Message

From: Jon Heylings [redacted]
Sent: 5/2/2019 3:36:29 PM
To: Travis Kim GBJH [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1528a9bee5884668b9ecf5910b6709f0-Travis Kim]
CC: Lewis Dick GBJH [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f4166edc367442acae4d5e7c1cd8cc49-Lewis Richa]; Botham Phil GBJH [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=675e0b3a54374a76b913a2fb682de1b2-Botham Phil]; French Dave CHBS [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1cbceced6ad94b52a994eea61b019eb7-French Davi]; McFarland Janis USGR [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a33943217ce44d2eb4ff015cd4b0b9bc-McFarland J]; Cook Andy GBJH [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=b012593ccd764559b2f9986da61a2e8f-Cook Andy A]
Subject: Re: New analysis of PP796 emetic dose-response in man

Dear Kim,
Thanks for the clarification that the data point on your best-fit dose-response curve for 2mg PP796 is from your new analysis and not directly from the Rose report. I concede that one. However, I still have an issue with your 3/19 value and the way it has been derived by combining data from patients with particular diseases (many of whom received multiple doses of 2mg) with data from normal volunteers. Surely, the focus for a reliable pharmacological effect of 2mg PP796 should be restricted to the controlled trials in normal fit volunteers (your Trials labelled A, B and C)? Trial A, in particular, was a full dose response in human volunteers with the largest group size receiving the 2mg dose. None of the volunteers vomited at any time at this dose. When you add in the other two volunteer trials (B and C), there was no vomiting in the first 30 min after the 2mg dose in these trials either. In fact, there was only one incidence of emesis in the 10 volunteers in Trials B and C and this was at 45min.

Your value of 3/19 only becomes apparent when you add in various incidences of vomiting from some of the disease trials evaluating the benefit of PP796. You have to pull in lots of patients and lots of dosings before you end up with a total of 3 incidences of vomiting at 2mg PP796. In fact, there was no vomiting in several of the trials where the 2mg dose was given multiple times per day. I am not saying your 3/19 is fabricated like the Rose 4/37 for the 2mg dose, but it is has been derived by combining any vomiting in trials E, J, B, C and D, and even incorporating vomiting well after the 30 min that eventually became a critical aspect of the FAO specification. I do note that you state "vomiting at any time" in the notes for your curve fit (Rose did not), but time to emesis is so critical with respect to survival following paraquat poisoning, hence the 30 min stipulation for an effective emetic in the FAO spec. This is why I believe you your best-fit-curve is misleading in relation to the effectiveness of the emetic in the regulatory context.

I am sure we could argue this one until the cows come home, Kim. However, at the end of the day it will be for the Regulators to make the call on this when they review the evidence for the effectiveness of the emetic in man and how the inclusion rate of 0.5g/L level PP796 in Gramoxone was arrived at back in 1977, and subsequently registered at this inclusion level by ICI Agrochemicals.

Speak to you tomorrow.

Regards
Jon

From: Travis Kim GBJH <kim.travis@syngenta.com>
Sent: 02 May 2019 11:44:11
To: Jon Heylings
Cc: Lewis Dick GBJH; Botham Phil GBJH; French Dave CHBS; McFarland Janis USGR; Cook Andy GBJH
Subject: RE: New analysis of PP796 emetic dose-response in man

Dear Jon,

I don't wish to make a complete response to your email, because we are already due to speak tomorrow. However, I just want to address one very specific point you raised about the new dose response analysis to clear up a misunderstanding and to give you time to look into it before we speak.

As a part of the human dose response data, you refer to the "4/37" vomiting response number used by Rose, and suggest that this is one of the points on the graph in the new analysis. You also suggest that I have omitted the 0/2 response from a volunteer trial in Bayliss (1973). In this new analysis I went back to the original source of the full data, ie Bayliss (1973) and did a fresh analysis, so I did not use any data from Rose (1976). The datapoints on the graph are all shown in the table that precedes the graph, and in that table each datapoint is cross-referenced to the individual clinical trials described in the first table in the document. I did this in order to be as transparent as possible about where every data point comes from. The datapoint you refer to is actually 3/19, and the table shows that this is a combination of data from trials labelled B, C, D, E & J. Consulting the first table, you will find that the vomiting responses in these five trials were for trial B 1/8, for trial C 0/2 (the datapoint you said was missing), for trial D 1/4, for trial E 0/1 & 1/1, and for trial J 0/3 – if you add these together you get 3/19, which is the point on the graph. So I have not used Rose's 4/37 value and I have not omitted the trial with the 0/2 result.

