DCI or inositol phosphoglycan mediators has been found in PCOS women and may contribute to their insulin resistance."*

27. In relation to MYO, the paper states:

> *"MYO, a precursor of DCI, is widely distributed in nature whereas DCI is relatively rare. MYO is present in human follicular fluid, where elevated concentrations appear to play a positive role in follicular maturity and provide a marker of good quality oocytes."*

28. Accordingly there is nothing in this paper to suggest any benefit from taking both DCI and MYO. MYO is identified as a pre-cursor of DCI. The skilled person would infer from this that only MYO supplementation is required, and that DCI will be formed in vivo by conversion of MYO.

29. O26 reports results of a similar study based on the same daily supplement of 4000mg of MYO and 400µg of folic acid. The benefits of DCI are stated as:

> *"Studies have shown that women with PCOS respond to DCI therapy increasing ovarian activity and menstrual frequency. In fact, an inositol phosphoglycan molecule containing DCI is known to have a role in activating enzymes that control glucose metabolism, acting as postreceptor mediator or as a second messenger of insulin signal. A defect in tissue availability or use of DCI or IPG mediators may contribute to insulin resistance."*

30. As with the previous paper, MYO is referred to as the precursor of DCI with no suggestion that additional supplementation with DCI is required. For example,

> *"Because MYO is the precursor of DCI, an ovarian insulin-sensitising action can be similarly hypothesised with a consequently positive action on hormonal profile, particularly on reduction of basal serum testosterone",* and
>
> *"MYO may prove useful in the treatment of PCOS patients undergoing ovulation induction, both for its insulin lowering activity and its intracellular role in oocyte maturation."*

31. O27 is a further paper looking at the effects of daily supplementation with 4000mg of MYO and 400µg of folic acid. It identifies that MYO and DCI are stereo isomers. It states that *"elevated concentrations of MYO in follicular fluid appear to play a role in follicular maturity and provide a marker of good quality oocytes*". More particularly, this paper suggests supplementation with either DCI or MYO as follows:

> *Recently a defect in the insulin signal pathway (inositol-containing phosphor glycan mediators) had been discovered to be implicated in the pathogenesis of insulin resistance. As consequence, the administration of different isoforms of inositol as DCI or MYO is newly demonstrated improving the physiological insulin-receptor activity, restoring spontaneous ovulatory function in most of PCOS women.*

32. This paper provides no explicit teaching for supplementation with a combination of MYO *and* DCI.

33. O28 is another example of a study of treatment of PCOS with MYO and folic acid. In this instance the subjects were given 2000mg MYO and 200µg of folic acid daily. The paper acknowledges the benefits of DCI supplements for reducing insulin resistance in PCOS patients. In particular, it concludes:

> *"Our data together with those of Papaleo [O25] suggest that a deficiency in the precursors of IPG such as MYO and/or DCI might be an additional co-factor contributing to the pathophysiology of the insulin resistance of PCOS patients. … Our study demonstrated that MYO administration, besides DCI, has a modulatory role on insulin sensitivity, gonadotropin and androgen secretion, though no significant differences for plasma or urinary MYO concentrations have been previously reported in PCOS patients. However, it cannot be excluded that a minimal part of such positive effects observed under MYO administration might be related to a minimal MYO-DCI conversion. … Since only small amounts of inositol are introduced with the diet, the supplementation with inositol in PCOS patients seems to be potentially beneficial especially in improving metabolic pathways under insulin control."*

34. There is no explicit disclosure of supplementing with both MYO and DCI.

35. O37 is a published patent application (JP 2003/511094). The requester refers to a translation of this application, but, to avoid any possibility of errors arising from the translation, it seems more appropriate to refer to the English language PCT application (WO 01/28356 A2) from which the JP application derives.

