From

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CONFIDENTIAL

Your ref	Our ref	Direct line	Tel ext	Date
	LLS438/JJB	0625 512878	2878	6 November 1990

RE: HUMAN DATA WITH PARAQUAT FORMULATIONS CONTAINING PP796.

Thank you for your memo of the 5 September 1990 discussing several issues associated with the concentration of emetic in formulations of paraquat. It is clear from the data you presented that there was probably some misunderstanding or confusion in the way the case for the inclusion rate of 796 at 0.05% was arrived at. However, I am sure you will appreciate that in attempting to reconsider the thinking and knowledge in 1976 when this decision was taken is extremely difficult. If my memory serves me correctly it was not even partly appreciated that the time to emesis in man that is required to prevent the absorption of paraquat is less than 30 minutes. In the mid 1970's we were still influenced by the data in rat which has an entirely different plasma paraquat profile to that of man.

Another important concern was the generation of prolonged, severe vomiting which would occur in patients who had consumed very large quantities of Gramoxone containing the emetic. This concern has been experienced in Japan. Several Japanese Doctors have expressed serious reservations at the difficulty of treating patients who have consumed large quantities of Gramoxone, due to prolonged and severe vomiting. I do not agree with their viewpoint and we have resisted this with the Regulatory Authorities. However, in a final analysis it is Regulatory Authorities that decide the level of inclusion that is acceptable.

As you are aware, I, and others at CTL, came to the view some years ago that it would be useful to increase the concentration of emetic in paraquat formulations. This view was arrived at on the basis on our experience of human poisoning and some experimental data generated in dogs. The dog data was much less comprehensive than the data you have subsequently obtained.

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However, it appears that there is no disagreement between us that an increase in emetic of 3-5 fold ought to be evaluated. I would emphasise that I cannot advise the Business that such an increase would certainly reduce the number of human fatalities. It is my experience that extrapolating data in experimental animals to man is not particularly easy with paraquat. However, I believe there is an opportunity to combine the increase in emetic concentration with the inclusion of Trisilicate to reduce the toxicity of paraquat formulations. Both Stuart and myself are fully suportive of seeing such a formulation evaluated in a few well controlled and well understood markets so as to establish whether there is an opportunity to reducing paraquat fatalities resulting from the intentional ingestion of the paraquat formulations.

In conclusion I do not intend to pursue any further the reasons for the inclusion of PP796 at 0.05% as decided in the early part of 1976. Rather, I wish to concentrate our efforts in agreeing a strategy with the Business that will prompt us to evaluate formulations of paraquat that are intrinsically less toxic and contain increased concentrations of emetic.

Lewis

DR L L SMITH