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THE PATENTS ACT 1977

01088/95

IN THE MATTER of Patent Application No. 9423929.0 in the name of Consultants Suppliers Limited

DECISION

Application No 9010129.6 was filed by Consultants Suppliers Ltd on 4 May 1990 without claiming priority from any earlier application. The claims were directed to a set of compounds *per se*, as well as to such compounds for pharmaceutical and non-pharmaceutical use, and to pharmaceutical compositions containing the compounds.

In a partial search under Section 17(4), a large number of prior-published documents were identified which indicated that the claimed compounds were not novel. In the first substantive examination report dated 14 April 1993, the Examiner, Mr S J Quick, initiated objection under Section 1(1)(a) on the basis of a selection of these documents. In response to a limited amendment of the application by the applicant's original Agent (by which the original claims to compounds *per se* were restricted and "Swiss-type" claims were introduced to embrace the full structural scope of the compounds originally claimed), a more complete search was conducted by the Examiner and the objection to lack of novelty was extended in a second substantive examination report dated 14 December 1993 on the basis of the additional documents that had been identified.

During the period offered to the applicant for addressing the lack of novelty, the issue of adequacy of support for further medical use claims, which had been deferred by the Examiner and not raised in the second examination report, was brought to the applicant's attention by a third party in a Section 21 observation dated 5 May 1994 and clarified by the Examiner in an Official Letter dated 17 May 1994.

The applicant's current Agents filed amendments under cover of a letter dated 17 June 1994 to overcome the objection to lack of novelty and an interview between the Agent, Mr

Couchman, and the Examiner took place on 11 August 1994 to discuss the issue of support. In the ensuing Official Letter of 2 September 1994, the Examiner formally set out the basis for his objection under Section 14(5)(c) that the "Swiss-type" further medical use claims were not supported by the description.

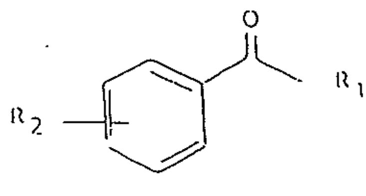
In order to expedite the grant of a patent for that subject matter within the application that was considered to be uncontentious, the applicant elected to transfer the "Swiss-type" claims to a divisional application. Thus the present application No 9423929.0 was lodged on 26 November 1994, the Section 20 period and the period for filing such an application having both been extended under Rules 100 and 110(1) respectively.

In the first substantive examination report on the divisional application dated 21 December 1994 the Examiner reiterated his objection under Section 14(5)(c) and offered a hearing. In a letter dated 1 February 1995, Mr Couchman took the opportunity to set out his arguments in writing. In a further Official Letter dated 16 February 1995, the Examiner acknowledged that there was no agreement on the issue, a hearing thereby being necessary, and took the opportunity to clarify a matter that appeared to have been misunderstood.

Mr Couchman responded in his letter of 6 March 1995 that the applicant did not wish to attend a hearing. In an Official Letter dated 13 March 1995 a period of two weeks was offered during which attendance at a hearing could be reconsidered and requested. That period having expired with no such request having been made, it now falls to me to decide the issue on the basis of the papers on file.

Claim 1 of the application reads as follows:

> "1. The use for the manufacture of a medicament for the treatment of human or animal patients to alleviate or cure disease or disease symptoms by inhibition of nuclear ADP-ribosyl and similar transferases of a compound of the general formula:



(I)

wherein:

R_1 is amino, substituted amino, hydroxy or alkoxy; and

R_2 is meta to the group -CO-R_1 and is acylamino including alkenoylamino and haloacylamino; alkanolamino, haloalkylamino; a mercapto amino derivative, including thioalkylamino; substituted hydroxy, including alkylhydroxy, alkanolhydroxy, alkenylhydroxy, alkenoylhydroxy, or a mercapto hydroxy derivative, including thioalkylhydroxy; mercapto and substituted mercapto, including alkanolmercapto, acylmercapto (including alkenoylmercapto) and haloalkylmercapto; guanidino or substituted guanidino; or ureido or substituted ureido, provided that, when R_1 is amino, R_2 is not any group other than hydroxyalkoxyalkanoylamino, ethenoylamino, haloacetylamino or aryl-containing acylamino and that, when R_1 is hydroxy, R_2 is not an aryl-containing acylamino group or an acylamino group containing conjugated double bonds."

