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Mr. Kevin Sweeney
(and Attn.: John Carley)
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Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency
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Summary of January 14, 2008 Meeting with EPA and AVON/ICR to Discuss Updates to the A117 Cage Study Protocol

Meeting Attendees and Affiliations:

Mr. John Carley (EPA/OPP)	Mr. Patrick Quinn (Accord Group)
Mr. Bill Jordan (EPA/OPP)	Mr. Andrew Pechko (Avon)
Mr. Kevin Sweeney (EPA/OPP/RD)	Dr. Ramez Labib (Avon)
Mr. Richard Gebken (EPA/OPP/RD)	Dr. Chris Bartlett (Avon)
Ms. Mary Frankenberry (EPA/OPP/HED)	Dr. Ralph Piedmont (Loyola Univ.)
Mr. Niketas Spero (ICR)	Dr. Robin Todd (ICR)
Mr. Bill Gaynor (ICR)	Mr. Micah Reynolds (toXcel, LLC)

Mr. Quinn began the meeting at approximately 11:15am with a round of introductions of all in attendance and followed with an outline of the agenda items to discuss, namely the revised plan for statistical analysis of the data to be produced by the cage study. In addition to this major item, Mr. Quinn also described the purpose of the cage study in that it is a confirmatory study on two registered Avon insect repellent products in order to make label claims for effectiveness at repelling mosquitoes that may transmit West Nile Virus (WNV). The two repellent products were tested in the field and achieved complete protection times of 6 hours (806-29) and 8 hours (806-31) for mosquitoes.

Further, Mr. Quinn noted that, pending the Agency's approval of the statistical analysis plan, testing could be initiated in early February followed by a formal submission to the Agency for consideration by the Human Studies Review Board (HSRB) at its April 2008 meeting. Mr. Carley quipped that such review would be highly unlikely at the April meeting but potentially for the June 2008 meeting.

Dr. Piedmont began the discussion of the revised statistical analysis plan. He outlined the straight-forward principles behind the statistical plan and the intended outcome for the evaluation of the strength of power and the accuracy of estimations. Dr. Piedmont

explained the main table in the revised statistical plan and that it is referenced from the publication by Rutledge and Gupta (1999). The Gupta publication was written to evaluate the number of subjects (n) needed to achieve a ±2 hour confidence limit at the 95% confidence interval. In order to make a claim of 8 hours of protection, a minimum of 11 subjects are needed in the study.

Mr. Jordan noted that he had spoken with Dr. Gupta about his research and asked Dr. Piedmont if the proposed statistical plan follows Dr. Gupta's methodology. Dr. Piedmont affirmed that it does and elaborated that the revised plan will involve a Kaplan-Meier analysis to determine survivorship of the test population. This will produce a good determination of the mean, median, standard deviation, and 95% confidence interval.

Ms. Frankenberry inquired regarding how the data would be interpreted if all 12 study subjects right censor (no repellency failure) after 10 hours in the study. Dr. Piedmont replied, based on the Gupta publication, that it would be determined that the product provides 8 hours of protection ± 2 hours. If more than one subject withdraws, then based on the Gupta publication, the product would be determined to provide 7 hours of protection ± 2 hours. Ms. Frankenberry inquired how the Kaplan-Meier analysis will be utilized in the determination of complete protection time as it seemed that values were being arbitrarily assigned based on the Gupta publication. Dr. Piedmont responded that the Gupta publication was only being utilized to establish the power of the data set. The complete protection time would be based on the mean value assessed from the Kaplan-Meier analysis.

Mr. Jordan posed a question regarding how data will be analyzed from participants who prematurely withdraw from the study. Dr. Piedmont answered that the Kaplan-Meier analysis uses all data from a given time point rather than deriving an overall estimate. That is, if 12 subjects participate at the 4.5-hour mark, but one withdrawals and only 11 subjects participate at the 5-hour mark, Kaplan-Meier will still perform its calculations based on the number of participants at a given time interval. A trend exists that as more subjects withdraw from the study, the power decreases and the confidence interval increases.

Dr. Piedmont confirmed that the Gupta publication is being used to establish power based on the number of subjects and the Kaplan-Meier analysis determines the mean complete protection time. Mr. Carley inquired of Dr. Todd the rate of subject withdrawal from ICR cage studies. Dr. Todd replied that ICR has historically seen zero dropouts from cage studies. Mr. Carley questioned why ICR is not using its own historical data to support the statistical analysis. Dr. Todd responded that the HSRB's concern was the need for an analysis plan that would evaluate multiple scenarios (all subjects experience repellency failure, multiple subject withdrawal, zero subjects experience repellency failure, etc). Mr. Carley questioned further the use of the Gupta publication when ICR has a plethora of historical data in its archives.

