**UNITED STATES ENVIRONMENTAL PROTECTION AGENCY**
WASHINGTON D.C., 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

*May 22, 2008*

**MEMORANDUM:**

**SUBJECT:** Ethics Review of Human Study of Mosquito Repellent Performance

**FROM:** John M. Carley
Human Research Ethics Review Officer

**TO:** Marion Johnson, Chief
Insecticide Branch, RD

**REF:** Spero, N. (2008) Evaluation of the Efficacy of Personal Repellents Against Mosquitoes in the Laboratory. Unpublished report prepared by ICR, Inc., under Protocol No. G0590607001A117 and Project No. 0607-059-0157. 98 p. MRID 47397701.

Reynolds, M.; Kelley, J. (2008) Additional Information to Fulfill 40 CFR §26.1303 for the Study: Evaluation of the Efficacy of Personal Repellents Against Mosquitoes in the Laboratory. Unpublished report prepared by toXcel, LLC, under Protocol No. G0590607001A117 and Project No. 0607-059-0157. 49 p. MRID 47413601.

I have reviewed all available information concerning the ethical conduct of the research reported in the referenced documents, which describe the execution of ICR, Inc., protocol number A117, for the evaluation in the laboratory of the repellency of two formulations containing picaridin against mosquitoes of the genus *Culex*.

ICR Protocol A117 was reviewed favorably by the Human Studies Review Board at its meeting in October 2007. In early January 2008 ICR submitted a revised protocol, statistical analysis plan, and consent form for informal EPA review. EPA met with ICR, the study sponsors, and others on January 14, 2008. In response to EPA's comments and suggestions, and to the draft report of the October HSRB meeting (released January 10, 2008), ICR made further revisions to the protocol and consent form, and submitted them to Essex Institutional Review Board, Inc., (EIRB) on February 14, 2008. After calling for some changes to the consent form, EIRB gave final approval to the revised protocol and consent form on February 25, 2008, and notified ICR of their approval on February

26. ICR conducted the study on March 4, 2008, and submitted the reports cited above to EPA on April 9, 2008.

## A. Scope of Review:

This review reflects consideration of the following documents in addition to the reports cited above:

- EPA Science and Ethics Review of ICR Protocol A117 (9/24/07)
- toXcel response to EPA Science and Ethics Review (10/17/07)
- toXcel summary of January 14, 2008 meeting with EPA (1/17/08)
- HSRB Final Report of October 2007 Meeting (3/6/08)
- toXcel 5/21/08 response to EPA E-mail request for clarifications

## B. Completeness of Study Submission:

The submitted documents cited above were reviewed for completeness against the required elements listed in 40 CFR §26.1303. EPA's checklist is appended to this review as Attachment 1. The following deficiencies in required documentation were noted in the submitted package:

- Although the required minutes of the EIRB meeting of February 18 were submitted, they did not show the EIRB's basis for requiring changes in the consent form. The relevance of some EIRB-requested changes to this research is unclear—especially the list of resources for additional information.

- Although a list of IRB members identified by name, earned degrees, and representative capacity was submitted, it did not include any indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations.

- Written procedures for the IRB were not submitted. The complete procedures manual for Essex IRB was previously submitted directly to EPA.

None of these deficiencies reach a level of significance sufficient to compromise EPA's review, or to constitute substantial non-compliance with the requirements of 40 CFR §26.1303

## C. Content of Study Submission

Volume 1 of the submitted package contains applications for registration and other administrative material which has not been considered in this review. Volume 2 of the submitted package included the following documents:

