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PATENTS ACT 1977

APPLICANT Advance Biofactures of Curacao NV

ISSUE Whether patent application number GB 0011969.3 complies with sections 2(6) and 4(2)

HEARING OFFICER A C Howard

STATEMENT OF REASONS

Introduction

1 This is the Statement of Reasons I promised following my decision given orally at a hearing held on 12 August 2004, where I allowed a claim of the so-called "Swiss type" on the above application.

2 At the hearing the applicants were represented by Dr John Miles and Dr Andrew Wright of Messrs Eric Potter Clarkson, and the examiner was Dr James Houlihan.

The application

3 The application relates to a treatment for Peyronie's disease, which is described in the specification as "an idiopathic condition resulting in penile deformity and disability as the result of scarring and contracture within the *tunica albugines* of the *corpora cavernosa*". In layman's terms it is a distressing condition the symptoms of which include bending of the penis. It is caused by the presence of dense fibrous masses of abnormal connective tissue. In the treatment described in the application, a composition containing collagenase is injected directly into a Peyronie's lesion.

4 In the course of the examination of the application, several forms of claims had been offered, none of which had proved acceptable to the examiner. Following this repeated failure to reach agreement, the applicant finally asked to be heard on a claim of the so-called "Swiss" or "second medical use" type, which read as follows:

> *"Use of an injectable composition in unit dosage form comprising at least 10,000 ABC units of collagenase in a pharmaceutically acceptable carrier in a concentration of 20,000 to 40,000 ABC units per ml in the manufacture of a*

medicament for treating Peyronie's disease".

5 At the hearing Dr Miles offered amendments to the claim as follows (the additions being shown in underlined type and the deletions struck through):

> *"Use of all of an injectable composition in unit dosage form comprising at least 10,000 ABC units of collagenase in a pharmaceutically acceptable carrier in a concentration of 20,000 to 40,000 ABC units per ml as the sole ingredient in the manufacture of a medicament for treating Peyronie's disease*".

6 This is the claim formulation which I ultimately allowed.

7 Other issues were also discussed at the hearing, including procedural questions and a possible alternative claim framed so as to cover a composition of matter *per se*. However, this Statement is not concerned with any of these other matters.

The Prior Art

8 Five documents were cited in the course of the examination, which have been referred to as follows:

Patent documents

D1. GB 2323530 (Advance Biofactures)

D2. US 4338300 (Gelbard)

Other references

D3. Gelbard et.al. *Urological Research* (1982) 10:135-140

D4. Gelbard et.al. *Journal of Urology* vol. 134 (August 1985)

D5 Gelbard et.al. *Journal of Urology* vol. 149 (January 1993), 56-58

9 D1 is the applicants' own prior patent and describes the use of an injectable composition containing collegenase at a concentration within the range specified in the application in order to treat Duputyren's disease. This is a fibrotic disorder affecting the hand. It has not been called into question that Duputyren's and Peyronie's diseases are separate disorders, and no argument has been raised to the effect that that the prior use in treating Duputyren's renders the use of the claimed composition to treat Peyronie's obvious.

10 D2-D5 are concerned with use of compositions containing collagenase in injectable form to treat Peyronie's disease. D2 and D3 describe *in vitro* tests, while D4 and D5 describe the treatment of actual Peyronie's patients. The dosages and especially the concentrations involved are considerably lower (by a factor of around five) than those according to the present invention, but in other respects there are close similarities.

The law

11 At the most basic level, the statutory provisions applicable in this case are to be found in section 1 of the Patents Act 1977 which govern novelty, inventive step and industrial applicability (subsection (1)) as well as excluded matter (subsection (2)). These general provisions must be read in the light of section 2(6), which provides that:

> "In the case of an invention consisting of a substance or composition for use in a method of treatment of the human or animal body by surgery or therapy or of diagnosis practised on the human or animal body, the fact that the substance or composition forms part of the state of the art shall not prevent the invention from being taken to be new if the use of the substance or composition in any such method does not form part of the state of the art."

and of section 4(2), which provides that:

> "An invention of a method of treatment of the human or animal body by surgery or therapy or of diagnosis practised on the human or animal body shall not be taken to be capable of industrial application."

12 These provisions are among those designated in Section 130(7) as being so framed as to have, as nearly as practicable, the same effect as the corresponding provisions of the European Patent Convention. The decisions of the EPO Boards of Appeal on this topic are therefore pertinent.

