Message

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Sent: 8/2/2006 3:49:45 PM
To: Elliott Barry GBAP [/O=MESSAGING/OU=BE-AG/CN=RECIPIENTS/CN=BARRY.ELLIOTT]
CC: Swain Cindy GBAP [/O=MESSAGING/OU=BE-AG/CN=RECIPIENTS/CN=CINDY.SWAIN]
Subject: Audit trail for XD Studies and presence of emetic

Barry

As requested, I have the following details for the Gramoxone studies undertaken at CTL between 1988 to the present day. From my own recollections the Gramoxone samples used as controls in dog kinetic studies that I was involved with were all coloured and stenched. The question is which of the various samples received by CTL can we demonstrate beyond reasonable doubt that they also contained the standard 0.5g/L emetic. In the early days the emetic was not measured in plasma. There are 3 reports of this work. Within the respective study files we have either direct or indirect evidence that the Gramoxone used was emeticised.

1. XD7388 (2004). The most recent study was a GLP one where there is full batch reference stating that the A3879D formulation contained 0.5g/L emetic. In addition, the plasma emetic was measured in this study which confirms that it was indeed emeticised.

2. XD1236/XD1328 (026118 Research Report). This is a compilation of all the Gramoxone studies undertaken at CTL at the 8mg/kg oral dose in the period 1987-1991. These research (non GLP studies) were operated under a Toxicity Section protocol and associated appendices with study dosing details. These appendices were generated for each dosing. There were many studies with Gramoxone involving capsule dosing, gavage dosing, 20% and 10% AI, all dosed at 8mg/kg PQ ion. We have located most of the study information including the description of the formulation used. According to the Toxicity Section data sheets in the study file, Gramoxone UK was used in the majority of cases. Other data sheets just state Gramoxone. According to the records at Jealotts Hill, Gramoxone UK is a 200g/L PQ formulation containing 0.5g/L emetic. Their records identify this as YF6917C, an emeticised formulation containing 0.5g/L PP796. Being research studies there is no QA audit of the study or C of A in the report, only the description that the formulation used in the majority of these studies was Gramoxone UK.

3. 026698 Research Report. This is a study undertaken in early 1990 to investigate PQ toxicity and plasma exposure to an increased concentration of emetic. The test substance was supplied by Jealotts Hill as Gramoxone Export and additional emetic was added at CTL to give an equivalent total loading of 2.4g/L emetic for a 20% AI formulation. The report states that the Gramoxone Export used to prepare the dosing solutions was Y No. 00061/131 and this contains 0.5g/L emetic, according to the report and Jealotts Hill records. There is supporting evidence from CDY records that Gramoxone Export is Y No. Y00061/131 (or YF6917F) and this contains 0.5g/L emetic. An issued batch sheet from CDY in the study file describes this Y No. as Gramoxone Export, a dark green liquid. A batch Y00061/131/004 was issued in 1989 to Biochem Tox as a 200g/L green/black liquid.

Hopefully, this is an accurate record, but please let me know if your own review of the paperwork says otherwise.

Jon

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