From: Heylings Jon GBAP
Sent: 16 August 2006 16:32
To: Botham Phil GBAP
Subject: FW: Final Inteon US presentation.PPT

Phil

Barry may have forwarded this note to you. I wanted to record the facts around the EPA presentation that annotated the old Gramoxone in the IRI studies as incorrectly having 0.5g/L emetic.

I felt rather uncomfortable at the end of yesterdays PLCM when you and Tim were discussing the EPA issue. Indeed, I felt that my colleagues will think that I was party to the EPA documentation and slides used.

The paraquat emetic issue is a long and complex story. I would be happy to take you through the facts (historic and current) as I see them, if this would help.

Jon

From: Heylings Jon GBAP
Sent: 04 August 2006 11:31
To: Elliott Barry GBAP
Subject: FW: Final Inteon US presentation.PPT

Barry

Just for the record…..

Mike sent me the US slides (see below) **after** the presentation to EPA. I was not asked to comment on the documentation used at the meeting or the content of the slides used. In fact, there are many slides in this set I had not seen before and I would not have used some of them in their present form if I had been consulted. As you know, I have built the story around INTEON kinetics using our own emeticised Gramoxone data and the fact that systemic exposure is reduced at multiples of oral doses of INTEON. Fitting this to the IRI curve without the detail of the pharmacology of the emetic was an extrapolation too far.

In addition. I was not party to which reports (apart from ones generated by my group) that were actually submitted to EPA, including the 1980s IRI studies. It is easy with the benefit of hindsight to see where the error could have been avoided if a more thorough review of the documentation and slides had been undertaken. However, we cannot now change what happened.

It does surprise me that anyone reading the IRI reports that were submitted would not have noticed the 4 places stating that non-emeticised Gramoxone was used including the C of A. that is in the reports. I can see, however, that the title of the report "Gramoxone…" is misleading and its summary does not mention the composition being non-emeticised. If a full overview of the studies including the purpose of the project and the interpretation of the kinetics and toxicity had been documented at the time by Bob Scott et al who managed these studies we would have been more aware of the context of these studies. Without this documentation we cannot confirm the purpose of the IRI studies and how they link to the commercial emeticised product on sale at the time. There may even be another IRI study we have not located on the commercial emeticised Gramoxone.

Scientifically, I still stand by the fact that the 0.5g/L emetic (in a minimally toxic dose of PQ) is sub-threshold for emesis in the dog, as evidenced by our Biochem Tox studies, Tox Section studies and Pharms studies (the latter on emetic alone). These old studies were quite consistent and inferred that 0.5g/L would be ineffective at reducing oral toxicity at a minimally toxic PQ dose in dogs (circa. 0.02mg/kg). All these studies point to an effective emetic dose being at least 0.1mg/kg. This requires about a 5 times higher amount of emetic in the formulation to cause emesis within 30 min. I was (and still am) a strong advocate that a 5 fold increase in emetic in the product would provide a safer option in its own right, albeit not at the level of safening you could get with the full INTEON package. This was tabled at the TRC in 1990, but the small improvement in tox in the dog was not judged as good as Magnoxone which had gel, purgative and 3X level of emetic and gave a far superior performance in dogs that 5X emetis alone.

Based on the evidence of emetic dose, if there had there been a control of the commercial emeticised product at 0.5g/L in the IRI series of studies then a similar picture of toxicity and kinetics to the non-emeticised versions may well have been observed.

To take this forward in a constructive way, I believe we have a good argument that the Gramoxone UK containing emetic at 0.5g/L gives plasma PQ values similar to unemeticised product in the 5-10 mg/kg PQ dose region. Furthermore, even when the emetic is increased 5 times to cause very early emesis (as fast as 3min) then dogs cannot tolerate 48mg/kg and this maneouvre could only offer limited protection. The full INTEON package of increased emetic, gel and purgative is a step change better. The uncertainly remains of how big this step change from 0.5g/L emetic to 1.5g/L emetic plus alginate and purgative actually is.

I am sure this debate over the role of the emetic will continue for some time. There are a lot of unanswered questions around its effectiveness in animals and man but what we do know is that the 0.05g/L addition to Gramoxone in the 1970s did not have the predicted impact on human survival.

I just wanted to record my thoughts on this.

Jon

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From: Clapp Mike GBAP
Sent: 27 April 2006 16:09
To: Heylings Jon GBAP
Subject: FW: Final Inteon US presentation.PPT

Jon,
US presentation for information.
Mike

From: Wells Jerry USGR
Sent: 26 April 2006 18:56
To: Clapp Mike GBAP
Subject: FW: Final Inteon US presentation.PPT

Mike,
Here is the presentation as shown at EPA.
Kind regards,
Jerry

From: Wells Jerry USGR
Sent: Tuesday, April 25, 2006 6:12 PM
To: Elliott Barry GBAP; Shaunak Richa CHBS; Wheals Ian CHBS
Cc: Abbott John USGR
Subject: Final Inteon US presentation.PPT

Final Inteon US presentation.P...

Attached is the presentation made to USEPA yesterday.
The meeting went well I thought. The follow up requested is a written report of the info covered in the slides with new data presented.
We expect no regulatory action on Inteon while this is being prepared/submitted.
Give me a call if you would like more details on the meeting.
Kind regards,

Jerry