13 The application of the above provisions to inventions relating to the medical use of known compositions of matter has been subject to very extensive interpretation by the courts. Most relevant in these proceedings are the decision of the EPO Enlarged Board of Appeal in *EISAI/second medical use* (GR05/83) OJEPO 1985, 64, and the judgment of the Patents Court in *John Wyeth's and Schering's Applications* [1985] RPC No. 23, p. 545. These cases approved the use of so-called "Swiss claims" in the situation where a "substance or composition" already having a known medical use is found to have "new and inventive therapeutic application".

14 Swiss claims can be drafted in more than one way, but all come down in essence to the use of a specified substance or composition in the manufacture of a medicament for treatment of a specified disease. Providing the use in the treatment of the specified disease is not known, such claims are considered to be novel.[1]

15 Further relevant authorities are *Bristol Myers Squibb v Baker Norton* (the "Taxol" case) [2001] RPC p. 1; *Merck & Co's patent* [2003] FSR 29 p. 498 and [2003] EWCA Civ 1545; *Monsanto v Merck* [2000] RPC p.77 and *Prendergast's Applications* [2000] RPC p. 446. All these cases were referred to in the course of the prosecution of the present application.

16 In the present context, it was important to understand in particular the terms "substance" and "composition". Although no judicial authorities were referred to which go to this specific point, I believe it is well established, and in practice there was no dispute, that for the present purposes

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[1] A useful summary of the circumstances under which such claims are accepted and the rationale underlying their use is given in paragraphs 79-113 of the Patent Office pamphlet entitled "Examination Guidelines for Patent Applications relating to Medical Inventions in the UK Patent Office" (March 2004), which is downloadable from the Patent Office website at http://www.patent.gov.uk/patent/reference/mediguidlines/index.htm.

"substance" can be taken to mean "active ingredient", while "composition" encompasses preparations containing at least one active ingredient in combination with other components (e.g. pharmacologically inert diluents or carriers).

17 A key question raised in the present case was whether medicaments formulated for administration to a patient can constitute distinct "compositions" in situations where the principal or only difference to a known formulation for treating the same disease lies in the concentration of the active substance. No authorities have been identified which address this issue, although some guidance can be found in the *Taxol* case in which the claim under consideration had the following wording:

> "Use of Taxol and sufficient medications to prevent severe anaphylactic reactions, for manufacturing a medicamentation for simultaneous, separate, or sequential application for the administration of from 135 mg/m^2 up to 175 mg/m^2 Taxol over a period of about 3 hours or less as a means for treating cancer and simultaneously reducing neutropenia."

18 The Court of Appeal held that this claim defined an improvement in the method of administering an existing treatment, and that it did not define a new and inventive therapeutic purpose (Taxol was known to treat cancer). In particular, it was noted that all the claimed steps were in fact directed at actions taken by the doctor, tailored to the individual patient, rather than being directed at the manufacturer. To quote Aldous LJ at paragraph 63:

> "*The claim is an unsuccessful attempt to monopolise a new method of treatment by drafting it along the lines of a Swiss-type claim. When analysed it is directed step-by-step to the treatment. The premedication is chosen by the doctor, and administered prior to the Taxol according to the directions of the doctor. The amount of Taxol is selected by the doctor as is the time of administration. The actual medicament that is said to be suitable for treatment is produced in the patient under supervision of the medical team. It is not part of a manufacture*."

19 Thus, it is not acceptable for Swiss-type claims to be distinguished from the prior art only by the mode of administration or the amount, timing or frequency of dosage.

20 This conclusion was followed by the Patents Court in *Merck's patents* [Alendronate], as upheld by the Court of Appeal. This is the case which has the closest parallel with the present case.

21 The claim in question as originally framed read

> "Use of alendronic acid, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for [treatment of a specified disorder] wherein such medicament is adapted for administration in a unit dosage form which comprises about 70 mg of alendronic acid or a pharmaceutically acceptable salt thereof, on an alendronic acid active weight basis, according to a continuous schedule having a dosing interval of once weekly."

22 This was amended in the course of the hearing before Jacob J but still related essentially to the use of alendronic acid for the preparation of a specified dose to be administered according to a specified schedule.

23 The Swiss-type claim in that case was based on a new dosage regime, namely a single weekly administration of 70 mg of Alendronate as opposed to daily administration of 10mg. The claim was held on its true interpretation as invalid as relating to a method of treatment. The only difference between the claim and the prior art was considered to lie in the method of administration, that is what is on the prescription. Although an attempt was made in the proceedings to argue that the 70mg dose in a single pill was a significant factor, the description itself disclosed that the dose could be administered as separate pills each containing less than 70mg of active substance. Moreover Jacob J observed that even if this had not been the case, following the *Taxol* reasoning would have led him to the same conclusion.

