INTELLECTUAL PROPERTY OFFICE

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PATENTS ACT 1977

APPLICANTS	Mr. A.M.H.S. El-Tawil
ISSUE	Whether patent application GB0611402.9 complies with Sections 1(1) and 14(5)(c)
HEARING OFFICER	Dr S Brown

DECISION

Introduction

1. Patent application GB 0611402.9 is entitled "A novel effective treatment for patients with inflammatory bowel disease (Crohn's disease & ulcerative colitis)". It was filed on 7th June 2006 and published as GB 2438931 A on 12th December 2007.

2. Throughout the examination process the examiner has maintained that the invention claimed is not supported by the description, lacks novelty, does not involve an inventive step, is not clear, and may comprise a method of treatment. In response Mr. El-Tawil has submitted various arguments disputing these objections rather than file any amendments, as he is, of course, entitled to do. These matters came before me at a hearing on 28th July 2011. In addition to myself & Mr. El-Tawil, hearing assistant Dr. Jason Bellia was also present.

The Application

3. The application concerns the use of zinc in the treatment of inflammatory bowel diseases (IBDs), which include Crohn's disease and ulcerative colitis. In particular the application alludes to the mechanism by which zinc treats these diseases and proposes specific treatments for these diseases by administration of zinc sulphate in either an enema or an infusion.

4. The 3 claims were filed on 7th June 2006. They read:

1) *The addition of zinc to current regimen for management of cases with Crohn's disease and ulcerative colitis will offer many advantages:*
Controlling diarrhoeal episodes, restoring mucosal integrity, reducing the associated increased intestinal permeability, modulating the immune-response, delaying the rates of relapses and improving the quality of life of patients.

2) *According to claim 1, zinc sulphate can be provided as an enema (new route) in a dose of 25-50micromol/ml/60ml normal saline, once daily for a period between 25-90 days for management of cases of distal Crohn's colitis and distal colitis.*

3) *According to claim 1, zinc sulphate can be prescribed as an infusion in a dose between 180-250 micromol/days divided in three doses over five-seven consecutive days for controlling severe cases of inflammatory bowel disease.*

Claim construction

5. At the hearing Mr. El-Tawil was careful to explain that his invention was characterized by the mechanism of action of zinc in the treatment of IBDs.

6. Clearly, determining new information about how a drug acts on the body can be vitally important in directing new avenues of medical research. However, for the purposes of patent law it is generally less important. Even if an earlier disclosure that a given substance can be used to treat a certain condition was based on faulty science, the correct mechanism was nonetheless being followed in the body. Taken at face value, new information about a mechanism of action of a known treatment could be considered to relate more to a discovery than to an invention, as such.

7. It is my view that the discovery of a mechanism cannot alone provide novelty (see paragraph 29, below, for a slightly more detailed discussion). However, for the sake of argument, I am willing, for now, to accept Mr. El-Tawil's point and construe the scope of claim 1 to be the use of zinc in the management of patients with Crohn's disease or ulcerative colitis to provide certain clinical benefits, the zinc acting by the mechanism defined in the application.

8. In the hearing Mr El-Tawil explained this mechanism in detail. Specifically, he explained that zinc acts on the IBD affected gut by antagonizing the pro-inflammatory mediators such as the cytokines TNF-alpha and interferon gamma. It thereby calms the immune response and inhibits the progression of the disease at an early stage. Furthermore, Mr. El-Tawil explained that zinc ions bind to the proteins of the gut mucosal epithelium so the gut wall is strengthened against the effects of IBD. These mechanisms are alluded to on page 3 of the application as filed.

9. Claims 2 & 3 go on to specify that zinc is delivered in the form of zinc sulphate in either an enema or an infusion and further specify specific dosage regimes. Mr. El-Tawil pointed out that the mechanism discussed above was important in claim 2 as it provided local absorption of zinc to particularly strengthen the gut mucosae by binding the proteins therein. It was also important in claim 3, where the immunological effects of zinc dominate as the infusion administration route means that local intestinal absorption is bypassed.

10. The examiner raised the issues of Support, Novelty, Inventive Step, and whether or not the invention is excluded as a method of treatment. I shall now address each of these issues in turn.