Regards,

Kim

From: Jon Heylings [redacted]
Sent: 01 May 2019 16:35
To: Travis Kim GBJH <kim.travis@syngenta.com>
Cc: Lewis Dick GBJH <dick.lewis@syngenta.com>; Botham Phil GBJH <phil.botham@syngenta.com>; French Dave CHBS <dave.french@syngenta.com>; McFarland Janis USGR <janis.mcfarland@syngenta.com>; Cook Andy GBJH <Andy.Cook@SYNGENTA.COM>
Subject: RE: New analysis of PP796 emetic dose-response in man
Importance: High

Dear Kim,

Dave French asked me to review your "New Analysis" report on the clinical data on the emetic ahead of our telecon on Friday. Sorry this is going to be a lengthy note. Firstly, I am pleased that you agree with me that the human data on PP796 is too weak to draw any conclusions on what is an effective dose of emetic in man or to derive an ED50 value, even if you include the disease trials and expand the time to emesis to 2 hours (ignoring the FAO Spec) and if you mix and match the volunteer trials with the disease trials. As with Mike Rose's fabricated dose response curve, the sigmoidal curve you have presented is pretty meaningless scientifically, having 95% confidence limits that are so wide and with so many uncertainties. However, to the uninformed, the curve in your report looks pharmacologically pleasing to the eye with its sigmoidal shape and has a similar psychological impact to the curve constructed by Mike Rose back in 1976. Once more I see this as a deliberate attempt by Syngenta to convince anyone reading your report that there is a plausible relationship between dose of emetic in man and % responding by vomiting. The various caveats that the data are scientifically pretty meaningless are in your text but it is the visual impact factor of your best-fit dose-response curve for vomiting that is almost as misleading as Mike Rose's fake sigmoidal plot. This is a very disappointing approach you have taken Kim and obviously ratified by Dick Lewis, as reviewer of the biological interpretations. I can, however, understand the pressure that Syngenta is under to try to defend such a weak position you have on the effective dose of the emetic in man.

Data Fabrication in the Rose Report CTL/R/390 (R)

As we both know, the single individual who vomited at the 8 mg dose took 2 hours to do so (not within the 60 min Rose criteria or the 30 min FAO requirement). If that single person had not vomited, your own best-fit dose response curve and the Rose curves would look pretty poor without that 1/1 (100%) data point on them! Of course, as my presentation showed, the 11% value for the 2mg dose (or 4/37 in Mike Rose's crossings out in his lab book) was created out of thin air. I note that you have not commented on where this has come from, yet it appears on your plot. As I showed in my analysis (see attached), Rose replaced the zero incidence of vomiting at 2mg in the volunteer trial (that the other data are based on) with this falsified 4/37 or 11% value because it looked just at the right place on his curve. I note that the Bayliss 0/2 response in the volunteer trial is not on your graph for the 2mg dose in human volunteers, so your plot is incorrect. Of course, the fabricated 11% response that you have replaced it with on your plot provides a nice threshold response with a good (and faked) group size that Rose then added to the sigmoidal curve he drew first! Of course, Rose went one step further by also omitting the 3mg dose in the same volunteer study since the absence of vomiting here would really spoil his curve. In fact the sigmoidal curve was quite convincing to both the Agrochemicals Main Board and the Regulatory Authorities back in 1977. Therefore, everyone believed him and his estimate of the 0.5g/L concentration required to cause vomiting in the "majority" of individuals in a "minimally lethal dose". Returning to your new curve, if you remove the 4/37 (11%) point which is falsified you are left with just 2 points above the x axis. The one individual who vomited at 4mg and the single individual who vomited at 8mg. Since the one at 8mg didn't vomit until 2 hours and was outside both the Rose and FAO time criteria, this point disappears too. Therefore, you are left with a single point on your new curve and 8 points along the zero vomiting baseline. Even Syngenta could not fit a sigmoidal dose response curve to that... or perhaps they can! Now I have your report I can point this out to US EPA, assuming Syngenta will use this in their response to my own report.

