Message

From: Heylings Jon GBAP [/O=NOVARTIS-AG/OU=GBRGCP01P/CN=RECIPIENTS/CN=802690]
Sent: 7/29/2004 1:22:59 PM
To: Clapp Mike GBAP [/O=NOVARTIS-AG/OU=GBRGCP01P/CN=RECIPIENTS/CN=802648]
Subject: RE: Paraquat : new Tox. Committee requirements

Mike

It seems odd that they want more detail than the information we have already sent them.

With regard to may patch I have looked back into my France file. I have a letter report to Lewis, Geoff and Saba that contains the data and its interpretation, dated Oct 26th 1990 - I am sure that I have already sent you this a while ago. It was also deposited in the PQ Correspondance file under reference JRH076/LCM. At the time the considered opinion of the PSAC was not to formally report this research, but to use it during Prof Rico's visit to CTL the following Frebruary (1991). There had been an issue about the high number of deaths in France before we introduced R Bix and we wanted to reassure them that their formulation (with high emetic and a thickening agent) had low oral toxicity.

The actual research study numbers and dates (that also cover Magnoxone and several other formulations) were:

XD1328 Study E44 Oct 2 1990 AV8700169 (R Bix) 32mg/kg PQ ion
XD1328 Study E45 Oct 9 1990 AV8700169 (R Bix) 64mg/kg PQ ion

With regard to the high emetic Gramoxone we showed a 5X safening by increasing the emetic alone. This research used the same colonies of animals and research study number as the above earlier that year, The study details were as follows:

XD1328 Study E32 Feb 13 1990 Gramoxone plus equiv 2.4g/l emetic 16mg/kg PQ ion
XD1328 Study E33 Feb 21 1990 Gramoxone plus equiv 2.4g/l emetic 32mg/kg PQ ion
XD1328 Study E34 Mar 20 1990 Gramoxone plus equiv 2.4g/l emetic 48mg/kg PQ ion

Lewis and I presented this to John Finney and his TRC team back in 1990. This research was reported in a Jealotts Hill Company Confidential (Category C) TRC report: Swaine H TMY387C, Feb 1990, titled Safer Paraquat Formulations. I guess with the right authority this could be loaned to you but it cannot be photocopied. The report also debates the case for increasing emetic alone or in combination with an acid triggered gel. The decision from that review was to develop a new global PQ formulation with high emetic, gel and purgative - Magnoxone.

Jon

Jon R. Heylings Ph.D.
Head, Absorption & In Vitro Toxicology
Research and Investigative Toxicology
Syngenta CTL. UK Tel:44(0)1625 514550

-----Original Message-----
From: Clapp Mike GBAP
Sent: 28 July 2004 17:50
To: Heylings Jon GBAP; Woollen Bruce GBAP; Bateman Berni GBAP
Cc: Swain Cindy GBAP
Subject: RE: Paraquat : new Tox. Committee requirements

Bruce, Jon,
I think this has already been sent to you. But we need to get a final draft response out by end of next week.

Bruce - please could you have a go at comparative table - however the best way in my opinion would be to provide analysis of using both methods on the same sample. Could you double check to see if Mike Farnworth (Cindy could you help) did this from memory he did! Also Bruce have you done any comparisons when you were validating the change in methods? If not is there any chance of creating a standard curve using both methods or is it now not possible to do the radioimmunoassy? Anything in previuos posters or in validation of analytical methods for Schenker group we could use?

Jon - still struggling re dog study numbers - Is there any chance we could pull out a report of effect of increasing emetic or effect of thickening formulation - which were the two attributes relevant to the change already made in France. Is there a summary letter which was produced for Geof/Lewis in the past?

Berni,
Please could you get Jon, Bruce and I together for I hour prefereable on Friday or very early next week. If possible I would also like to involve John Doe and John Bembridge (by teleconference).
Thanks very much. Mike

-----Original Message-----
From: Bembridge John GBGU
Sent: 21 July 2004 18:30
To: Clapp Mike GBAP
Cc: Heylings Jon GBAP; Woollen Bruce GBAP
Subject: FW: Paraquat : new Tox. Committee requirements

Mike

As promised please find attached below the comments from Francois Massenot as my earlier message seems not to have reached you. The comments are within the Word document. To give us enough time to meet the deadline of the 15th of August we really need to get a draft by early August (sorry).