Support

11. Section 14 of the Patents Act sets out various requirements that must be met by a patent specification. The most relevant pieces are the parts of section 14(5) which state:

The claim or claims shall -
(a) define the matter for which the applicant seeks protection;
(b) be clear and concise;
(c) be supported by the description; …

12. In addition, I am bound to follow the precedents laid out in relevant case law. On the issue of support for medical use claims, the key case is Prendergast's Applications[1]. In this case Mr. Justice Neuberger held that:

"...where you have a claim for the use of a known active ingredient in the preparation of a medicament for the treatment of a particular condition, the specification must provide, by way of description, enough material to enable the relevantly skilled man to say this medicament does treat the condition alleged...pure assertion is insufficient."

13. This requirement is necessary to stop the speculative filing of applications on any, and all, combinations of substances and medical conditions. Neuberger J. went on to say:

"It was not practical to lay down what the tests should be in each case but it was clear that, in general, relatively rudimentary tests would suffice. It was not necessary for an applicant to have carried out full rigorous detailed and conclusive tests."

14. Mr. El-Tawil argued that the description provides enough material to show that zinc would work as it explained the mechanism of how zinc acts in treating IBDs.

[1] Prendergast's Applications [2000] RPC pg. 446

15. I am not sure that I can accept this argument. Neuberger J.'s direction seems very clear. While the description discusses the mechanisms by which Mr. El-Tawil believes zinc to act these amount to no more than assertions. I have read the application carefully and I can find no test data or other *evidence* supporting the effectiveness of zinc to treat IBDs.

16. On this point Mr. El-Tawil referred to a literature reference that he said was filed along with his application on 7th June 2006. Mr. El-Tawil argued that it was this document which provided the experimental tests in support of his application. The document in question is a journal article entitled "Effects of exogenous zinc supplementation on intestinal epithelial repair *in vitro*"[2], henceforth referred to as "Cario".

17. There are two issues, however, with relying on 'Cario' to provide the required support. Firstly, there is nothing on file to corroborate Mr. El-Tawil's claim that it was filed at the same time as his application. There is no mention of it on patents form 1/77. Indeed I can find no reference to the document before Mr. El-Tawil's letter of 23rd September 2010.

18. Secondly, even if I accept that this document was filed on 7th June 2006, it still does not form part of the application. There is no reference in the application incorporating 'Cario' into the description. Mr El-Tawil argued that this document was referenced in the description by way of the passage on page 3 which reads:

    "Zinc is a very effective measure for controlling diarrhoea (well documented)".

19. I am afraid that I do not find the phrase "well documented" to be specific enough to lead the reader to 'Cario'.

20. Finally, Mr El-Tawil argued that it was not necessary to refer to clinical trials to provide support. For evidence he referred to the IPO's own guidelines[3] which read:

    "..it is common practice that a patent literature document in order to be an enabling disclosure of a medical indication for pharmaceutically active compounds…does not necessarily need to include either clinical tests (Phase I, II, or even III) or in vivo human assays."

21. Turning to these guidelines[3] I find that the case law referenced is SmithKline-Beecham[4]. In context it can be seen that the above quote relates to the minimum disclosure in a *citation* that may render a second medical use claim anticipated. As such, it is not relevant to the current issue. However, Mr. El-

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[2] European Journal of clinical investigation vol.30 [2000], Cario et al, "Effects of exogenous zinc supplementation on intestinal epithelial repair *in vitro*", pp. 419-428.

[3] Examination Guidelines for Patent Applications relating to Medical Inventions in the UK Intellectual Property Office, July 2008, paragraph 104.

[4] T1001/01 SmithKline Beecham (unpublished).

Tawil is correct in that clinical trials are not required – but some form of evidence is. Overall, I am bound to follow Prendergast[1] and thus must conclude that the claims lack the required level of support.

Novelty

22. Section 1(1) of the Patents Act begins:

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;

23. Sections 2(1) & 2(2) of the Patents Act define what is meant by an invention being 'new'. They read:

An invention shall be taken to be new if it does not form part of the state of the art.

The state of the art in the case of an invention shall be taken to comprise all matter (whether a product, a process, information about either, or anything else) which has at any time before the priority date of that invention been made available to the public (whether in the United Kingdom or elsewhere) by written or oral description, by use or in any other way.

