COMPANY SECRET

R 50796 REVIEW 9 JUNE 1976

Personnel attending:		
	Miss J Proctor,	Jealott's Hill
	Dr C B Barlow	" "
	Dr B Cavell	" "
	Dr B Johnen	" "
	Dr A H Todd	Pharmaceuticals Div
	Mr W M Riding	" "
	Dr M Rose	CTL
	Dr P Slade	Fernhurst
	Mr R D Wiseman	"
	Mr J Page	UKDD, Farnham
	Mr G R Lee	Jealott's Hill
	Dr D M Foulkes	" "

The objective of the meeting was to review progress of all aspects of the work relating to the production of a formulation of paraquat containing an emetic agent, important consideration being given to the validity of this concept. The following areas were covered.

1 Formulation

It is now clear that it will be possible to formulate R 50796 in Gramoxone yes S Gramoxone UK and Gramoxone Export. Stability information to date indicates no physical or chemical problems. The material which has been used in tests so far has been of pure pharmaceutical grade and consideration will be given to checking the stability produced from a formulation made up from R 50796 of 90% purity. In addition in order to give satisfactory patent coverage, formulations containing the emetic agent at much higher concentrations would be examined from the stability aspect.

2 Metabolism and Environmental work

Radiolabelled R 50796 will be available by the end of July, it is planned that this material will be used to examine the fate of the compound in plants, water and soil. It is not possible at this stage to accurately predict the likely fate of this compound in the foregoing environments; it is clearly necessary to obtain this information as soon as possible. A method for the analysis of the compound will be available by August; it is intended that residue samples be taken from current and forthcoming trials which in combination with the information from metabolism studies would give an indication as to the environmental aspects of this compound. A combination of a reasonable amount of degradation, coupled with the extremely low rate of application during spraying may indicate that it will not be necessary to embark on extensive cattle palatability or animal transfer studies. At the present time it is not intended to embark upon soil leaching studies, these can however be put on at short notice if it is felt necessary to do so.

3 Process Chemistry

Pharmaceuticals Division are currently investigating the process development required to produce tonnage quantities of R 50796, at present a four stage process is employed which it is felt is capable of improvement, however, it is important to emphasise that, at this stage, little experience of production of this compound has been obtained. The present estimated price per kilogram will be

£130·00, this figure includes charge for process development. It is estimated by 16 July between 600 and 1000 grams of material will be available, a further 1 kilogram will be produced by the end of July, followed by a further 5 kilograms by the end of August. In order to examine the stability aspect referred to above and in addition to show that a 90% pure material will also be capable of producing emesis material of 90% purity will be made available as soon as possible for Formulation Section and for CTL. It is envisaged that material for trial work and of course for future production of an emetic formulation will be produced at Mond Division, and for this reason a meeting will be held between members of Mond Division, Pharmaceuticals and PPD at an early opportunity to dicuss technical aspects of the handling and formulation of R 50796.

The present requirements for the compound estimated by PPD are 0·9 tons by the 1 January 1977, to be followed by two further batches of a similar size at intervals during 1977. These estimates will be put to critical review during the week beginning 14 July and a formal request will be put to Pharmaceuticals Division as soon as approval is obtained within PPD. In order to purchase the necessary starting materials to meet our UK requirements of 2·7 tons by 1977, expenditure on the part of Pharmaceuticals Division of £40,000 will be required; clearly PPD will be required to underwrite this expenditure in case, for any reason, the project ceases to be valid.

4 Patents

Dr Barlow outlined our present current patent strategy, which is both comprehensive and intensive, covering as many territories in the world as possible, both for R50796 itself and for compounds in other chemical classes, which could be deemed to have emetic potential. Dr Foulkes agreed to discuss with Dr Barlow at an early opportunity the extent of our patent programme so that the necessary work could be requested through RATLS to CTL.

5 Herbicidal Activity

Mr G R Lee outlined the results from metre box trials which have been undertaken this spring, all of which clearly demonstrate that the presence of the emetic agent has no effect at all on the efficacy of paraquat.

6 Biological Efficacy

Dr Rose of CTL gave an account of the work that has been done in rats, dogs and monkeys to demonstrate that the presence of the emetic agent is capable of reducing the fatalities likely to ensue from swallowing paraquat solutions. The evidence to date, which has yet to be fully completed, is extremely encouraging, in that groups of dogs and monkeys, when receiving fatal quantities of paraquat in the presence of the emetic agent, were seen to survive. Information from these present studies will be written up as soon as possible, in order that they may be submitted to Patents Section for application for USA and Pan American Convention coverage. The information from the rat studies, a species which does not vomit, indicated that there is possibly an effect of reducing gastric emptying produced by R50796· Dr Todd of Pharmaceuticals Division undertook to search for information within their files to substantiate this possible effect. It was also agreed that CTL should do further work to qualify these initial findings.

7 Registration

It is planned that a letter will be sent to PSPS to be received in time for their meeting to be held on 22 June, outlining the emetic concept. It is hoped that the PSPS will operate a quick review of this data, thereby giving us trials clearance for the early autumn. This trials clearance will permit us to study in greater depth the possible hazard, in terms of side effects of nausea, which could ensue from the large scale spraying of an emetic formulation. A proposed protocol for such studies has already been produced, but in view of the limitations on supply and timing, Dr Foulkes agreed to discuss with Dr Howard and Mr Page a possible modification of the protocol to employ a smaller amount of R 50796 than previously envisaged, although on theoretical grounds there is no reason to believe that operators will suffer from any side effects from the use of this compound, it is clearly felt important that this aspect of formulation be examined to our full satisfaction. This information will form part of the second phase of our registration strategy which is application for a Provisional Commercial Clearance to be submitted at the end of October this year, this submission will include the toxicology information, environmental aspects, formulation stability, herbicidal effects together with information on residues and possible taint. The latter is being examined at Chipping Camden using material from potato trials.

In summary it was clear from the review that all aspects of a proposed emetic containing formulation are extremely favourable

D. M. Foulkes

Copy to:

Those present at meeting
Mr A W Waitt, Fernhurst
Mr T Frears "
Dr A Calderbank
Dr T E Tomlinson
Dr J T Braunholtz