Claims 2 to 10 are appendant to claim 1 and merely introduce preferred aspects of the general chemical formula (I) specified in claim 1, the statement of claim then continuing with claim 11 as follows:

"11. Use according to claim 1, wherein said compound is:

ethyl-m-propenoylaminobenzoate;
3-propenoylaminobenzoic acid;
3-chloroacetylaminobenzamide;
3-bromoacetylaminobenzamide;
3-N(3_-chloropropyl)aminobenzoic acid;
ethyl, 3-methylureidobenzoate;
ethyl, 3-(N-methyl,N-nitroso ureido)benzoate; or
ethyl-3-guanidinobenzoate.

12. Use according to claim 1, wherein said compound is:

ethyl-m-propenoylaminobenzoate;
3-propenoylaminobenzoic acid;
3-chloroacetylaminobenzamide;
3-bromoacetylaminobenzamide;
3-N(3_-chloropropyl)aminobenzoic acid; or
ethyl, 3-(N-methyl,N-nitroso ureido)benzoate.

13. Use of a poly (ADP-ribose) polymerase inhibiting compound of any of claims 1 to 12 for the manufacture of a medicament for the treatment of retroviral diseases or African trypanosomiasis, for cancer chemotherapy or in cases of immune disease susceptible to treatment by inhibition of poly (ADP-ribose) polymerase, or for the treatment of conditions caused by bacterial toxins which have an ADP-ribosylating activity.

14. Use according to any of claims 1 to 13, wherein the medicament is for administration of the compound at a level of from 0.01 to 5 mmoles per kg.

15. Use according to claim 1 and substantially as hereinbefore described."

Thus all of the claims are of the so-called "Swiss-type", ie "Use of substance X for the manufacture of a medicament for the treatment of disease Y". Claims of this construction have been allowed by both the enlarged Board of Appeal of the European Patent Office (Decision Gr 05/83, OJEPO 3/85) and in the United Kingdom by the Patents Court (John Wyeth and Brother Ltd's Application; Schering A.G's Application [1985] RPC 545). Whilst claims to a product *per se* characterised by a medical application are precluded if that product has already been described for another medical use, it has been held that it is legitimate in principle to allow claims directed to the use of a substance for the manufacture of a medicament for a specified new and inventive therapeutic application, even if the process of manufacture does not differ from known processes using the same active ingredient.

The issue in this case is whether or not the claims are supported by the description as required by Section 14(5)(c).

The requirements for support of "Swiss-type" claims were considered in some detail by the Hearing Officer at pages 7 to 11 of the decision in Wilhelm Hoerrmann's Application SRIS O/95/93, which reads as follows.

> " . . . in considering what is adequate support in the description for medical inventions having at their heart a further medical use the emphasis must be towards finding description that demonstrates that use not by mere reference to a condition that may be treated but by reference to tests that show that treatment to be a reality. Only in this way, it seems to me can it be shown that invention has been made and not merely contemplated as a possibility.
>
> Dr Hoerrmann refers in his letter to the fact that in his opinion the essentials of the invention, namely the chemical nature of the compounds, the dosage and the new medical indications are all to be found in the specification. I would not want to disagree with Dr Hoerrmann that these are indeed the essentials of the invention but the effect of their disclosure and the extent to which they are disclosed are matters which I must consider in coming to a decision as to whether they provide support for the invention claimed.
>
> In any case relating to the medical use of a compound or composition it is obviously necessary for there to be adequate disclosure enabling the compound or composition to be identified. It would also be expected that information concerning the dosage to be administered would be disclosed as enabling a full understanding of the invention. This information, in itself, might provide adequate support for a claim that is not purpose limited. However, in my opinion, it cannot provide support for an invention

in which the only form of protection is via a "Swiss" type claim. Resort to such a claim is an indication that the compounds or compositions as well as the dosage amounts and forms in which they are administered are well known in the art.

