

SMITHKLINE

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1982 No. 7900P



THE HIGH COURT

IN THE MATTER OF THE PATENTS ACT 1964

and

IN THE MATTER OF LETTERS PATENT NO. 30666
dated 19th December, 1966 of SMITHKLINE
BECKMAN CORPORATION

and

IN THE MATTER OF A PETITION UNDER SECTION 27
OF THE PATENTS ACT 1964 FOR THE EXTENSION OF
TERM OF THE SAID PATENT.

Judgment delivered by Mr. Justice Costello on 8th March 1983.

MLL

This is an application under section 27 of the Patents Act, 1964 for the extension of Letters Patent No. 30666, dated the 19th December, 1966, entitled "Anthelmintic compositions containing benzimidazole derivatives." The patent relates to veterinary medicines and in particular to two drugs known as Parbendazole and Oxibendazole used for the treatment of infections caused by parasitic worms in cattle sheep and pigs, and in the case of Oxibendazole, for the treatment of horses. The patent expired on the 19th December, 1982 but the petition was filed before that date and having heard submissions in support of it (also before the 19th December) I reserved my judgment on the matter. I am satisfied that if it is a proper case in which to exercise my discretion in favour of the petitioners that I have jurisdiction to do so notwithstanding the passing of the expiry date.

The section provides that if it appears that the patentee has been inadequately remunerated then the court may extend the term of the patent. The petitioner's evidence is that if the research and development costs of the drugs are properly apportioned it will be seen that the patentee has suffered a loss on the Irish market, and that in addition when viewed on a world-wide basis it will be seen that an over-all loss was sustained. But of course the fact that a patentee fails to make a profit from his patent is not in itself a reason for extending its life. The section provides that in deciding an extension application I must have regard to the nature and merits of the invention in relation to the public, to the profits made by the patentee as such and to all the circumstances of the case. It has long been established under similar English legislation that what a petitioner has to prove is that the invention is one of more than ordinary utility, that it has not been adequately remunerated, and that the absence of remuneration is not due to any fault on the part of the patentee (Flemings Patent, 36 R.P.C. 55, 70). It is also well established that the onus of proof is on the Petitioner to prove these matters to the courts satisfaction.

What the Petitioners say is this. The lack of remuneration of Parbendazole was partly due to the suspicion which existed between 1968 and 1974 that it was teratogenic and partly to the failure of the regulatory authorities in the United Kingdom to approve its use in lactating cattle. In the case of Oxibendazole they say that its lack of remuneration was due to the "slow realisation of the full potential of the invention" and to attendant delays in getting regulatory approval for it. To consider these submissions and to assess the merits of the invention I must briefly trace the history of the two compounds which are the subject matter of the patent.

In the year 1957 the Petitioners established an animal health department in Philadelphia to investigate veterinary pharmaceuticals for use, in particular, in the treatment of internal parasitic infections in livestock. It was known that the most common economically damaging helminth infection from which sheep, cattle, pigs and horses suffered are gastrointestinal nematodes (round worms). In the early 1960 there were three principal anthelmintic agents of which a drug called Thiabendazole was the most effective. The Petitioners began a random screening of compounds for anthelmintic activity in the course of which it was found that a certain benzimidazole compound (designated SK and F. 6695) had a significant level of anthelmintic activity. Further tests resulted in positive results and a chemical synthesis programme to investigate other benzimidazole derivatives was carried out. This programme proved successful and from it there resulted the compounds which are described in the specification of the patent in suit. Only two of the compounds described in the patent have in fact been used in veterinary medicine, Parbendazole, described in Example 1 and Oxibendazole described in Example 2 (and claimed in Claims 6 and 14 respectively). Parbendazole was first made in April, 1966 and it was then found to be about three times more active than Thiabendazole. It was immediately selected for toxicity and efficacy tests. Oxibendazole was not synthesised until August 1966. But because initial studies indicated that it was only marginally superior to Parbendazole and because development work on Parbendazole had already begun a decision was taken (and carried out which is of considerable significance for this present application) not to do any further work on this drug and to concentrate instead on developing Parbendazole for launching the market.