36. This application discloses a body-building supplement comprising amino-acids and other constituents. Those other constituents include *"a substance which mimics or enhances insulin activity preferably selected from the group consisting of N-acetyl cysteine, a-lipoic acid, myo-inositol, preferably d-myo-inositol, cis-inositol, epi-inositol, allo-inositol, muco-inositol, neo-inositol, scyllo-inositol, d-chiro-inositol, 1-chiro-inositol, d-pinitol and glucomannan, most preferably glucomannan".* The only instance of a specific supplement comprising both MYO and DCI is found in Example 1, but no specific proportions are disclosed. The ingredients list includes:

Insulogen ™ A blend of the following:
MYO-Inositol
CIS-Inositol
EPI-Inositol
Allo-Inositol
MUCO-Inositol
NEO-Inositol
SCYLLO-Inositol
D-Chiro-Inositol
L-chiro-inositol
Inzitol (D-Pinitol)

37. Despite the reference to a "*compound which mimics or enhances insulin function*", I do not consider that the skilled person would identify this document as relevant to a composition for treating insulin resistance or PCOS. This document relates specifically to a body-building supplement. There is nothing in the skilled person's common general knowledge to link a body-building supplement with insulin resistance or PCOS. Accordingly, the skilled person would not consider this document when formulating a composition for treating these conditions.

38. O39 (EP0659349) is directed to the use of MYO as a supplement for the treatment of diabetes. A comparison is made of the effects on plasma glucose levels in Rhesus monkeys of supplementing with MYO or DCI. The conclusion of the comparison is:

> *"The results of the study demonstrate that myo-inositol was even more effective than DCI in reducing the plasma glucose levels during the single meal tolerance test as well as the urinary excretion of glucose for the three days during which myo-inositol was a component of the diet."*

39. That conclusion speaks for itself. There is no suggestion that a combination of MYO and DCI would be better than MYO alone.

40. Although some of these documents hint at a combination of MYO and DCI to treat PCOS, no specific or even general ratios of these compounds are suggested other than in O35. I will consider O35 further below.

41. There is a suggestion from the requester that it would be obvious to try a combination that matched the natural ratio of MYO to DCI found in the body.

42. O34 (which was also considered by the EPO as part of the opposition proceedings) discusses supplementation solely with DCI. It provides a table which includes MYO and DCI levels in healthy and PCOS subjects. The requester has used this data to calculate the ratios of MYO:DCI in these subjects. For healthy people the ratio is said to be between 70:1 and 176:1, and for PCOS subjects it is said to lie between 118:1 and 320:1. The data in the table shows average plasma DCI levels of 0.10 µmol/l in PCOS subjects and 0.19 µmol/l in healthy subjects. Plasma MYO levels are similar between the two sets of subjects with an average of 20.6 µmol/l in PCOS subjects and 21.2 µmol/l in healthy subjects.

43. The requester suggests that it would be obvious based on this data to supplement

with a specific combination of MYO and DCI that falls within the healthy range, such a combination also falling within the range of claim 1 of the patent.

44. I do not agree that this follows. O34 specifically discloses supplementing only with DCI. The difference in the MYO and DCI levels between healthy and PCOS subjects indicates a deficiency in DCI. That points to DCI being an appropriate supplement to counter this deficiency, at least based on the teaching of this document. Although MYO is converted to DCI in the body, I do not consider it obvious based on this document to try a combination of MYO and DCI to improve the MYO:DCI ratio. Including MYO would seem to run counter to the findings of this document that the MYO:DCI ratio is too high in patients with PCOS. It is certainly not obvious, based on this document, to supplement with a combination of MYO and DCI which matches the natural healthy ratio. There is no suggestion that such a ratio would rebalance the PCOS MYO:DCI ratio so that it matched the healthy ratio.

Summary

45. The requester summarises their position as follows:

> **Novelty is challenged by:**
>
> > **O28, O29, O31, O34:** These documents disclose ratios of MYO:DCI in plasma/urine or suggest doses of MYO:DCI that fall within the patent's claimed range.
>
> **Inventive step is Challenged by:**
>
> > **O24 to O29, O39:** Establish the safe use of MYO in insulin resistance at doses of 4000mg a day.
> > **O7, O15, O29, O29:** Establish the safe use of DCI in insulin resistance at doses of 200mg to 1200mg a day.
> > **O25 to O29, O34:** Highlight that benefits of MYO are due to its conversion into DCI, reducing the inventive step of combining both.