Such is the case with the present application. There is no doubt that hydroxylysine and lysine are known compounds and that the dosages in which they are used as well as the form of their administration are well known. This much is evident from the specification on pages 6 and 7 where it is stated:-

> "The drugs according to the invention are to be administered in ways basically similar to those normally employed in usual amino acid treatment, i.e. preferentially per os or intravenously, or by the central intravenous route. Administration by way of tablets, coated tablets, injection or infusion solutions would likewise be identical."

and

> "In view of the fact that the compounds in question are non-toxic, dosages may range widely even though they might initially be based on normally used therapeutical amino acid dosage levels of between 0.01 and 0.1 g of substance per kg of bodyweight."

Clearly then in an application like the present where the invention resides in finding a further medical use for a known compound or composition, administered in conventional amounts and in a conventional manner, support for a claim based on that new use is going to be found primarily in that part of the description which provides evidence that the new use has been effected.

In the present application, and with particular regard to claims 1 to 5, it is contemplated that something like twelve different medical conditions may be treated by administration of hydroxylysine or lysine. If those claims are to be considered as supported by the description then, in my opinion, that description should demonstrate by relevant in vivo or in vitro tests that the specified compounds are indeed effective against each one of those twelve conditions.

However, on turning to the description all I can find under the heading "Fields of application for the drugs according to the invention:" on page 5 is a list of conditions in very much the same terms as that of claims 1 to 5. There is a complete absence of any pharmacological data to demonstrate that the invention, which I take to be the treatment of the specified conditions, has in fact been carried out, let alone has proved to be effective.

The examiner, in paragraph 3 of the Official letter of 8 October 1992 raised objection in these terms:-

> "In amended Claims 1-5 (which now take the form of what are generally known as "Swiss Type Claims") the claimed therapeutic activities of the isomers of Lysine or Hydroxylysine are not supported by the description where there is a complete lack of any pharmacological data to show that Lysine or its hydroxy derivative is active against the ailments specified in Claims 1-5. Without such data it is not clear how such new therapeutic

indications have been arrived at. Any patent application in which claims are dependent for their novelty on new therapeutic uses would be expected to include in its description in vivo or vitro pharmacological tests to demonstrate the new activities, otherwise the new uses claimed could be construed as being merely speculative."

I have come to the conclusion that this objection must be right.That is not to say that I do not sympathise with Dr Hoerrmann's problem of having to conduct long and expensive clinical trials but unless there is some indication in the description of applications of this type of tests, however rudimentary, demonstrating that the invention has been carried out in an effective manner then the application must fail for lack of support for the invention claimed."

Thus, the Hearing Officer's view in the Hoerrmann case was that some disclosure of testing data was necessary to support "Swiss-type" claims.

A subsequent decision in which support for "Swiss-type" claims has been considered was that of McManus's application [1994] FSR 558 where the Patents Court upheld the Hearing Officer's decision which included, *inter alia*, the following statement on the subject of the support necessary for such claims:

"It follows therefore that the novelty of such an invention so claimed must necessarily reside, not in the composition of the medicament itself but in the particular treatment to which it is directed and in consequence a clear indication that such a treatment has been tried and tested is essential to provide the necessary support for the claim."

Reference to both these prior decisions was made by the examiner in the present case when setting out his objection to the present claims under Section 14(5)(c) in the Official Letter dated 21 December 1994, the examiner explaining that, in his opinion, the phrase "a clear indication that such a treatment has been tried and tested" used in the McManus decision was consistent with the Hearing Officer's view in Wilhelm Hoerrmann's Application that the presence of some detail regarding testing is necessary, and that a mere statement that the claimed invention has been tested is not a 'clear indication' but an unsupported assertion.

A contrary view was expressed by Mr Couchman in his letter dated 1 February 1995 in reply, Mr Couchman arguing in the following terms:

"It appears to us that the only directly relevant decision binding on the Office is that of Mr Justice Aldous in the *Anne McManus* Case. We agree in this respect with the Examiner that Mr Justice Aldous upheld the Hearing Officer's view that "a clear indication that such a treatment has been tried and tested is essential to provide the necessary support for the claim".