Applications for patents in respect of these inventions were filed in the United States of America and subsequently elsewhere throughout the world, all of which were granted. Parbendazole was sold in many countries, either through subsidiaries of the Petitioners or through distributorship agreements or licence agreements. After it had been introduced internationally the Petitioners decided to carry out further field tests on it. These were carried out in South Africa, their purpose being to determine whether any toxic effects could be observed if amounts in excess of the recommended dose were administered. Although no toxic symptoms were observed a number of instances of embryotoxicity and teratogenicity were discovered and lambs born to ewes pregnant at the time of dosing were stillborn or were born deformed. The Petitioners of course were notified of these results and they, in October 1968 in turn notified the veterinary profession and the national regulatory agencies.

Following the South African tests the Petitioners instituted a general research programme both in sheep, cattle

swine, rats and rabbits. It is unnecessary to detail the course this took but generally it can be said that after very careful study it was established that a high dose was teratogenic when administered on days 16-24 of pregnancy in sheep, but not in the case of swine or cattle. It was, however, appreciated that the procedures in the field for estimating doses are imprecise and so the Petitioners thereafter did not recommend Parbendazole for pregnant ewes in the first month of pregnancy. The results of the Petitioners research (which had been carried out in the United Kingdom, Australia, South Africa and the U.S.A.) were published in the "Cornell Veterinarian", 1974.

The results of the South African trials naturally had an effect on the attitude of the regulatory authorities to the drug. As there is no separate regulatory authority in this country for veterinary medicines the introduction of a new drug on to the Irish market depends on approval from the United Kingdom authorities. In 1967 when the medicine was ready to be marketed there was no statutory provision in the United Kingdom for the regulation of veterinary drugs but a voluntary evaluation scheme, known as the Veterinary Products Safety Precautions Scheme (the "VPSPS") was in operation. In 1971 a statutory body which issued product licences was established, known as the Veterinary Products Committee (the "VPC"). In 1967 an application for clearance for Parbendazole drench for administration to sheep was made and granted and in 1968 clearance was given for a Parbendazole drench for cattle and medicated pellets for administration to pigs. But approval was given only in respect of non-lactating cattle. As a result of the South African trials provisional clearance was withdrawn in March, 1969, but restored in June 1969. In August, 1970 full clearance for sheep and beef cattle only was granted subject to the packaging having a warning that the recommended dose should not be exceeded during pregnancy. The Petitioners tried to obtain clearance to use the drug in dairy cattle but this was refused in December, 1970 and was never obtained.

Once provisional clearance had been obtained in the United Kingdom Parbendazole was introduced into Ireland in 1968 in drench form for administration to sheep. After November, 1970 it was sold in medicated pellets for administration to pigs and later, in 1972, as medicated pig food. From 1968 it was also sold as a drench for cattle, but not, of course, for dairy cattle. Sales for the first five years were low, but rose in 1973 to £38,045 and to £86,347 in 1977. In 1978 they dropped back, due to the fact that in that year the petitioners introduced a new drug on to the Irish market called Albendazole. This largely replaced Parbendazole as an anthelmintic for cattle although sales of the medicine for sheep still continued.

I turn now to Oxibendazole. It will be recalled that the Petitioners took a deliberate decision to concentrate on the development of Parbendazole and after Oxibendazole had been synthesised in 1966 no further work was done on it, until 1972.

After the South African field trials and after the subsequent teratogenicity studies carried out on Parabendazole it was decided in November, 1972 to try to find an alternative and a project group was established to consider the possible development of Oxibendazole. By 1973 it was found that the compound was non-teratogenic in sheep and by the middle of 1975 it was found to be non-teratogenic in cattle. An application to the VPC made in the United Kingdom for use in cattle in August, 1976 granted in April 1977. An application for its use in lactating cattle was made in May, 1977 and granted in September, 1977.

Oxibendazole was not introduced on to the Irish market until 1977. Since then sales have been poor. According to Mr. Gilmore, the National Sales Manager of the Animal Health Products Division of the Petitioner's Irish subsidiary, the product was never a success for use with cattle, sheep and pigs, "mainly because it was superseded in 1978 by Albendazole".