Dr. Piedmont responded to Mr. Carley's concerns in saying that the use of the Gupta publication provides the HSRB with transparent variability. Additionally, the ICR historical data is not readily available in a format such as Rutledge and Gupta (1999) and the Gupta publication is peer-reviewed public literature. Mr. Jordan interjected to say that the use of the Gupta publication is appropriate for this protocol since the test species is mosquito, but for future protocols where the test species is different, the ICR historical data may be more appropriate. Mr. Carley agreed and further noted that previously submitted data can be utilized to establish ICR historical data.

Mr. Pechko reminded the meeting participants that the primary goal of the study is to confirm the test materials' effectiveness against mosquitoes that can transmit WNV. He added that repellency label claims were previously established when conducting the field efficacy trials.

Mr. Jordan and Ms. Frankenberry concurred that ICR established a sufficiently revised statistical analysis plan using a Kaplan-Meier analysis but concern remained with how data would be treated in the event that all study subjects right censor (no repellency failure in any subject at 10 hours). Dr. Piedmont responded that in the event that all study subjects were to right censor, then the products will be determined to have a protection time of 8 hours ± 2 hours at the 95% confidence interval.

Mr. Jordan recommended that the statistical analysis be conducted in two ways:
1) perform Kaplan-Meier analysis to determine mean complete protection time and use the Gupta publication for the determination of power and confidence interval; and
2) perform Kaplan-Meier analysis alone to determine mean complete protection time, standard deviation, and confidence interval.

Mr. Pechko noted that if two different methods are used to analyze the data, then there will be two determinations of complete protection time. Dr. Piedmont responded in that one value will have stronger power. Mr. Sweeney recommended performing both methods and providing explanations of both methods in the protocol so the HSRB can properly evaluate each method.

Mr. Jordan inquired if there was any analysis to determine if the data are normally distributed. Dr. Piedmont answered that such analysis is unnecessary because the data are proportional. Mr. Carley recommended that a statement be amended to the revised statistical plan explicitly stating this. Mr. Sweeney asked whether there was to be any analysis of a bite that is not followed by a confirming bite. Dr. Todd replied that there is no analysis for this event, but that all bite events will be reported in the raw data and submitted with the final report.

Mr. Carley noted some necessary revisions to the revised informed consent document (ICD). In order to comply with EPA's rule for third party research (40 CFR § 26.1116), identification of the test sponsor as well as the test materials must be disclosed in the ICD. He perceived that no claim of confidentiality was being made to the study documents since the two test materials are registered products. Mr. Carley also noted that he had not had adequate time to perform an informal review of the submitted materials, but that he would provide comments within a few days. In order to facilitate future protocol reviews, he suggested that the page margins be set to 1.25 inches and that a line number function be appended to the pages of any draft version.

Mr. Sweeney recommended that the revised statistical analysis plan be updated further based on items discussed during the meeting and that it be resubmitted for his review. Mr. Pechko outlined Avon's intentions to make the WNV claims for the 2009 selling season after the label amendment is approved by the Agency and the state registration process is complete.

Mr. Quinn introduced the upper age limit for study participants as a final discussion topic and requested feedback from the Agency. Due to WNV not being a risk factor, it is believed that there is no limit to the age of study participants so long as they consider

themselves to be in good health, but Mr. Spero noted that it is a requirement of the IRB to identify an upper age limit. Mr. Carley responded to the question that inevitably ICR will have to recruit a younger subject population for its studies. Further, he noted that there were no reasons that an upper age limit of 70 was inappropriate, but followed in saying that he is uncertain of the HSRB's consideration.

Mr. Quinn outlined the next steps in preparation for the submission to ICR's IRB. Mr. Carley reminded the group that he would perform an informal review of the informed consent document and provide his comments within several days. Mr. Spero indicated that the protocol would be revised to tighten the margins and include a line numbering function for ease of reading and that the statistical analysis plan will be updated to include the items discussed during the meeting, namely: 1) a statement indicating that a test to determine normality of the data is unnecessary; and 2) explanation of two methods of data analysis. Once Mr. Carley's comments are received and incorporated into the documents, a revised submission will be made to Mr. Sweeney for his final review and approval of the statistical analysis plan.

After fruitful discussion, the meeting concluded at approximately 12:45pm. If you have any questions or require additional information, please feel free to contact me by phone at (703) 335-5670 or by e-mail at micah@toxcel.com.

Sincerely,

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