- Primary report (pp.1-8)[1]
- Appendix I: Protocol, Amendment, Deviation (pp. 9-52)
    - Protocol version of 2/8/08, approved by EIRB 2/18/08 (pp. 9-40)
    - Product labels (pp. 41-50)
    - Amendment covering protocol version of 2/8/08 (p. 51)
    - Deviation report dated 3/13/08 (p. 52)
- Appendix II: Informed Consent Document version of 2/20/08 approved by EIRB 2/25/08 (pp. 53-64)
- Appendix III: Raw Data
    - Efficacy raw data forms for treated and control subjects (pp. 66-71)
    - Results of attractiveness testing (p. 72)
    - Temperature/humidity data (p. 73)
- Appendix IV: Statistical Analysis (pp. 74-79)
- Appendix V: Sample log and use forms (pp. 80-88)
- Appendix VI: EIRB Approval letters
    - Letter dated 8/2/07 reporting conditional approval 6/30/07 of protocol dated 6/12/07 and consent form dated 7/17/07 (pp. 90-92)
    - Letter dated 8/7/07 reporting approval of protocol with amendments 1-8 on 8/6/07 and consent form dated 8/2/07 on 8/7/07 (p. 93)
    - Letter dated 2/26/08 reporting EIRB approval of protocol dated 2/8/08 on 2/18/08 and of consent form dated 2/20/08 on 2/25/08 (p. 94)
- Appendix VII: Sample Characterization (pp. 95-98)

Volume 3 of the submitted package contained these supporting documents, all considered in this review:

- Introductory matter (pp. 1-5)
- Summary of revisions to A117 since October 2007 HSRB meeting (pp. 6-8)
- ICR transmittal of amended protocol to EIRB 2/14/08 (p. 9)
- Amendment covering protocol v. 2/8/08 (Duplicate of V2:51) (p. 10)
- Consent form dated 2/8/08 (pp. 11-20)
- Email EIRB→ICR reporting approval of 2/8/08 protocol without comment and conditional approval of 2/8/08 consent form with comments (pp. 21-22)
- Email correspondence EIRB↔ICR (pp. 23-31)
- ICR→EIRB transmittal of 3/13/08 deviation report (pp. 32-35)
- Minutes of 2/18/08 EIRB meeting, with EIRB roster and member profiles (pp. 36-40)
- 3/18/08 note to file reporting follow-up calls to subjects (p. 41)
- Reprint of Rutledge and Gupta article cited in protocol (pp. 42-49)

[1] The convention used throughout this review is to identify first the volume number—i.e., V2 or V3, indicating Volume 2 (MRID 47397701) or Volume 3 (MRID 47413601)—and then the page number(s). Many pages bear more than one page number. All references to Volume 2 are to page N of 98; references to Volume 3 are to page N of 49.

## D. Deviations from Protocol

One deviation from the protocol was acknowledged in the study report (V2:6, 52) and was reported to the EIRB (V3:32-35). The protocol called for treating twelve subjects in six pairs, and using the time of application of the second test material to each pair as the starting time for measurement of complete protection time (V2:27). Instead subjects were treated in two groups of six. The explanation that this was to "minimize confusion among the treated subjects regarding when they were required to enter the insectary for the next half hourly exposure to mosquitoes" does not suggest that the deviation was necessary to deal with an unexpected event or condition on the day of testing; this appears to have been an anticipatable change to the protocol, and would have been better handled by an amendment. Because it was not necessary to address an imminent hazard to the subjects, the amendment should have been reviewed and approved by the responsible IRB before it was implemented.

In its May 21 response to EPA's E-mail request for clarification on this point, toXcel explained further:

> There were six cages dedicated to two subjects each and it was known that three cages could be managed at a time (six subjects; two at each cage). The logistics of moving two groups of six in and out of the insectary was more manageable and less disruptive than the logistics and timing associated with moving around six groups of two and using only one cage at a time.
>
> This type of change has never been made in prior tests. The reason no such change was ever made is that this study involved the largest group tested at ICR. Most comparable studies at ICR involve a group of 6 subjects total. Occasionally ICR has conducted studies using 8 subjects, but this is believed to be the first time that 12 subjects were involved. ICR has never needed to make such a protocol deviation in the past. It was deemed to be a reasonable precaution to ensure smooth performance of the study and avoid any potential disruption.