It would seem that the Petitioners main interest in Oxibendazole as far as the Irish market is concerned is use in the treatment of horses, and they claim that for such use it has exceptional properties. But this was not discovered until very late in the day. Not until 1975 were trials of the drug on horses begun. The principal helminth infections in horses are caused by small strongylus and one of the difficulties in treating the infections which they cause arises from the fact that strongylus strains have developed which are cross-resistant to benzimidazole therapy. In 1976 initial reports of tests carried out by Dr. Drudge at the University of Kentucky showed that oxibendazole was unusual in that it was effective against benzimidazole cross-resistant strongyle infections. Between 1976 and 1979 further work was carried out which appeared to confirm this initial finding.

In the United States of America the introduction of new veterinary drugs is regulated by the Bureau of Veterinary Medicine, Food and Drug Administration (the "FDA"). In April 1977 an application was made to the FDA for approval for the use of Oxibendazole in the treatment of horses but due to no fault of the Petitioners it was not until November, 1980 that approval was obtained. This delay caused delays in the application for a licence to the VPC in the United Kingdom. Application was finally made in March, 1981 and approval obtained in October, 1981. The end result of the concatenation of events which I have briefly summarised was that it was not until very nearly the end of the life of the patent, in May of 1982, that oxibendazole was introduced on to the Irish market for administration to horses - in a paste formulation sold under the trade mark "Equitac".

Let me now look a little more closely at the reasons for the disappointing level of sales and, in particular seek to ascertain whether the Petitioners themselves must take

responsibility for the inadequacy of the remuneration they received.

Firstly, Parbendazole. I am quite prepared to accept that after the 1968 South African trials a suspicion must have arisen that Parbendazole was teratogenic and that this suspicion must have existed for some years and to some extent at least have adversely affected sales in this country and world-wide. But I am far from sure that the Petitioners can rely on this fact in support of their present application. The South African trials were carried out under their direction and they quite rightly made their results known to the profession and the regulatory authorities. However, if a patentee tests a drug, then puts it on the market and then deems it necessary or desirable to carry out further tests on it which produce seemingly unfavourable results as a result of which the patentee suffers a loss of sales until he has had an opportunity to correct the mistaken impression which his first tests had produced, the attendant losses are directly attributable to his own actions and cannot in my view be relied on to support an application under the section. I am also prepared to accept that a very obvious factor contributing to the inadequacy of the remuneration which the Petitioners obtained from Parbendazole was their inability to sell it for the treatment of dairy cattle. This arose in this country because of the failure of the VPC to license its use for this purpose. But before the Petitioners can blame the VPC for their lack of sales they must show, and it seems to me that the onus is fairly and squarely placed on them to do so, that the VPC had acted unreasonably. I do not think that the Petitioners have discharged that onus. I am entitled to assume that the VPC is a highly responsible body and the Petitioners have failed to satisfy me that it acted with excessive caution, and therefore unreasonably, in limiting the Petitioners licence in the way it did. In this connection I think I can have regard to the fact that the Petitioners had never received approval for Parbendazole from the FDA in the United States. I have been given no evidence as to why this occurred, but I think I can conclude in the absence of a satisfactory explanation that, if nothing more, it lends support to the attitude taken by the VPC to the use of the drug with lactating cattle.

There is another factor in the case which seems to me to be relevant in explaining some of the lack of sales of this product. Parbendazole did not sell well in the last three years of the life of the patent and the principal reason for this, as the Petitioners themselves accept, was their introduction on to the Irish market of an improved drug, Albendazole, which could be administered to dairy cattle. Quite clearly the fall in remuneration which the Petitioners thereby suffered cannot be relied on to support a section 27 application.

Taking all the evidence into account the Petitioners have not shown that they were not themselves responsible for the lack of remuneration of Parbendazole. This means that they have failed to make out a case under the section in relation to the sales of this drug.

I have reached similar conclusions about the Petitioners responsibility for the lack of remuneration of Oxibendazole. No development of this drug took place for a number of years after it was first synthesized. It was not until 1975 that it was found that it was non-teratogenic in cattle. No delay took place in processing the licence application on the part of the VPC. It was not until 1977 that it was first introduced on to the Irish market for use in cattle. Sales of the drug have been extremely small due to the introduction to the market of Albendazole. So, on the evidence it would appear that major contributing factors to the lack of remuneration was due to (a) the Petitioners own decision not to develop it until late in the life of the patent and (b) the fact that it was superseded by a drug which the Petitioners themselves introduced.

