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October 14, 2008

Tammie Bell  
Office of the Commissioner  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

Subject: Comments on the Draft Document “M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals” in response to Docket No. FDA-2008-N-0484

Dear Ms. Bell:

These comments are submitted on behalf of the Physicians Committee for Responsible Medicine, the Humane Society of the United States and the Humane Society Legal Fund. We appreciate this opportunity to comment.

We are pleased that the fixed requirement for single dose toxicity studies has been removed from the M3(R2) guidance in favour of a recommendation to use available toxicity data from other studies, such as repeat dose studies. This change is in keeping with recent analysis by European pharmaceutical companies published in Regulatory Toxicology and Pharmacology demonstrating the marginal scientific contribution of acute toxicity studies to pharmaceutical development<sup>1</sup>.

We are not, however, in agreement with the proposed guidelines concerning the duration of repeat-dose non-rodent studies. We wish to call attention to several retrospective analyses of the regulatory value long-term chronic dog studies for pesticides which determined that, with a small handful of possible exceptions, dog studies in excess of 90 days contribute no additional scientific value.<sup>2,3,4</sup> These findings led some, such as the EPA’s Office of Pesticide Programs, to only request the non-rodent chronic toxicity test in extenuating circumstances, while most chemicals require only a non-rodent sub-chronic toxicity test. We are disappointed that the draft guidance continues to advocate nine month non-rodent studies and we encourage the FDA and ICH to revisit this issue.

<sup>1</sup> Robinson S, Delongas J-L, Donald E, et al. European pharmaceutical company initiative challenging the regulatory requirement for acute toxicity studies in pharmaceutical drug development. *Regulat Toxicol Pharmacol.* 2008; 50: 345-52.

<sup>2</sup> Spielmann H, Gerbracht U. The use of dogs as a second species in regulatory testing of pesticides. Part II: subacute, subchronic and chronic studies in the dog. *Arch Toxicol.* 2001; 75: 1-21

<sup>3</sup> Box R, Spielmann, H. Use of the dog as non-rodent test species in the safety testing schedule associated with the registration of crop and plant protection products (pesticides): present status. *Arch Toxicol.* 2005; 79: 615-626.

<sup>4</sup> Baetcke K et al. A Comparison of the Results of Studies on Pesticides from 12- or 24-Month Dog Studies with Dog Studies of Shorter Duration. Washington, DC: US EPA; 2005.

We have several concerns related to microdosing--specifically, the guidance on duration of animal studies, the number of animals used, and setting the limit dose. With regard to study duration, we agree with Xceleron's findings that a 7-day study in animals is sufficient for the purposes of conducting any microdosing study in humans.<sup>5</sup> In terms of the number of animals used, we again offer Xceleron's position that 3 males and 3 females per dose group overall would be sufficient to estimate a safe microdose in humans,<sup>5</sup> as opposed to 10 rodents/sex/group, as called for in the guidance document. We also take issue with the 10 mg/kg recommended limit dose in rats, which is stated to be "~6000x the 100 µg clinical dose on a mg/kg comparison basis. By comparison, the FDA has suggested a safety margin of 100x the proposed human microdose be used in animal studies. We encourage the FDA to maintain this position at the ICH.

Another area of concern is that of phototoxicity. We urge ICH to endorse the *in vitro* 3T3 NRU phototoxicity test as the preferred nonclinical test method. The 3T3 NRU is the only formally validated test for this endpoint and the only phototoxicity test accepted by the OECD.

Finally, regarding genotoxicity studies, we strongly favor a tiered approach, as opposed to a battery of genotoxicity tests. The first tier, comprised exclusively of *in vitro* assays, would, if negative, preclude any *in vivo* testing. This, together with the generally low prevalence of genotoxic agents within the chemical and pharmaceutical universe, favors a tiered approach. Not only would such an approach be more in line with other developed nations seeking to harmonize test guidelines, it is more consistent with ICH's stated aim of 'more economical use of animal resources'.

Thank you for your attention to these comments.

Sincerely,

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<sup>5</sup> Lappin G, Garner RC. Big physics, small doses: the use of AMS and PET in human microdosing of development drugs. *Nat Rev.* 2003; 2: 233-40.