Best regards

John Bembridge
Regulatory Manager, EAME Regulatory Affairs
Syngenta, European Regional Centre
Priestley Road, Surrey Research Park
Guildford, Surrey, GU2 7YH
Tel: +44 (0)1483 260044
Mobile: +44 (0)7979 328678
Fax: +44(0)1483 260019

-----Original Message-----
From: Clapp Mike GBAP
Sent: 09 June 2004 09:16
To: Bembridge John GBGU
Cc: Heylings Jon GBAP; Woollen Bruce GBAP
Subject: RE: Paraquat : new Tox. Committee requirements

John,

Rather than tackle twice I have now drafted a response for us to debate. The critical point is how to respond to question 3 which is essential the research work we did on magnoxone and othere formulations at that time. I am assuming we would not wish to share all this work with Marzin, since we would have to submit research review reports and confidential company documents and explain why it nevber go to market. Hence a brief response suggested.
Also my sense is that we need to take care in phrasing responses so that we do not leave ourselves immediately open to additional questions. Clearly we wish to concentrate on the results of any new studies.
Fairly hectic and in meetings most of today but suggest we discuss tomorrow - I am free after 10am - we can then agree process for moving this forward - hence just copied to you at this time.
Regards, Mike.
<< File: Draft Response to CET Questions 19th May 2004.doc >>
Bruce, Jon - please let me have aany comments on the draft - Thanks, Mike

-----Original Message-----
From: Bembridge John GBGU
Sent: 04 June 2004 10:44
To: Clapp Mike GBAP
Subject: RE: Paraquat : new Tox. Committee requirements

Mike

How is our assessment of the scale of these requirements going? Last time we spoke you were awaiting feedback from some of your colleagues.

Best regards

John Bembridge
Regulatory Manager, EAME Regulatory Affairs
Syngenta, European Regional Centre
Priestley Road, Surrey Research Park
Guildford, Surrey, GU2 7YH
Tel: +44 (0)1483 260044
Mobile: +44 (0)7979 328678
Fax: +44(0)1483 260019

-----Original Message-----
From: Bembridge John GBGU
Sent: 20 May 2004 09:34
To: Clapp Mike GBAP
Cc: Wheals Ian CHBS
Subject: FW: Paraquat : new Tox. Committee requirements

Mike

Could you please give me a first feedback on how difficult or easy it is to provide the information required.

Thanks

John Bembridge
Regulatory Manager, EAME Regulatory Affairs
Syngenta, European Regional Centre
Priestley Road, Surrey Research Park
Guildford, Surrey, GU2 7YH
Tel: +44 (0)1483 260044
Mobile: +44 (0)7979 328678
Fax: +44(0)1483 260019

-----Original Message-----
From: Massenot Francois FRSC
Sent: 19 May 2004 17:57
To: Castle Diane GBGU; Bembridge John GBGU; Wheals Ian CHBS; Clapp Mike GBAP; Wilks Martin CHBS; Campbell Clive CHBS
Cc: Tardit Denis FRSC; Berengier Jean FRSC; Mucchielli Robert FRSC; Guggiari Fabienne FRSC; Verrier Catherine FRSC
Subject: Paraquat : new Tox. Committee requirements

On 14th of April, the Tox. Committee reviewed (once more) paraquat. On the agenda, it was mentionned : "*Update on Risk Management*".

They took the occasion to discuss the complementary informations required by MARZIN on the new AWT formulation. He probably had chance to study the reports on the toxicokinetic I sent him on the 7th of April.

We received today a letter from the Tox. Committee requiring the following informations (within 3 months) :

1. Validated data concerning anlysis methods (méthodes de dosage)
2. Detailed compositions of the different formulations
3. Original reports of the 2 first studies
4. Histological examination of all the sampled organes
5. A documented discussion on the possible role of several administration dose on the adosrption in the same animal

6. A comparison between the 2 analytical methods used.

Point 2 (detailed composition of the formulations) were already sent in november 2003.

Point 3 : Marzin probably wants to have the original reports of the following studies : CTL XD1236 and CTL XD1238

Please, could you let me know when I could receive all these informations (dead line : 14th of August 2004) ?

Thank you in advance,

Best Regards,

François