CTL Emetic Enquiry

My other thoughts on your "New analysis" are as follows. It is quite understandable that as a Syngenta employee you (and your colleagues) are trying to limit the damage that may be caused by a new review in 2019 by the Regulators on the original decision to add 0.5g/L PP796 to Gramoxone back in 1977. This may have maintained paraquat registrations round the world where the National Authorities were convinced by this very laudable manoeuvre by ICI Agrochemicals. However, when I exposed this as a problem in 1990, the error of judgement with the emetic level in Gramoxone should have been thoroughly investigated by the company internally at the time, when I raised this firstly with Lewis Smith and then later with various CTL and RAD colleagues responsible for the safety, registration and stewardship of paraquat products. However, nothing was done about it and all these years on children are still being poisoned from one sip of Gramoxone because no one has had the bottle to stand up and speak the truth about the fabricated data and put this right.

During the emetic enquiry commissioned by Stuart Jaggers in 1991, after Lewis left CTL, we were asked to compare the Bayliss Pharms data with the data in the Rose report and its validity to set the 0.5g/L level of emetic in Gramoxone. The enquiry was chaired by Gerry Oliver with Bob Scott and myself. Gerry moved on to Pharms Division shortly afterwards, without concluding the enquiry. Stuart and Rod Morrod also left CTL soon after, but we exchanged a number of interesting memos on the emetic deliberations if you wish to see them. Iain Purchase and I had a number of meetings on this in the next few months. Iain understood and agreed with me that mistakes had been made and it was judged as a very serious reputational issue that needed to be managed very carefully. Like me, he was confident that Lewis (before he left CTL) had informed the relevant people in RAD at Fernhurst, including Geoff Willis and it was now down to Agrochemicals to make the next move. Following our meeting at Jealotts Hill this year I am less confident that the right people had been provided with the correct details.

Meredith and Vale

Returning to your new analysis, despite the way you have tried to present the Syngenta case using statistical analysis on what we all agree is a very weak set of human data, that shows a threshold vomiting response at best, you conclude that everything is OK since Syngenta meets the FAO specification for the emetic based on the Meredith and Vale

investigation undertaken 10 years later. Do you not realise that the FAO specification was based on the unpublished information cited in their paper so it didn't contradict the issue of the emetic causing more vomiting, that there was a higher proportion of vomiting within 30 min etc. Are you aware where this information on vomiting within 30 min in the Meredith and Vale publication came from? The source of this information was Bernie Hart the former Chief Medical Adviser at Fernhurst. Bernie was working closely with Lewis on Paraquat poisoning matters right through the 1980s including our deliberations with France where Agrochemicals rapidly introduced a 6-fold increase in PP796 to try to maintain the registration. Again I have kept some interesting memos on these exchanges. This data on early emesis following PP796 addition was never peer reviewed and is cited by Meredith and Vale as "unpublished by ICI" in their paper. I am sorry Kim, but based on the goings on the emetic at the time, how can I even trust that this information coming out of Fernhurst to Allister Vale was correct? There was no improvement in survival in accidental and suicide cases following inclusion of the emetic, as reported by several other Authors, unsurprisingly at this ineffective concentration of 0.5g/L. The FAO text was written many years after the Meredith and Vale publication and basically obliged the other manufacturers of paraquat to purchase and use Syngenta's emetic in their own paraquat products, as mandated by the FAO.