24. In other words, anything that was made public prior to the filing date of the application, regardless of the country, language or medium, can be used to dispute whether the invention claimed is new or inventive. As regards claim 1, the examiner identified one key document:

"Zinc supplementation tightens "leaky gut" in Crohn's disease"[5] ("Sturniolo");

25. Mr. El-Tawil argued that this citation was not relevant as it related to a mechanism of action of zinc involving non-specific anti-inflammatory effects without any contribution from the immunological effects I have summarised in paragraph 8, above. However, I note that 'Sturniolo' indicates giving zinc sulphate to patients with established but quiescent Crohn's disease in order to prevent relapses and provide greater gut barrier integrity. The document discusses several mechanisms by which zinc may act on the gut. Page 97, line 35 onwards states:

"The pathogenesis of mucosal damage in IBD may involve abnormal cytokine regulation with excessive effects from pro-inflammatory cytokines or a reduced synthesis of anti-inflammatory cytokines. In vitro studies have demonstrated

[5] Inflammatory Bowel diseases Vol. 7, No. 2 [2001], Sturniolo et al, "Zinc supplementation tightens "leaky gut" in Crohn's disease", pp. 94-98.

that zinc is crucial to maintain endothelial cell integrity in the presence of cytokine-mediate damage (25). Zinc protects cell monolayers exposed to tumor necrosis factor against damage (26), and it can inhibit oxidative stress-responsive transcription factors activated in inflammatory disease states where endothelial integrity is compromised",

26. In this regard at least I find that Sturniolo proposes some of the beneficial effect of administering zinc to Crohn's disease patients may be via immunological effects in the same way as Mr El-Tawil has explained in relation to the current application.

27. Mr El-Tawil was also careful to point out that nowhere in the prior art is it proposed that zinc is used in conjunction with existing therapies for IBD. However I find Sturniolo proposes doing just this. On page 95, line 3, it reads:

"All patients were on Mesalazine (1.2-2.4 g/day) as maintenance therapy".

28. I thus find that Mr El-Tawil's mechanism for the action of zinc in IBD is envisaged in Sturniolo, and that Sturniolo describes the use of zinc to treat Crohn's disease in conjunction with maintenance therapy. I Therefore conclude that 'Sturniolo' anticipates claim 1 even if I follow Mr. El-Tawil's construction and include the mechanism of action in its' scope.

29. However, I am not convinced that it is necessary to go this far. Even if Sturniolo et al's understanding of how zinc affected the disease was flawed, and I'm not convinced it was, the material itself was inevitably following the correct mechanism in the body of their patients. The disclosure of zinc being used to treat IBD in addition to existing therapies is enough to destroy the novelty of claim 1.

Inventive step

30. Section 3 of the Patents Act defines what is meant by the required inventive step. It reads:

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).

31. Furthermore I am bound by the decision in Pozzoli[6]. Paragraph 23 of this decision sets out the steps to be followed when assessing inventive step as follows:

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

(1)(b) Identify the relevant common general knowledge of that person

[6] Pozzoli Spa v BDMO SA & Anor [2007] EWCA Civ 588 (22 June 2007)

(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?

32. Starting with step 1(a), I find the notional skilled person in the art to be a pharmaceutical scientist with an interest in the modes of administration of drugs. Such a skilled person may also have access to the advice of a clinician. I find the common general knowledge of that person to be standard techniques of administering drugs to patients, and access to information about basic anatomy and very well accepted therapies for a range of conditions including IBDs.

33. In regard of step 2 I have already construed claims 2 and 3, above. In summary, I find that both of these claims relate to a particular dosage range of zinc sulphate administered as an enema or infusion for the treatment of specific IBDs.

34. With regards the state of the art the examiner identified two key documents:

"Zinc supplementation tightens "leaky gut" in Crohn's disease"[5] *("Sturniolo");*

ES 2238177 A1[7]

35. Mr El-Tawil argued that ES 2238177 was irrelevant as its claims were supported by administering oral or rectal doses of zinc to rats, wherein the rats had chemically induced lesions in the gut. I agree with Mr El-Tawil that this document does not anticipate the present claims. However, a machine translation of the claims reads:

> *1. Use of acexamato of zinc for the pharmaceutical preparing a composition for the treatment in human of the Intestinal Inflammatory disease.*
>
> *2. Use according to Claims 1, characterized because mentioned pharmaceutical composition is for the treatment in humans of Ulcerative Colitis.*

[5] Ibid.