Although this is an acceptable explanation of the reasoning behind the change, it does not suggest the problem could not have been anticipated and addressed by an amendment to the protocol.

In addition to this acknowledged deviation from the protocol, the recruiting process was initiated a week before EIRB, Inc., approved the consent form. This was not acknowledged in the study report, nor was it reported to EIRB, Inc. It is discussed in detail in section E(2) below.

## E. Summary Assessment of Ethical Aspects of the Research

1. **Societal Value of Proposed Research:** The stated objective of the research was to fulfill the EPA requirement for a confirmatory laboratory efficacy study of two registered repellent products containing picaridin on a West Nile vector species.

Although these products had previously been tested in the field for efficacy against other genera of mosquitoes, they had not previously been tested for efficacy in repelling *Culex*. EPA requires product-specific laboratory efficacy data with *Culex* sp. to support proposed label claims of repellent efficacy against "mosquitoes which can vector West Nile virus."

The protocol discussion of expected societal benefit of the research was revised after the October 2007 HSRB meeting consistent with the recommendations of EPA and the HSRB. There are potential societal benefits from testing to identify registered repellents which are effective against mosquitoes that can transmit WNV.

2. **Subject Selection:** Subjects were recruited from a database including previous subjects of similar ICR tests and "friends and colleagues" of previous subjects. This pool was characterized as being "as representative of potential repellent users as we are able to make it." Children, adults over 70 (a change from the age cap of 55 in the protocol reviewed by the HSRB), pregnant or nursing women, non-English speakers and those in poor health are excluded as subjects. One subject selected by lot served as an untreated control to verify aggressiveness of the caged mosquitoes.

   There is no indication that any subjects were from populations potentially vulnerable to coercion or undue influence. All employees and relatives of employees of ICR, of the sponsor, or of any other interested party were excluded as subjects. No enrolled subjects were reported to have withdrawn.

   The process to be used to recruit and seek the consent of candidates was described sketchily in the protocol reviewed by the HSRB in October, and both EPA and the HSRB called for its clarification. The revised protocol as approved by EIRB, Inc., on February 18 describes the process in the following terms:

   > "ICR will select individuals from our candidate database of potential test subjects. This will be accomplished by drawing numbers that correspond to a particular candidate number in the database. We will attempt to select even numbers of male and female candidates in order to eliminate any gender bias in this test." (V2:18)
   >
   > "The Informed Consent Document will have been approved by an Institutional Review Board before it is presented to the candidates for the study." (V2:18)
   >
   > "ICR uses the following initial telephone script to recruit test subjects:
   >
   > "ICR will be conducting a repellent project on these dates . . . at (exact study site) would you be able to participate in this study?"
   >
   > "If the candidate is available, the inclusion/exclusion criteria will be discussed in detail and verified whether the candidate would qualify to participate. The ICD will also be discussed with the candidate at this time. In addition, ICR will mail a copy of the ICD to each interested candidate for their review. He or she will be instructed to

contact the P.I. to verify receipt of the ICD and to ask any ICD or study related questions they may have.

"The P.I. will contact all interested persons by phone several days after receipt of the ICD to fully explain the ICD with them. We will discuss every line of the ICD with them. All contacted individuals will be offered the opportunity to come to ICR to go through the consent process in person by reviewing the ICD with the P.I.. During the recruitment process all candidates will be properly informed of the risks of the study and study parameters via telephone communication with the Principal Investigator, the mailed ICD, and visits to the ICR facility during the informed consent process. Candidates are encouraged to schedule a time to review the ICD with the Principal Investigator in person at ICR. When candidates have had adequate time to review the material they will contact ICR to express interest. At this time, Candidates will either come to ICR to sign the informed consent or provide verbal confirmation they intend to sign the ICD the day of the study. When a sufficient number of candidates have expressed interest, and given verbal confirmation they intend to sign the ICD either on a visit to ICR prior to the study, or on the day of the study, recruitment will stop." (V2:24)

The study report says only "Thirteen subjects (7 men and 6 women), all between the ages of 18 and 70, were recruited to participate in this study." (V2:6) It is silent with respect to how candidates were selected from the database, how many were contacted, how many were unavailable or declined to participate, when the recruiting process took place, or any other aspects of the conduct of the recruiting and subject selection process. It is thus not possible to determine with confidence how closely the process actually employed corresponded to that defined in the protocol. The very short time lapse between initial contacts and actual study execution suggests that some steps in the process described in the protocol may have been left out.