> The *Wilhelm Hoerrmann* case is consistent with the *Anne McManus* decision but, if isolated passages are taken out of context, could be construed in a way which contradicts the binding *Anne McManus* judgement.
>
> In the paragraph bridging pages 7 & 8 as well as in the first two paragraphs on page 10 of the *Hoerrmann* decision the Hearing Officer makes reference to tests and to pharmacological data. However, it is clear that the Hearing Officer did not consider it necessary for worked examples and tabulated data actually to be presented, since he concluded in the first full paragraph on page 11 that the requirement was "some indication in the description of applications of this type of test, however rudimentary". If the Hearing Officer in the *Hoerrmann* case had gone beyond that and required detailed worked examples, his decision would have been rendered nugatory by the subsequent approval by the Patents Court of the Offices's position in the *McManus* case that "a clear indication" of testing provides the requisite support.
>
> The Examiner acknowledges that the applicant need do no more than show the presence of a clear indication but apparently goes on to say in paragraph 17 of the Official Letter that protocols and data must be presented. However, in both the *McManus* and the *Hoerrmann* cases the Office carefully avoided any stipulation that protocols and data must be presented and, instead, referred to the need for an indication. It is an abuse of the English language to state that protocols and tabulated data are required to "indicate" that tests have been performed. To the contrary, in normal English usage, reference to somebody having indicated certain information covers the conveyance of that information by all kinds of subtle and indirect means. Thus, if you mean to say that protocols must be presented, that is what you say. The word "indication" must be interpreted as meaning what it says, i.e. an indication."

Mr Couchman further argues that the requirement of the law is not that patent applications should contain a detailed description of the working of the invention, but rather that they should enable the skilled person to work it, and in the present case the skilled person can make the compounds of claim 1 and manufacture medicaments therefrom, thus meeting the requirements of the law. He distinguishes a speculative application which is one where the applicant does not know whether the invention works or not from the present case where, if the applicant has conducted at least rudimentary tests with satisfactory results and has indicated the finding of such results in the application, then the requirement for support is met. Mr Couchman further comments that one of the inventors has confirmed that at the time the application was filed there were available *in vitro* data supporting the invention, thus the application was filed in good faith upon the basis of suitable tests.

There is, I think, no dispute in this case that certain passages in the description do provide an 'indication', in the ordinary meaning of that word, that certain compounds have been tested by the applicant and found to exhibit the specified enzyme inhibitory activity. The issue is, rather, whether or not they provide adequate support for the present claims and just what is necessary to satisfy the "clear indication" requirement set out in the McManus decision.

Whilst Aldous J approved the Hearing Officer's decision in the McManus case, he made no specific comment on the question of what is needed to support "Swiss-type" claims nor on the support requirement specified by the Hearing Officer. When interpreting the Hearing Officer's words in that case, it is necessary, I think, to keep in mind the context in which they were made. In that case, the Hearing Officer was considering a hypothetical oral-use "Swiss-type" claim and the potential supporting passages in the description provided no suggestion that the medicament had actually been tested for such use. Thus the Hearing Officer was commenting on a situation where there was no indication at all of testing and thus there was no need for him to consider what level of disclosure of testing or use would provide adequate support for a "Swiss-type" claim. In this light and in the absence of any indication that such was his intention, I think it would be wrong to interpret his words as denoting any change in approach from that set out in the earlier Hoerrmann decision where the question had been more fully considered or to infer that by the phrase "clear indication" he meant no more than a 'mere indication' without further testing detail.

The Hearing Officer's view in the Hoerrmann case was that, to support "Swiss-type" claims, there should be disclosure of at least rudimentary tests to demonstrate that the invention has been carried out in an effective manner and that the treatment it promises is a reality, and that mere disclosure of the active agent, the dosage and the new medical indication is not adequate in this regard. He was further of the opinion that each distinct medical use claimed should be so supported. I am in agreement with this approach, the consideration for granting claims for a subsequent medical use of a known medicament must lie in clear demonstration of the effectiveness of the medicament for the subsequent use, rather than in mere assertion of its effectiveness which would leave the path open for speculative patenting of ranges of new potential but untried uses for known medicaments.