46. In respect of the novelty argument, none of these documents discloses a specific combination of MYO and DCI. There is accordingly no disclosure of a composition that falls within the scope of claim 1 of the patent. The fact that the ratio of MYO:DCI in plasma or urine falls within the scope of the claims does not provide any basis for supplementing at that ratio. Furthermore, I do not consider it obvious to supplement at these natural healthy plasma or urine ratios as it is not obvious that doing so would restore the balance in PCOS patients. Additionally, the known conversion of MYO to DCI would clearly effect the quantity and proportions of each required to restore normal levels such that it is not obvious to use the natural healthy ratio.

47. In relation to the inventive step argument, it is not clear that the combination of dosages referred to would have been considered suitable by the skilled person. Nor do they relate to the maximum safe dosages, for example O13 describes DCI dosages of 3000mg per day. In any event, I do not consider that it would be obvious to supplement with both MYO and DCI at the doses suggested by the requester. As

both are known to play a role in reducing insulin resistance, the skilled person would anticipate that lower levels are required. Furthermore, the fact that MYO is converted into DCI would lead the skilled person to reduce the amount of DCI required to be supplemented.

EPO Opposition Proceedings

48. As noted above, opposition proceedings against the patent were commenced by a third party at the EPO. Those opposition proceedings considered inventiveness principally in relation to O35. Although the third party withdrew from the process, the proceedings were continued by the EPO of its own motion. Accordingly, a reasoned decision was issued by the opposition division rejecting the opposition and maintaining the patent as granted.

49. In considering O35, I do not consider that I should deviate from the reasoned decision of the EPO opposition division unless there are very good reasons to do so based on compelling evidence and/or argument.

50. The requester's argument based on O35 is very limited. There is nothing in the argument put forward that would persuade me there is any error in the EPO's reasoning.

51. Having said that, I am not sure I agree with the EPO's characterisation of O35 that it cannot be considered as a suitable closest prior art document because *"[it] does not evaluate any of the core PCOS symptoms related to fertility or the lack thereof*". I note that O35 specifies that the invention provides a composition for treatment of PCOS. However, this characterisation seems moot as the EPO went on to consider inventiveness of the patent on the basis that O35 was the closest prior art.

52. I have additionally considered whether or not the prior art documents submitted with this request are evidence of further common general knowledge which was not considered by the EPO and which would give rise to a different outcome.

53. O35 discloses a composition comprising MYO and DCI used to ameliorate insulin resistance, hyperinsulinemia, or insufficiency of glucose tolerance. It links these impaired glucose tolerances to diseases such as type 2 diabetes and PCOS. The specified composition of MYO:DCI is in the range 1:3 to 9:1, in particular 3:1 to 9:1. The teaching of O35 specifically seeks to reduce the amount of DCI in view of its higher cost compared to MYO, whilst maintaining an effective synergistic effect.

54. The EPO identified the difference between O35 and the claims of the patent as follows:

> *D3[O35] differs from the subject matter of independent claims 1, 7 and 9 in that it does not disclose a MI/DCI ratio of between 10:1 to 100:1.*
>
> *The technical effect provided by the above distinguishing feature is the normalizing the ovulation cycle, and ameliorating hormonal and metabolic values, such as testosterone, dehydroepiandrosterone (DHEA), sex-hormone-binding globulin, luteinizing hormone.*

55. In general agreement with the requester, I consider that the evidence provided shows that the skilled person's common general knowledge included:

    - DCI's role as an insulin sensitiser.
    - MYO's role as an insulin sensitiser.
    - Deficiencies in DCI or MYO give rise to insulin resistance and DCI or MYO may be used as a supplement to address the deficiency.
    - PCOS may be linked to insulin resistance and corresponding deficiencies in DCI or MYO.
    - DCI or MYO may be used to treat insulin resistance and is effective to treat symptoms of PCOS.

56. When considering the teaching of O35, the skilled person would see that the general principles conform with their common general knowledge, i.e. it relates to the use of DCI or MYO to treat PCOS based on reducing insulin resistance as a consequence of MYO and/or DCI deficiency. Further to that common general knowledge, O35 additionally teaches a range of effective compositions of DCI and MYO. There does not appear to be any motivation for the skilled person to seek to identify a composition which lies outside of the range specified. In particular, based on the fact that O35 is directed specifically at minimising the amount of DCI in the composition whilst remaining effective, I do not consider that the skilled person would find it obvious to reduce the proportion of DCI further.