In its May 21 response to EPA's E-mail request for clarification of the sequence of events in the recruiting process, toXcel explained:

"The final ICD [Informed Consent Document] was available on February 25th. However, ICR started calling people to determine their potential availability for the study on February 18-19, 2008. On February 26, 2008 (the day after receipt of the final ICD) those people that indicated their likely availability were contacted by phone to confirm their availability for this study. The ICD "phone script" was read to each person that confirmed their availability and each potential subject was invited during that call to come to ICR to go over the ICD in detail with ICR staff. If a potential subject decided not to take advantage of that offer to go over the ICD at ICR prior to the study date, they were notified that they should come prepared on the morning of the test to ask any questions and sign the consent form in order to participate in the study. Consent packages were mailed out to all but three potential subjects who could not receive the packages prior to the study date. All potential subjects agreed to go over the ICD, get any questions they might have addressed, and to being prepared to sign the consent on the day of the test. All subjects signed the consent form on the day of the study, March 4, 2008."

EIRB, Inc., notified ICR of its approval of the revised consent form by letter of February 26 (V2:94), over a week after recruitment was initiated on February 18-19. It is not clear whether the as-yet unapproved consent form was actually discussed with the candidates during the initial telephone conversation. If it was discussed with them during the initial telephone interview, it was not approved by the IRB at the time; if it was not discussed, that would have been a deviation from the protocol. It is also unclear what version of the consent form was mailed to all but three of the subjects, or when it was mailed.

The protocol was also unclear concerning the precise number of subjects to be recruited. It reads in part:

> "The number of subjects required to achieve an estimated among-subjects standard deviation of 2.0 hours at a 95% confidence level for an 8 hour complete protection time was calculated to be between 10 and 11 subjects. This study, therefore, will use twelve treated test subjects. There will be an additional control subject, plus two additional treated test subjects to replace anyone that either drops out or is ineligible to participate due to a positive pregnancy test or other unforeseen circumstances. These additional two treated test subjects will help to ensure a minimum 'n' of ten and will aid in protecting the privacy of any subject who drops out." (V2:24)

One possible reading of this passage is that the intention was to recruit 15 subjects: 12 treated subjects, plus "an additional control subject, plus two additional treated test subjects." In its May 21 response to EPA's E-mail request for clarification of the number of alternate subjects recruited, however, toXcel explained:

> "Yes, the two extra subjects were recruited to serve as alternates. The target number of subjects was 10. Since there were no drop outs, all 12 available subjects were evaluated."

Accepting this explanation, there appears to have been no deviation in this aspect of recruitment and subject selection.

3. **Risks to Subjects:** Risks of four kinds are discussed in the protocol and consent form: the risk of discomfort from the heat and humidity in the laboratory, the risk of a reaction to the tested repellents, the risk of a reaction to mosquito bites or probes, and the risk of contracting an arthropod-borne disease.

    - Discussion of the risk of discomfort from high temperature and humidity in the testing environment was added to the protocol and consent form at the suggestion of the HSRB. This risk is minimized through limiting exposures to 5-minute intervals every half hour, and by monitoring subjects for reactions to elevated temperatures.

    - Risks of reaction to the repellents were reduced by excluding candidates with known sensitivity to repellents or skin care products, by ensuring an

ample margin of exposure for the applied dose, and by monitoring subjects closely for reactions. The description of this risk was revised in the consent form consistent with EPA and HSRB recommendations.