Summary of the arguments put in the present case

24 The essence of the examiner's objection was that notwithstanding that the candidate claim covered a concentration range of active ingredient not disclosed in the prior art for treating Peyronie's disease, the prior use of lower concentrations of the same ingredient meant that the claim could not be regarded as relating to a different "composition". Underlying this was the view that the concentration was an element of the dosage regime, which has always been considered to be within the domain of the medical practitioner. In fact, the claim initially under consideration before the amendment offered in the hearing did include an explicit reference to the composition being in unit dosage form, and was limited by the amount of the unit dose as well as the concentration of collegenase expressed in units per ml.

25 In support of his argument, the examiner referred me to paragraph 87 of the judgment of the Court of the Appeal in the *Taxol* case where, in a section entitled *'The limits of second medical uses as recognised in Eisai*", Buxton LJ summarises the law by saying "*The novelty* [of a Swiss claim] *cannot lie in the method of use, but in the new therapeutic purpose for which the substance is used"*. In the examiner's view the message from this judgment was that "a new therapeutic purpose" was considered to mean the treatment of a different medical indication or disease. Further, he submitted that there is nothing in the case law which indicates that a composition in a second medical use claim can be characterised in a way the applicants propose.

26 The response of Dr Liles to this was to argue that the present situation was materially different. His arguments can be summarised as follows:

- Although the use of the "substance" collagenase for treating Peyronie's disease is known, the candidate claim recites a novel and inventive "composition";

- The candidate claim would not restrain the actions of a medical practitioner in prescribing a method of treatment; the composition is more concentrated than prior art compositions and could not therefore readily be made up (e.g. by a pharmacist acting under the instructions of a medical practitioner using prior art compositions as a starting point);

- Administration of the medicament which is the subject of the claim requires the exercise of no medical discretion;

- The claims in *Taxol* and *Merck* were rejected because in essence they related to how the medicament was used (in terms of administration and dosage), rather than what was used to

prepare the medicament;

- The concentration of collegenase in the claimed injectable concentration has technical advantages related to the dose delivered, the volume that can feasibly be injected into the penis, and the recognition that the high collagenase concentrations according to the invention can in fact safely be used despite having previously been thought to be harmful.

Discussion

27 Given that (1) the use of the *substance* collagenase for treating Peyronie's disease is known; and (2) the use of the claimed formulation in an injectable form for treating a *different* disease is known, the point at issue can be very simply summarised in terms of "does the claimed formulation amount to a new "composition" for the manufacture of a medicament within the meaning of the principles laid down in *EISAI*?" If the answer to this question is "yes", then this is a "second medical use" situation and a "Swiss" type claim is allowable.

28 Both the examiner and the applicant recognised, correctly in my view, that the authorities require that the correct approach to this question involves a consideration of what is properly within the ambit of what the medical practitioner might do in terms of specifying a dose or treatment regime for a pre-existing substance or composition. This includes the giving of instructions to a pharmacist to make up a preparation for administration to a patient.

29 Turning to the arguments put by the applicant, I can dismiss relatively easily the point that the proposed claim relates to a new composition because it is envisaged to be sold as a ready made up formulation and therefore involves the exercise of no medical discretion. It seems to me that in the absence of clear indications to the contrary, an injectable composition defined in terms of the content and concentration of active ingredient can in principle be made up by a pharmacist under the directions of a medical practitioner. That the product may in practice be sold in a form suitable for direct administration does not change this fact, and therefore as such has no bearing on the question of whether the alleged invention relates to a composition as opposed to a dosage or treatment.

30 Related to the above is the argument that the claim cannot be readily performed by a pharmacist or medical practitioner because all prior art compositions are more dilute, and cannot therefore be combined to make the more concentrated solution as claimed. This is an interesting point, but again I do not think it has a direct bearing on the question at issue. In the situation where a medical practitioner may specify a particular course of treatment in the light of what is known to be available to treat a particular disease, I find it difficult to accept that for the purposes of patent law a distinction should be made between concentrations of active ingredients which are more dilute than those used in earlier treatments and those which are more concentrated.

31 It follows that, other things being equal, the specification of a particular concentration and amount of active ingredient will normally comprise mere elements of the dosage regime. Something more is needed before a claim characterised in such a way can be regarded as relating to a new "composition" worthy of protection under a "Swiss" claim.