I guess if I was in your position I would try to pursue as many angles as I could to make the situation appear as if the emetic concentration that was approved by the regulatory authorities throughout the world in 1977 wasn't too far off the mark. If I had seen the Rose report CTL/R/390 and not seen the actual undoctored Bayliss data I would also be convinced that 0.5g/L was about right too. This is how I discovered the falsification by Rose by a thorough cross-checking of the original ICI Pharmaceuticals studies with the single author CTL research report CTL/R/390, because my scientific instinct is to review the data myself.

Emetic Response in other Species

The key issue I have it centred on during our deliberations over the last 6 months is the fabricated human dose response curve by Mike Rose in CTL/R/390, which convinced the Agrochemicals Business and the Regulators that the emetic PP796 was 10 X more potent in man compared to the far more comprehensive studies on PP796 in 3 other vomiting species (dog, pig and marmoset). This led to an ineffective emetic level of 0.5g/L PP796 being added to all paraquat products in 1977. The full rationale for inclusion at the Rose recommended level of 0.5g/L plus all the commercial and global registration strategy information is in the Peter Slade Agrochemicals Board Paper that I have. It is EDC Paper No 729, October 1976. I am sure you can access it if you haven't already. It has the full Rose report in its Appendix with lots of other information on how crucial it was to add the correct and effective concentration of PP796 to Gramoxone to meet what later became the FAO specification..

Further proof that the company had ignored my deliberations on this in 1990 were obvious through the mid-1990s with several regulatory submissions, including the EU MII submission where it was stated that the emetic was 10 X more potent in man compared to 3 other vomiting species and again used the falsified Rose level of emetic addition and cited his report. Again I wasn't listened to nor my findings challenged. I guess the £30m per annum cost to put this right plus a new emetic plant was too much for the commercial guys to bear. I have memos on this fact too! Best to keep the costly emetic additive as low as possible and the paraquat as high as possible for manufacture, shipping and distribution. This maintained the high profitability of the non-selective herbicide. This fits with the misleading information in the FAO spec to keep the emetic as low as possible, as you will see below.

To re-iterate my position on this, I carefully documented my findings to Lewis Smith in September 1990 (attached) explaining the fabrication of the human dose response in man by Mike Rose, as presented in his infamous CTL/R/390 report. This directly led to the inclusion of 0.5g/L PP796 being added to Gramoxone in 1977, based on the claim that humans were particularly sensitive to the emetic, compared with 3 other vomiting species where there is much more dose response data. Interestingly, Kim, you do not refer to the wealth of data on the effect of PP796 to cause vomiting in the 3 other species at all, yet, as toxicologists we should take this into account, or at the very least question, why humans should be more 10 X more sensitive to a centrally acting emetic compared to species that are actually more prone to vomit. Even Mike Rose was smart enough to do this and as a way he could construct a false parallel dose response curve in man right between the dose response curves for the other vomiting species (My presentation attached). He simply changed the x axis so the dose of emetic required in man instantly dropped by a factor of 10. This

was much more favourable to the Agrochemicals Division as a commercial manoeuvre to maintain failing registrations than a new emetic plant and £30m per annum off the bottom line. I got the same treatment from Rob Morrison when I presented the case for Magnoxone with 5 X emetic at the TRC chaired by John Finney in 1991 and again with Gramoxone Inteon with 3 X emetic by David Evans a decade later. Expensive solutions to product safety don't go down well with Syngenta.

Omission of the level of emetic in your report in the FAO specification

The use of the Meredith and Vale paper in 1987 to back up the statements in the FAO Specification was a clever approach to defend the mandatory inclusion of Syngenta's own emetic at a particular level. This makes it appear everything is OK, yet there were hundreds of paraquat deaths in developing countries in particular between 1977 and 1987, including many accidental deaths. By the 1990s the Company knew that the inclusion of the emetic at 0.5g/L hadn't saved lives. Do you not realise that the value for the concentration of PP796 quoted in the FAO spec comes from directly from the falsified Rose report? Can I ask you why you have not quoted all of the wording in the FAO spec on the emetic, and **omitted the most important final sentence on what the minimum level of emetic must be to meet the written criteria?** Why have you chopped this last sentence off the text in your report, yet quoted everything else in the FAO spec in Note 1 on the emetic verbatim? Please don't say that this was a copy and paste error! You even state "*In full, the current FAO specification (FAO 2008) states*"..., but it's not "in full". You have left out the critical sentence on what this concentration of emetic must be to fulfil the FAO criteria!