- Risks of reactions to mosquito bites or probes were reduced by excluding candidates known to be "unduly sensitive" to them, by intermittent exposure of only a small area of treated skin, by minimizing the number of untreated control subjects, and by exposing the untreated control subject only long enough to confirm continued mosquito landing pressure. A reference to the testing of all subjects for attractiveness to mosquitoes was added to the consent form as recommended by the HSRB.

- As recommended by EPA and HSRB, a new passage was added to the consent form characterizing the mosquito species used for the test as capable of transmitting WNV in the field. The risk of contracting a disease from these laboratory-reared and disease-free insects was accurately characterized as zero.

4. **Benefits:** The consent form states that participating in the research will be of no benefit to subjects, and acknowledges a potential societal benefit. The 2/8/08 draft consent form reviewed by EIRB, Inc., also acknowledged the likely benefit to the study sponsors; EIRB, Inc., directed that this be deleted, without explanation. The protocol as approved by EIRB, Inc., acknowledges that the sponsor will gain the most direct benefit from the research. References to the benefit of bringing new products to market were deleted from the protocol discussion of benefits after the HSRB meeting in October.

5. **Risk/Benefit Balance:** An improved discussion of the balance of risks and benefits was added to the protocol after the HSRB meeting in October. Because this research offers no direct benefits to the subjects, its justification depended on the anticipated benefits to society from the information likely to be gained. The risk to subjects was very low, and outweighed by the societal benefit associated with identifying registered repellents which are effective against *Culex* mosquitoes that can transmit WNV.

6. **Independent Ethics Review:** Oversight of this research was by the Essex Institutional Review Board, Inc., (EIRB, Inc.) of Lebanon, NJ. EIRB, Inc., is registered with the federal Office of Human Research Protections (OHRP), but does not hold a Federal-Wide Assurance. Although the protocol and study report assert that EIRB, Inc., is accredited by PHRP, EIRB does not appear among the accredited organizations listed on the PHRP website (www.phrp.org). The protocol also asserts that EIRB, Inc., "is in the process of obtaining accreditation from AAHRPP," but as of this writing EIRB, Inc., is not on the list of accredited organizations on the AAHRPP website (www.aahrpp.org). AAHRPP does not identify entities for which accreditation is pending. The reported status of accreditation of this IRB has not changed for over a year.

The protocol and consent form were revised after the October HSRB meeting and the January 14 meeting with EPA, and submitted to EIRB, Inc., on February 14. EIRB, Inc., reviewed them in a convened meeting on February 18, 2008. At that meeting the protocol was approved without comment, and the consent form was conditionally approved, with requests for numerous changes.

Requested changes to the consent form included deleting two sentences, making 14 minor editorial changes (one of which failed to correct an obvious error), and adding four passages of standard language, one of which—the new section titled "Research Participation Information"—refers subjects to organizations and websites for more information, none of which is likely to be useful to the subjects of or relevant to this research.

A further amended consent form dated February 20 responded to all EIRB requests for changes with the exception of the request to change the text from "a potentially important public health pest" to "a noxious pest."

The letter from EIRB, Inc., notifying ICR of approval of both the protocol and consent form was issued on February 26. It confirmed previous e-mail notification of approval of the protocol on February 18, and reported approval of the consent form on February 25.

Minutes of the EIRB, Inc., meeting of Feb 18, 2008 do not explain the basis or rationale for any of the changes requested in the consent form. It is not clear whether approval of the revised consent form on February 25 was by the Chairman only, or by the full Board; in any event, no minutes of an EIRB meeting on February 25 were provided.

7. **Informed Consent:** The study reports include two versions of the consent form—the version of 2/8/08, extensively revised after the HSRB's October meeting and submitted to the EIRB on February 14 (V3:11-20), and the further revision of 2/20/08 approved by the EIRB on February 25 (V2:53-64). The final approved consent form satisfied the applicable requirements of 40 CFR §26.1116 and §26.1117.