32 This brings me to the applicant's argument that the concentration of collegenase in the claimed injectable preparation has a technical significance beyond mere specification of a dose. Dr Liles

submitted to me that this is because to inject the claimed amount of collagenase using the more dilute prior art compositions would involve too large a total volume to be feasibly injected into the penis. Although this factor on its own might not be sufficient to justify a conclusion favourable to the applicant, he also submitted that the very high concentrations described in the application would previously have been thought to cause undesirable side effects. Thus the composition now claimed fell outside the range of what would be have been reasonably considered by a medical practitioner when specifying a dose according to the prior art. Moreover, the invention as claimed had been shown to have significant new therapeutic effects in that it had benefited patients with severe disease who had not responded to the prior art treatment even after repeated injections involving total accumulated doses approaching those specified in the present application.

33 I believe this part of the argument has greater merit. The distinction over the prior art is clearly more than simply one of dose, since similar total doses administered using more dilute compositions do not have the same effects. In the *Merck* case, administration of a single large dose (as opposed to a number of smaller doses over a period of time) was considered still to be within the ambit of a method of therapy, but the situation here is distinguished by the practical limitation on the volume which can be delivered in one injection coupled with the alleged prior prejudice against using very high concentrations. This combination of factors was not present in *Merck*. Although in that case, an argument was also raised that a single high dose pill would have been considered unacceptably dangerous, there was held to be insufficient evidence to support this contention (paragraphs 88-92). In contrast, in the present case there are indications from the prior art documents that collegenase was and is regarded as a powerful and potentially destructive substance and must be treated with care when injected into such a sensitive part of the body. Given the *ex parte* nature of the proceedings, I am prepared to give the applicant the benefit of the doubt on this point and therefore to conclude that on balance there was likely to have been, at the time of making the invention, a real prejudice against the use of the claimed concentration of collagenase.

34 Furthermore, in *Merck*, a consideration was that the claim covered not only a dose comprising a single pill containing 70mg of active ingredient, but also the administration of multiple (prior art) pills to achieve a total 70mg dose. As mentioned above, the simultaneous administration of multiple doses of prior art compositions is not an option in the present case. Taking all this together, I do not feel that it is reasonable to come to the conclusion that the matter claimed amounts to no more than a new dosage regime involving a prior art composition.

35 Nevertheless, I have to say that even taking account of the above factors, I consider that overall the arguments are finely balanced.

Support

36 I should briefly here mention a further objection that the examiner raised at the last moment to the effect that support in the form of evidence of clinical trials is normally required for Swiss type claims, and the description of the present application is insufficient for these purposes as it gives relatively brief information about the experimental treatment of only a single patient and asserts that others had also benefited, without giving details. He referred to the judgment in *Prendergast's Application* [2000] RPC 446, where Neuberger J said (p. 450 lines 16-18) that

it would not be right to allow Swiss type claims in relation to "all sorts of speculative uses for established drugs and other chemicals without a shred of evidence as to whether they would work …". However the judgment also makes clear that although tests do have to be carried out to support a Swiss claim, these can be, where appropriate, very rudimentary (lines 11-12).

37 I agree that the present description does not provide details of clinical trials to the standard that would be expected for publication in a peer-reviewed journal. However I do not believe that *Prendergast* requires this. The description contains information about the condition of a patient who has been treated according to the invention and states that others have also benefited. It seems to me that this is perfectly sufficient in the light of *Prendergast*, and it is for this reason that I rejected this particular objection.

Summary and Conclusions

38 What I considered important in coming to my decision is whether the Swiss type claim offered related to the use of a new "composition" or merely a method of therapy within the art of the medical practitioner.

39 I did not accept that specifying a particular novel concentration of active ingredient, whether or not limited by total dose, will necessarily amount to a new "composition" for these purposes.

40 Nor did I accept that specifying a concentration which is greater than is disclosed in the prior art will necessarily be outside the scope of the medical practitioner's art simply because it cannot be made readily from prior art compositions. On the contrary, I believe that specifying the dose to be delivered and the concentration of active ingredient does in principle lie within the ambit of the medical practitioner's art. These are parameters which can be specified in a prescription to be made up by a pharmacist.

41 Nevertheless, the following factors led me to the conclusion that on the facts of this case, the invention does amount to more than a mere dosage regime and is therefore entitled to be covered by a "Swiss" claim:

- The substantial difference between the concentrations specified in the candidate claim and those of the prior art, and the fact that the required dose could not in practice be delivered through administration to the patient of prior art compositions;

- My finding that there would have been a prejudice at the time of making the invention against the use of the claimed composition because it might have been expected to produce harmful side effects;

- The fact that the composition is successful in treating certain patients who derive no benefit from the more dilute compositions of the prior art.

A C HOWARD
Deputy Director acting for the Comptroller