I can actually understand why this final sentence of the FAO spec is missing, since it **confirms that Syngenta still regard the emetic level in the Rose report to be correct**. This was 0.5g/L in standard Gramoxone and 0.8g/L (pro rata) in Gramoxone Max. I am sure you realise that the minimum concentration value in the FAO Spec is based on the Rose report and comes from the falsified dose response curve in man in CTL/R/390. Obviously, I did not make myself clear at Jealotts Hill on Jan 15th. It is the ratio between paraquat and PP796 in the product that is important. Rose set this at 400 :1 rather than 40 :1. The 40 :1 ratio was much more likely to have improved survival (as shown in France when Zeneca added 6 times the level of emetic). However, Zeneca could not bear the cost of this globally. To reiterate, the minimum level of 0.8g/L PP796 in the TK that you have omitted in your New Analysis Report, for some reason, is an **ineffective** loading of emetic in paraquat products. This is why this matter must be communicated to the Agencies and the FAO themselves. I can check the FAO process for updates with Alan Boobis who was on the FAO panel at the time.

Notification of US EPA OPPTS

As you are all aware I intend to contact US EPA first in order to begin a dialogue with OPP on the inclusion of the emetic agent, PP796 and the evidence for the inclusion rate at 0.5g/L in Gramoxone and 0.8g/L in Gramoxone Max. I will explain that the minimum level of PP796 emetic in paraquat products described in Note 1 does not actually meet the FAO Specification that was required to ensure prompt effective emesis within 30 min, in a minimally lethal volume of product, in the majority of victims, since it originated from a fabricated human dose response curve. I will explain that this may well be the reason why the emetic has not been effective in human poisoning since the day it was first registered as an additive in 1977. I will need, of course, to cite the evidence I have for this important declaration and my long history associated with paraquat formulation research within Syngenta and its former companies. I am sure that EPA receive a lot of negatives about paraquat toxicity every year from various Poisons centres, the Pesticide Action Network, Public Eye, the press etc. My approach will be different but if the response from OPP is not to my satisfaction, I will have to open the matter with other Regulatory Authorities where paraquat is still registered and where I have personal contacts.

I was not going to give too much detail to begin with and see what reaction I get. However, the tone and style of your "New Analysis" report, and, in particular, the final sentence of your conclusions has certainly fired me up. I can understand the impact that falsification of data could have on Syngenta, but to dress up this new report with a sigmoidal dose response curve that is basically giving the same message as the falsified Rose dose response curve is very concerning to me. Furthermore, your final concluding paragraph stating that everything is basically OK has really antagonised me. Therefore, I am going to change my tack on communicating this with the relevant authorities. I was going to use a "softer" scientific approach but it may be better if I forward my full analysis of the situation to EPA. I

keeping hoping you guys will come up with a solution that proves me to be wrong. However, this has not happened and you appear content to defend the Rose position that the current level of emetic in paraquat products is quite reasonable. At the end of the day it will be the Regulatory Authorities to decide how to deal with this but we are obviously poles apart on this one.

As I have said many times, I have nothing against any individual or the company as a whole, I just want to ensure that the next child taking a sip of Gramoxone has a fighting chance at removing the poison by vomiting within a few minutes and before a lethal dose of paraquat is absorbed into the blood. This is why the company employed me in the first place back in 1986 and I am determined to see this through.

I look forward to our teleconference call on Friday.

Best regards

Jon Heylings

Professor Jon R. Heylings
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[redacted]
Jon

From: Travis Kim GBJH [mailto:kim.travis@syngenta.com]
Sent: 29 April 2019 17:26
To: Jon Heylings <[redacted]
Subject: New analysis of PP796 emetic dose-response in man

Hi Jon,

The document is attached,

Regards,

Kim

This message may contain confidential information. If you are not the designated recipient, please notify the sender immediately, and delete the original and any copies. Any use of the message by you is prohibited.