   The processes of recruiting and informing candidates and seeking their consent are described acceptably in the revised protocol, and were clarified in response to the recommendations of EPA and the HSRB. It is not clear, however, that these processes were executed as described in the protocol; this is addressed in section E(2) above.

8. **Respect for Subjects:** Methods proposed for managing information about prospective and enrolled subjects protected their privacy from compromise. Data forms providing for subject signature were revised before use, as recommended by EPA and the HSRB.

## F. Compliance with Applicable Ethical Standards

This was third-party research involving intentional exposure of human subjects to a pesticide, conducted with the intention of submitting the resulting data to EPA under the pesticide laws. Thus the primary ethical standards applicable to this proposal are 40 CFR 26, Subparts K and L. In addition, the requirements of FIFRA §12(a)(2)(P) for fully informed, fully voluntary consent of subjects apply.

40 CFR 26 Subpart L, at §26.1703, as amended effective August 22, 2006, provides in pertinent part:

> EPA shall not rely on data from any research involving intentional exposure of any human subject who is a pregnant woman (and therefore her fetus), a nursing woman, or a child.

All subjects were reported to be at least 18 years old. The report is silent with respect to the pregnancy or nursing status of the six female subjects, but pregnant or nursing females were excluded from participation by the protocol. Assuming compliance by the investigators with this exclusion, §26.1703 does not forbid EPA to rely on this study.

40 CFR 26 Subpart L, at §26.1705, provides in pertinent part:

> . . . EPA shall not rely on data from any research initiated after April 7, 2006, unless EPA has adequate information to determine that the research was conducted in substantial compliance with subparts A through L of this part

It was inconsistent with the protocol to initiate recruitment of subjects before the overseeing IRB approved the consent form. Since no subject signed a consent form unapproved by the IRB, it is less clear that this early start on recruitment rises to the level of substantial noncompliance with EPA's rule. EPA welcomes the advice of the HSRB on this question.

Attachments:

1. §26.1303 Criteria for Completeness of Reports of Human Research
2. Chronology of ICR A117

## § 26.1303 Submission of Completed Human Research for EPA Review
## ICR Protocol No: A117: MRIDs 47397701 and 47413801

Any person who submits to EPA data derived from human research covered by this subpart shall provide at the time of submission information concerning the ethical conduct of such research. To the extent available to the submitter and not previously provided to EPA, such information should include:

| | Requirement | | Y/N | Comments/Page References |
|---|---|---|---|---|
| (a) Copies of all of the records relevant to the research specified by §26.1115(a) to be prepared and maintained by an IRB | §1115(a)(1): Copies of<br>• all research proposals reviewed,<br>• scientific evaluations, if any, that accompany the proposals,<br>• approved sample consent documents,<br>• progress reports submitted by investigators, and reports of injuries to subjects. | | Y<br>n/a<br>Y<br>n/a | V2:9-51; V3:10-20<br><br>V2:53-64 |
| | §1115(a)(2): Minutes of IRB meetings which shall be in sufficient detail to show<br>• attendance at the meetings;<br>• actions taken by the IRB;<br>• the vote on these actions including the number of members voting for, against, and abstaining;<br>• the basis for requiring changes in or disapproving research;<br>• a written summary of the discussion of controverted issues and their resolution. | | <br>Y<br>Y<br>Y<br><br>N<br>N | V3:36-37<br><br><br><br><br>Basis for requiring changes not reported.<br>No controverted issues. |
| | §1115(a)(3): Records of continuing review activities. | | n/a | |
| | §1115(a)(4): Copies of all correspondence between the IRB and the investigators. | | Y | V2:90-94; V3:21-35 |
| | §1115(a)(5):<br>• A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations;<br>• any employment or other relationship between each member and the institution, for example, full-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant. | | Y<br><br><br><br>Y | V3:38-40<br>Experience sufficient to describe each member's anticipated contributions not reported<br>V3:40 |
| | §1115(a)(6): Written procedures for the IRB in the same detail as described in § 26.1108(a) and § 26.1108(b). | | N | Previously submitted directly to EPA under claim of confidentiality |
| | §1115(a)(7): Statements of significant new findings provided to subjects, as required by § 26.1116(b)(5). | | n/a | |
| (b) Copies of all of the records relevant to the information identified in §26.1125(a)-(f) | §1125(a) A discussion of: | (1) The potential risks to human subjects; | Y | V2:20-22 |
| | | (2) The measures proposed to minimize risks to the human subjects; | Y | V2:20-22 |
| | | (3): The nature and magnitude of all expected benefits of such research, and to whom they would accrue; | Y | V2:22 |
| | | (4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and | Y | V2:17 |
| | | (5) The balance of risks and benefits of the proposed research. | Y | V2:22-23 |
| | §1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB. | | Y | Original: V3:10-20<br>Approved: V2:53-64 |
| | §1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used. | | Y | V2:14-15; 24-25 |
| | §1125(d): A description of the circumstances and methods proposed for presenting information to potential human subjects for the purpose of obtaining their informed consent. | | Y | V2:14-15; 24-25 |
| | §1125(e): All correspondence between the IRB and the investigators or sponsors. | | Y | V2:90-94; V3:21-35 |
| | §1125(f): Official notification to the sponsor or investigator, in accordance with the requirements of this subpart, that research involving human subjects has been reviewed and approved by an IRB. | | Y | V2:93-94 |
| (c) Copies of sample records used to document informed consent as specified by §26.1117, but not identifying any subjects of the research | | | Y | V2:53-64 |
| (d) If any of the information listed in paragraphs (a) through (c) of this section is not provided, the person shall describe the efforts made to obtain the information. | | | n/a | |

# Chronology of ICR A117

| | |
|---|---|
| 8 Aug 07 | Initial submission of ICR protocol A117 to EPA |
| 24 Sep 07 | EPA Science & Ethics Review of ICR protocol A117 |
| 17 Oct 07 | toXcel response to EPA review |
| 26 Oct 07 | HSRB discussion |
| | |
| 4 Jan 08 | ICR submit revised statistical analysis plan for informal EPA review |
| 10 Jan 08 | ICR submit revised protocol (1/3/08) and consent form (1/4/08) for informal EPA review |
| 10 Jan 08 | HSRB issues draft final report of October 2007 meeting |
| 14 Jan 08 | ICR, Avon, & others meet with EPA to discuss revisions |
| 16 Jan 08 | EPA comments on revised protocol and consent form |
| | |
| 8 Feb 08 | ICR further revises protocol and consent form |
| 14 Feb 08 | ICR submits revised protocol and consent form to EIRB, Inc. for review |
| 18 Feb 08 | EIRB. Inc. reviews and approves 2/8/08 protocol; reviews and conditionally approves 2/8/08 consent form, but calls for numerous changes |
| 20 Feb 08 | ICR revises consent form per EIRB, Inc., comments |
| 25 Feb 08 | EIRB, Inc., approves 2/20/08 consent form |
| 26 Feb 08 | EIRB, Inc., notifies ICR of approval |
| | |
| 18 Feb 08 | ICR begins recruitment of subjects |
| 4 Mar 08 | All subjects sign consent form |
| 4 Mar 08 | Study test day at ICR |
| 6 Mar 08 | HSRB issues final report of October 2007 meeting |
| 14 Mar 08 | Change in dosing regimen reported to EIRB, Inc., as deviation from protocol |
| 18 Mar 08 | Study Director reported making follow-up calls to subjects |
| 4 Apr 08 | Reported completion date of study |
| 9 Apr 08 | Submission of final report and supplement |
| | |
| 19 May 08 | EPA E-mail request for clarification |
| 21 May 08 | toXcel response to EPA request for clarification |

Note that the title page of the final report (MRID 47397701) shows the "Study Initiation Date" as 25 July 07, an obvious error.