Turning to the details of the case in hand, the body of the specification contains no worked examples illustrating use of the compounds in inhibition of nuclear ADP-ribosyl or similar transferases or in the treatment of those diseases listed in claim 13. Support for the claims, thus, must be found in the general description and I will consider the relevant passages in detail. With regard to these passages, it must be borne in mind that only certain of the compounds mentioned relate to the invention claimed in this divisional application, since the description, which is as yet unamended, corresponds to that of the original parent application as filed which envisaged a broader class of compounds. In particular, of the 28 specific compounds listed at pages 8 to 10 and thereafter identified by number, only compounds 11, 12, 14, 15, 17, 18, 21 and 25 are within the general formula (I) of claim 1 (these are in fact the eight compounds listed by name in claim 11). Those passages of the description which make reference to the medical use are five in number and are as follows:

(i) At page 1 lines 1 to 5,

> "The present invention relates to substituted benzene compounds and, in particular, to substituted benzamides, typically for use in inhibiting ADP-ribosyl transferases such as those known as poly(ADP-ribose) polymerase or synthetase."

This is no more than a statement of the intended use.

(ii) At page 4 line 15 to page 5 line 1,

> "We have now found that certain other novel benzamides act as inhibitors of nuclear ADP - ribosyl and similar transferases and, thus, are useful in medicine, for example, in the treatment of retroviral diseases and African trypanosomiasis, as an adjuvant in cancer therapy or in certain cases of immune disease, or in the treatment of conditions caused by certain bacterial toxins. In addition, in view of their inhibitory activity it is thought possible that one or more of the said compounds may be useful in the treatment of patients infected with a human immunodeficiency virus (HIV). Furthermore, certain non-inhibitory chemical analogues of said novel benzamides are useful as intermediates and as controls in toxicity and other testing."

This passage refers only to <u>benzamides</u> acting as inhibitors of nuclear ADP - ribosyl and similar transferases whereas claim 1 embraces the use also of benzoic acid and benzoate compounds. At the end of the passage there is a reference to "chemical analogues of said novel benzamides" but whether or not this passage is referring to the acid and ester compounds is not clear and, in any case, these compounds are stated to be 'non-inhibitory'.

(iii) At page 11 lines 6 to 11,

> "As indicated above the compounds of the invention are useful as inhibitors of ADP - ribosyl transferases. As such they are believed to be useful in the treatments set out above at levels ranging from 0.01 to 5 mmoles per kg. For example, at a level of about 0.02 mmoles per kg for compound 27 above."

This passage makes a positive statement to the effect that the compounds of the invention are useful as inhibitors of ADP - ribosyl transferases. However, the following reference to the dosage range for usage is in speculative terms. The final sentence of the passage is in somewhat more definite terms but, as previously indicated, use of compound 27 is outside the scope of claim 1 and thus this statement does not directly support the invention claimed.

(iv) At page 11 line 21 to page 12 line 2,

> "Some of the compounds of the invention act as reversible inhibitors in the same manner as known compounds. Surprisingly, however, certain of the compounds, namely those of formula (IV) below, in particular compounds 4 to 7, 11 to 17 and 19 to 21 are able to form covalent compounds. Moreover, compounds 4, 7, 14, 15, 16 and 19 exhibit a preferred feature in that they act by forming a covalent compound with the enzyme specifically and thus inhibit the enzyme. These are new and unexpected features."

This passage is indicative of testing in that it describes how some of the compounds act in the same manner as known compounds whereas others act in a new manner by virtue of forming a covalent bond with the enzyme. I read the passage as suggesting, however, that only certain of those compounds which form covalent compounds also act as enzyme inhibitors. Claim 1 embraces use of certain compounds specified here as forming covalent compounds (compounds 11, 12, 17 and 21) but not further included in the list of enzyme inhibitors.