57. Although the patent recognises the role of MYO in improving insulin resistance, it states additional benefits of MYO such as the role of MYO in morphogenesis and cytogenesis, lipid synthesis, cell membrane formation and cell growth. The patent finds that a composition which has increased levels of MYO relative to DCI is beneficial.

58. The question then is whether or not these additional benefits of MYO form part of the skilled person's common general knowledge.

59. Amongst the prior art documents referred to by the requester, there are a few which identify that MYO has a role in improving oocyte quality. For example, O25 specifies that "*MYO is present in human follicular fluid, where elevated concentrations appear to play a positive role in follicular maturity and provide a marker of good quality oocytes".* O26 states *"MYO may prove useful in the treatment of PCOS patients undergoing ovulation induction, both for its insulin-lowering activity and its intracellular role in oocyte maturation".*

60. I do not consider that the requester has provided sufficient evidence to establish that supplementation with MYO to improve oocyte quality in PCOS women was part of the skilled person's common general knowledge. The fact that it is acknowledged in a couple of papers is not considered sufficient. Even O25 and O26 are primarily interested in the use of MYO as an insulin sensitiser as an alternative to DCI. That use is the main thrust of the requester's arguments and their evidence. They have

established that the role of MYO as an insulin sensitiser and its consequent role as a supplement for treating PCOS is part of the skilled person's common general knowledge. I do not consider that supplementation with MYO to improve oocyte quality forms part of the skilled person's common general knowledge.

61. In the absence of this additional role of MYO as part of the skilled person's common general knowledge, I do not consider that the skilled person would be motivated to increase the levels of MYO proposed in O35 to arrive at a composition falling within the scope of the claims of the patent.

62. The EPO Opposition Division similarly decided that:

> *"Therefore, in view of the teachings of D3 [O35], the skilled person would have no motivation to change the MYO:DCI ratio disclosed therein with any expectation of success in improving the hormonal profile of the luteinizing hormone in PCOS patients. To do so would have required an ex-post facto analysis by the skilled person."*

63. In line with the decision of the EPO Opposition Division, I do not consider a composition falling within the scope of claim 1 of the patent to be obvious based on O35.

Insufficiency

64. The requester also makes the following arguments regarding the sufficiency of the patent:

> **Insufficient Disclosure Arguments:**
>
> 1. **Enhanced Effects of Soft gels (O7 and O8)**
>
>   - Evidence from O7 and O8 indicates that the patent holder was aware of the superior efficacy of soft gel formulations over powder forms. This information was not fully disclosed in the patent, suggesting a potential exaggeration of the results presented.
>
> 2. **Optimal ratio of 40:1 (O9, O10, O11 and O16)** [n.b. O9, O10, O11 published after priority date]
>
>   - Documents O10, O11 and O16 provides evidence that the 40:1 MYO:DCI ratio is optimal due to its physiological nature.
>
>   - This critical information was omitted in the patent, which could mislead about the discovery's originality and significance.
>
> 3. **Duration of Use(O25):**
>
>   - O25 presents evidence that longer durations of use are more beneficial. The omission of this data from the patent filing could

misrepresent the treatment's efficacy and expected outcomes.

65. Irrespective of the merits of the basis of these arguments, I do not see that there is any insufficiency in the patent. The skilled person would have no difficulty in working the invention across the whole breadth of the claims.

66. The requester has also suggested that the patent is insufficient for failing to disclose maximum and minimum doses. However, I consider that the skilled person would be able to determine an effective dose based on their common general knowledge.

Conclusion

67. Based on the evidence and arguments put forward in the request, I am not persuaded that the claims of the patent are invalid by virtue of a lack of novelty, lack of inventiveness, or insufficiency.

68. I am therefore of the opinion that the patent is valid.

Matthew Jefferson
Examiner

NOTE

This opinion is not based on the outcome of fully litigated proceedings. Rather, it is based on whatever material the persons requesting the opinion and filing observations have chosen to put before the Office.

Annex 1

References

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