[7] ES 2238177 A1 and also WPI abstract Accession No. 2005-575566 [59].

3. Use according to Claims 1, characterized because mentioned pharmaceutical composition is for the treatment in humans of Crohn's Disease.

4. Use according to anyone of Claims 1 to 3, characterized because mentioned pharmaceutical composition only contains acexamato of zinc like active principle.

5. Use according to anyone of Claims 1 to 4, characterized because mentioned pharmaceutical composition is intended to the oral administration.

6. Use according to anyone of Claims 1 to 4, characterized because mentioned pharmaceutical composition is intended to the rectal administration.

36. The state of the art thus includes the knowledge that zinc axcemate can be used to treat IBDs in humans by rectal or oral administration. As discussed above, *'Sturniolo'* indicates that it was also known to use zinc sulphate to treat IBDs in humans by oral administration.

37. Thus the differences between the state of the art and the inventive concept of claim 2 are the use of a specific zinc salt, zinc sulphate, in an enema, the use of a specific dose, for a specific period, and the treatment of a particular form of the IBD diseases confined to the distal part of the colon.

38. I believe that the skilled person would appreciate that an enema was an obvious form of rectal administration. Furthermore, that one pharmacologically tolerable salt could readily be exchanged for another. Thus I do not find that the use of a zinc sulphate enema is enough to render claim 2 inventive over the state of the art.

39. Claim 2 is also limited to the treatment of distal colitis. Mr. El-Tawil explained that the distal portion of the colon was that part up to the splenic flexure which, on average, is a distance of some150 cm from the rectum. I thus conclude that the skilled person would consider an enema to be an obvious choice of administration in such cases. Additionally, I see no evidence that the skilled person would treat this specific form of IBD differently to how they would treat IBD in general. Consequently, this limitation cannot represent the required inventive step.

40. Thus we are left only with the specific dosage regime disclosed in claim 2. With regards to the inventive step of dosage regimes I am bound by the judgment in Activis v Merck[8]. In this decision it was pointed out that the inventiveness of dosage regimes should be very carefully scrutinised. Paragraph 32 stated that:

[8] Activis v Merck [2008] EWCA Civ 444

"…nearly always such dosage regimes will be obvious – it is standard practice to investigate appropriate dosage regimes. Only in an unusual case such as the present (where… treatment for the condition with the substance had ceased to be worth investigating with any dosage regime) could specifying a dosage regime as part of the therapeutic use confer validity on an otherwise invalid claim."

41. In short, Activis v Merck[8] advises me that dosage regimes are inventive only in unusual circumstances. Unfortunately I can find no evidence that the circumstances of claim 2 are in any way unusual, for example there is no particular prejudice in the prior art against the dosage regime contained therein. I believe that the person skilled in the art would experiment to find a suitable dose for an enema in line with the standard practice in their common general knowledge. Thus following Activis v Merck[8] I am forced to conclude that the dosage regime of claim 2 does not confer the required inventive step.

42. Turning now to claim 3, the differences between the inventive concept of this claim and the state of the art are the use of a specific dose of zinc sulphate which is delivered as an infusion.

43. The skilled person would appreciate that infusions are a well known alternative for administering a wide range of substances. Further they would know that means to administer zinc as an infusion existed. Thus again we come down to the specific dosage regime disclosed. Once again following Activis v Merck[8], I am forced to conclude that the dosage regime of claim 3 does not confer the required inventive step.

Method of treatment

44. The examiner also objected that claims 2 and 3 contributed no more than a method of treatment of the human body and thus were excluded under section 4A(1)(a) of The Patents Act. However, having decided that these claims lack both support and an inventive step I see no need to address this issue.

Conclusion

45. I have found that the invention defined in the claims lacks support, is not new, and does not involve an inventive step. I have read the specification carefully and I can see nothing that could be reasonably expected to form the basis of a valid claim. I therefore refuse this application under section 18(3).

Appeal

46. If Mr. El-Tawil disagrees with my decision, he has a right of appeal to the Patents Court. Under the Practice Direction to Part 52 of the Civil Procedure Rules, any appeal must be lodged within 28 days.

47. Mr. El-Tawil should note that the compliance date for this application was 16th June 2011. If he wishes to apply for an 'as of right' retrospective extension to the compliance date he needs to do so by the 16th August 2011.

Dr S Brown

Deputy Director acting for the Comptroller