I will deal later with the merits of Oxibendazole in the treatment of horses. Let me assume that it has exceptional qualities and that had the tests which were carried out between 1975 and 1979 been carried out sooner its potential would have been recognised at an earlier date and greater remuneration would have been earned by the patentee. But the decision to defer development was the Petitioners and the failure to realise the potential of the drug was also the Petitioners. I do not think that a patentee who carries out tests late in the life of the patent which establish the inventions unexpected qualities can successfully rely on this fact in support of his submission that he was inadequately remunerated.

What I have said already is sufficient to dispose of the claim in the Petition. But because the Petitioners might like my views on all the aspects of the case I think I should express my opinion on the merits of the invention I am considering.

The onus is on the Petitioners to prove that the invention is one of more than ordinary merit or utility - that, in fact, some considerable benefit has been given to the public. Professor Cunningham, who is head of the Department of Veterinary Pathology and Microbiology at University College Dublin, has shown that after the discovery of Thiabendazole (which had become available in the early 1960s) research followed for more effective anthelmintics by applying chemical modifications to the benzimidazole molecule and that as a result Parabendazole was produced, the first of a new family of anthelmintics in which a new side-chain was introduced at the 5-position of the benzimidazole ring. His view (which, of course I entirely accept) is that Parabendazole has a wide spectrum of activity and is effective against the effects of various species of helminths; that the drug is widely used in this country in treating helminth infections in sheep, pigs and beef cattle and that it "enjoys a high reputation for efficacy and safety."

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But the practical utility of the drug has been diminished by the fact that it has not been used in the treatment of dair cattle. As I have already explained the Petitioners have not established to my satisfaction that the limitations placed on its use by the VPC were unreasonable, and I am not satisfied that they have been able to discharge the onus on them by showing the exceptional nature of this particular drug.

It is urged that I should regard the drug as exceptional because of the impetus to research and development of other anthelmintics given by the publication and use of Parabendazole. But I do not consider that this is a relevant consideration. I must try to assess the actual utility to the Irish public of the patent in suit, and in doing so I do not think it is relevant to consider whether or not it has been used by others to produce new inventions or stimulate further research. If the Petitioners' submission was correct it would mean that an indolent patentee whose inactivity in marketing his invention resulted in little or no public benefit could claim an extension of his patent merely because it spurred a more energetic rival to a new discovery - surely a development not contemplated by the legislature.

In relation to the exceptional merits of Oxibendazole the Petitioners case is based almost exclusively on the claims made on its behalf for the treatment of horses. Tests on horses only took place in recent years and it was not until 1976 that Dr. Drudge of the University of Kentucky found that the drug had an important characteristic, - it appeared to be effective against cross-resistant strongyle infections. Further larger studies carried out by him confirmed this view, and these were published in the 1981 volume of "Modern Veterinary Practise." Professor Herd of Ohio University also carried out trials with Oxibendazole on horses and he concluded that they indicated that "Oxibendazole is effective against resistant small strongyles."

I do not for a moment doubt the outstanding professional qualifications of those who have carried out research on Oxibendazole; my concern arises from the limited time during which Oxibendazole had been used in the treatment of horses. Will the drug live up to its promise? Research was carried out in Sydney on the treatment of horses with the drug, whose results were published in the 1981 "Australian Veterinary Journal." The authors pointed out that it was to be expected that new BZ anthelmintics would show a reduced efficiency with frequent or continual use and that they predicted that the efficacy of oxibendazole, if widely used (it was not then commercially available in Australia) would decrease over time. I take Professor Herd's point in answer to this prognosis and I accept that it is not possible to predict how quickly, if at all, the efficacy of a new drug will decrease due to its constant use. But the onus is on the Petitioners to establish that the drug possesses this outstanding characteristic and I do not think that from the limited number of tests that have

taken place in the limited span of time during which trials have occurred that I can conclude the matter in their favour.

to show

For the reasons I have given I must decide that the Petitioners have failed to discharge the onus which is on them that this is a case in which the Court's discretion should be exercised in their favour.

Approved
JL