(v) And, finally, at page 12 line 24 to page 13 line 16,

> "In the compounds of the invention the utility exhibited may be in terms of one or more of:
>
> Inhibitory activity,
> Utility as an intermediate, and/or
> Utility as a control compound.
>
> Generally speaking, the meta or 5- or 8- compounds defined or described above will exhibit inhibitory activity, whereas the ortho or para compounds (6- or 7- substituted compounds in the two ring compounds) may find better use as intermediates or controls. However, it may be the case that some of the ortho compounds also will

exhibit useful inhibitory activity. Also, those compounds wherein R_1 is amino are good inhibitors, whereas those compounds wherein R_1 is other than amino are better used as intermediates and controls.

Moreover, the compounds which exhibit inhibitory activity are not necessarily those which form covalent compounds and vice versa. Thus, for example, compounds 12, 17, 20 and 21 form covalent compounds, but are not enzyme inhibitors."

This passage states that the meta compounds (to which claim 1 of this application specifically relates) generally inhibit inhibitory activity, but continues by stating that those compounds where R_1 is amino (ie the benzamides) are good inhibitors whereas the compounds where R_1 is otherwise are better used as intermediates and controls. Formula (I) of claim 1, of course, embraces compounds of the latter type. Further, the last sentence of the passage explicitly states that certain compounds "are not enzyme inhibitors". Three of these compounds Nos 12, 17 and 21 are not only within the scope of formula (I) specified in present claim 1, but are specifically identified in claim 11 (being compounds 3-m-propenoylaminobenzoic acid, 3-N(3'-chloropropyl)aminobenzoic acid and ethyl, 3-(N-methyl,N-nitroso ureido)benzoate, respectively).

In summary, therefore, whilst the passages quoted above from the description do give some indication that certain compounds have been tested and found to exhibit inhibitory activity for ADP - ribosyl transferase, there is no detail whatsoever given regarding such testing nor is there any indication that the said compounds have been tested against the diseases listed in claim 13. Further, the passages quoted above from pages 4 to 5 and pages 12 to 13 provide contrary indications of activity by suggesting that not all the compounds envisaged are enzyme inhibitory in nature and that this latter category includes three of the compounds specifically identified in claim 11 as preferred embodiments of the enzyme-inhibitory medicament.

I do not, thus, see the description as providing adequate support for the claims. Such references as do exist as regards the enzyme inhibitory activity of the compounds and their resultant applicability for treatment of the diseases listed in claim 13 are no more than mere assertion that the compounds are so effective. Whilst these assertions may indeed be validly based on *in vitro* tests as Mr Couchman states, I do not see that it is right that this is something that the reader of the patent should have to take on trust. I think that something more is needed to meet the requirement of support in such cases, not necessarily fully worked examples and tabulated data, but at least rudimentary data regarding the testing done and the results obtained to show that the asserted activity is a reality. In the absence of such information, I do not see that the description provides the <u>clear</u> indication that the treatment has been tried and tested identified as necessary in the McManus decision.

Also, as a separate issue in this case, the passages in the description relating to the enzyme inhibitory activity of the compounds do not clearly link this activity to the full range of compounds as defined by formula (I) in claim 1 and, indeed, suggest lack of inhibitory activity for some of the compounds embraced by the claim. Thus from a different aspect, there is again lack of support for the claims in the description.

In conclusion, therefore, I find that the examiner's objection under Section 14(5)(c) is well founded against all of the present claims. As previously indicated, this divisional application was filed specifically to allow consideration of the disputed "Swiss-type" claims separately from the other allowable embodiments of the original application which remain in the parent application. Accordingly, having found that the description is not adequate to support "Swiss-type" claims, I do not see that the setting of a period for submitting amendments to meet the lack of support objection would be appropriate. Accordingly, I refuse this application. Any appeal should be lodged within 6 weeks of the date of this decision.

Dated this 30 day of March 1995.

[redacted]

G M Bridges
Principal Examiner acting for the Comptroller.

THE PATENT OFFICE