

From: Andy Cook  
COOK AR@A1@FHVAXC

Date: 25-Feb-1995 15:34

TO: Bob Scott - CTL  
CC: Jon Heylings

( SCOTT RC@A1@APVXC1 )  
( HEYLINGS JR @ A1 @ APVXC1 )

Subject: RE: PQ/EU/Emetic

Bob,

Thanks for your note.

Re. the emetic, it would seem entirely appropriate to use CTL/T/2471 in answering part of the question from Germany.

However, I propose that we do not prepare an EU Tier I summary of this study report. I propose to address the issue of the emetic in an Appendix to the paraquat Tier II document on toxicology (Document M-II, Section 3). Since all of the studies to be submitted on the emetic are 'supplementary' in that they are not strictly required for EU review/approval of the active substance I believe that we can submit without corresponding Tier I summaries of the individual studies. This approach obviously suits us in that many of the studies are research-orientated and do not follow specific guidelines. However please bear in mind that there is no guarantee of success and we may find ourselves compelled to produce Tier I summaries at a later date (post-submission). Given the commercial importance of PP796 I will offer (at the time of submission) to supply Tier I summaries of the key PP796 studies on request.

I have now completed a first draft of the document to be submitted to the EU on the emetic (minus the contributions from yourself and Martin on the 'exam questions'). I attach a copy for urgent review by yourself and Jon (Heylings). ALL comments gratefully received, in particular whether or not I have included the most appropriate references.

Thanks.

ANDY

P.S. I do not require a Tier I summary for the rabbit plasma modelling report.

From: **Jon Heylings  
HEYLING JR**

Date: 27-Feb-1995 18:03

TO: **Bob Scott - CTL**

( SCOTT RC )

Subject: **Emetic document**

Bob,

As I am sure you are aware I will have to vent my concern over the validity of the Rose (1977) conclusions which are cited in Andy's report.

I am surprised that he is unaware of the issue. Martin Wilks certainly is aware of the issue around the human emetic data and it may be time to re-open the case and get a thorough independent review.

Jon

~~CONFIDENTIAL~~

From: Jon Heylings  
HEYLING JR

Date: 01-Mar-1995 10:40

TO: Andy Cook  
CC: Bob Scott - CTL  
CC: Martin Wilks

( COOK AR@A1@FHVAXC )  
( SCOTT RC )  
( WILKS MF @ A1 @ FHVAXC )

Subject: PQ/EU/Emetic review

Andy,

Following your request for me to give comments on the EU/Emetic document and my discussions with yourself and Martin Wilks my response is as follows:

Section 1 is fine. It is along the lines of Peter Slade's paper (EDC 729).

Section 2. Page 2, line 8 cites human as being "particularly sensitive" to the emetic compared to the pig, dog and monkey. I do not agree. I carried out an extensive review of the human volunteer data at Pharmaceuticals in 1990 (PH20992, Bayliss). In the first trial with normal healthy volunteers there was no emesis at the 5 doses below 0.06mg/kg, yet CTL/R/390R (Rose, 1977) quotes an emetic response of 11% at 0.03mg/kg. Only 2 out of 12 subjects actually vomited in the whole study. The one subject who was given the top dose of 0.1mg/kg did not even fulfil the suggested criteria for the emetic in paraquat of "emesis within 1 hour". In fact, emesis occurred at 2 hours.

Overall, the 0.1mg/kg dose is a threshold response in man - not an effective dose. This is consistent with the inclusion of the emetic in PQ products having had some discernable improvement in survival, but clearly not as good as had been anticipated back in 1977.

Given the fact that we have human data and sound animal data with the emetic and that the emetic response curves are steep and parallel across species, basic pharmacological principles tell us that a 3-5 fold increase in emetic concentration will markedly improve the efficiency of emesis in man. By extrapolation this would suggest a 5 fold improvement in oral toxicity.

I do agree with the animal data presented in the document. Indeed, dog studies conducted by my research group with Gramoxone containing different levels of emetic (as I presented to the TRC in 1991) are in full agreement with the Brammer and Robinson data. Here we demonstrated that dogs could tolerate 5 lethal doses of Gramoxone by increasing the emetic from 0.5g/l to 2.4g/l.

(Magnoxone contains 1.5g/l emetic plus other safening ingredients balanced out to trade off the commercial penalty of a 2.4g/l emeticized Gramoxone).

In view of this background information, the rationale for including the emetic at a concentration of 0.5g/l in Gramoxone based on "greater sensitivity in humans" is unsubstantiated. Thus, the second paragraph in Section 4.1 needs to be changed including the "within one hour" statement.

I fully understand the sensitivity of this whole issue and regard this as highly confidential within Zeneca. However, as a matter of scientific integrity, having been asked to comment on the document, I feel I should share these views with you.

Regards,

Jon

From: Bob Scott - CTL  
SCOTT RC

Date: 01-Mar-1995 14:41

TO: Andy Cook  
CC: Jon Heylings  
CC: Martin Wilks

( COOK AR@A1@FHVAXC )  
( HEYLINGS JR )  
( WILKS MF @ A1 @ FHVAXC )

Subject: PQ/EU/Emetic

Andy,

Thanks for the opportunity to comment on Review of the PP796 data.  
I have made hand-written comments on your document and these will be Fax'd to you.

I believe you have presented the facts as they appear in the relevant reports accurately and you have not altered the conclusions of these reports.

I am sure you realise that some of these reports are in the vintage category and might not stand firm under a thorough 1995 QA-type interogation.

You will see I have attempted to 'soften' some of your statements re PP796 so we do not appear to be too up-beat about its merits and effect.

I am sure Jon and Martin Wilks will send you more comments.

Bob.