UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

March 15, 2007

MEMORANDUM:

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Ethics Review of a Completed Human Study of Dermal Irritation of Two Repellent Products

FROM: John M. Carley
Human Research Ethics Review Officer

TO: Linda Hollis, Chief
Biochemical Pesticide Branch

REF: Georgeian, K.; Dosik, J. (2005) Primary Irritation Patch Study Supplemented with Additional Supporting Materials Satisfying 40 CFR §26.1303 for [Repellent Code] 1000718-008, concentrate of 1000718-009. Unpublished study prepared by TKL Research, Inc. under Project No. DS200105-1. 100 p. MRID 47077101.

Kelley, J.; Reynolds, M. (2007) Supplemental Information: Response to Agency Comments Regarding Human Skin Patch Studies Under Review by the Human Studies Review Board. Unpublished document prepared by toXcel, LLC, to supplement previous submissions concerning TKL Research, Inc., Project Nos. DS200105-1, DS200105-3, DS104005/104105-1, and DS104005/104105-2. 12 p. MRID 47077201.

Georgeian, K.; Dosik, J. (2005) Primary Irritation Patch Study Supplemented with Additional Supporting Materials Satisfying 40 CFR §26.1303 for [Repellent Code] 1004006-005. Unpublished study prepared by TKL Research, Inc. under Project No. DS200105-3. 100 p.

Kelley, J.; Reynolds, M. (2007) Supplemental Information: Response to Agency Comments Regarding Human Skin Patch Studies Under Review by the Human Studies Review Board. Unpublished document prepared by toXcel, LLC, to supplement previous submissions concerning TKL Research, Inc., Project Nos. DS200105-1, DS200105-3, DS104005/104105-1, and DS104005/104105-2. 12 p. MRID 47077601.

I have reviewed the documents referenced above, all of which taken together document a single execution using a single human panel of a single protocol for assessing the skin irritation potential of five repellent materials. The primary reports cited above include results for two of the five materials tested concurrently in the same panel of subjects. No information is available to EPA concerning the other three materials. Supplemental MRIDs 47077201 and 47077601 are identical in content, but were submitted separately, identified with each of the two test materials.

This review characterizes the ethical conduct of the research relative to ethical standards prevailing when the study was performed in 2005.

Background

The subject studies were initially submitted to EPA in May, 2006, unaccompanied by the documentation of ethical conduct required by 40 CFR §26.1303. In response to EPA's request, the studies were resubmitted in November, 2006, with the required documentation. At the time of the November resubmission, the submitter registered supplemental claims of confidentiality for many identifying elements in the studies. EPA concluded that these claims were insupportably broad, and after the submitter narrowed the scope of confidentiality claims, corrected redacted versions of both studies were submitted in February, 2007—these are the primary entries cited above. In addition, redacted versions of the submitter's responses to specific EPA questions concerning these studies were submitted separately on March 2, 2007, and are also cited above.

Completeness of Submissions

40 CFR §26.1303 provides that "[a]ny 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." The rule goes on to list the specific kinds of information required.

The initial submissions in May, 2006 occurred after the effective date of this rule, but the required information was not provided "at the time of submission." Pages 46-100 of the revised submissions were appended to address this requirement after EPA called it to the submitters' attention. EPA's assessment of the completeness of these submissions is based on a review of the complete, non-redacted November resubmissions. It appears as Attachment 2 to this review.

In summary, most of the documentation requirements of §26.1303 have been addressed well enough to support review. The weakest aspect of documentation is the "discussions" of

potential risks to subjects, risk minimization, the nature and distribution of benefits, alternatives to the research, and the balance of risks and benefits. On pp. 47-49 the submitters direct attention to the Informed Consent document and one page of the recruiter's telephone script as the location of these discussions; these are inadequate to meet the intention of the rule, but are apparently all that is available.

Summary Assessment of Ethical Conduct of the Research

Attachment 1 to this review applies the "Framework for Ethical Assessment" developed by the EPA Science Policy Committee's Human Studies Work Group. The detailed observations recorded in the attachment are summarized in the narrative review below.

1. **Value of the Research to Society**: The purpose of the research was "[t]to determine the ability of [two] experimental insect repellent product[s] . . . to cause an immediate irritation by topical application to the skin of humans under controlled patch study conditions." The sponsor of this research, as a matter of corporate policy, avoids "unnecessary use of animals in testing," and has submitted this as a substitute for animal testing of dermal irritation as is normally required by EPA. If it is considered scientifically acceptable, this work could provide a basis for classification and labeling of the tested products.

2. **Scientific Validity of the Research**: I defer to others for a full review of the scientific validity of this study. If it were determined not to have scientific validity, it would also not be ethically acceptable.

3. **Subject Selection**: 54 subjects were enrolled in the study. One was lost to followup; 53 completed the study. Subjects included 8 males and 46 females, ranging in age from 19-71. Pregnant or nursing women were excluded. Three subjects were Hispanic, one was Black, and the rest were White. The sampling frame from which subjects were selected included prior subjects in tests conducted by this laboratory and others referred to the lab by prior or current subjects. Recruiting focused on subjects just completing a previous test, who were already at the laboratory; this served the convenience of the investigators but does not appear to have been related to the goals of the study. Compensation was low enough to attract primarily economically disadvantaged subjects. Otherwise there is no indication that subjects were from susceptible groups.

4. **Risks and Benefits**: Subjects were told that "Some of the materials may be irritating under certain conditions, but the degree of irritation is not expected to be greater than . . . . redness, swelling, itching, cracking, peeling, or in rare cases, small blisters or sores. . . . On rare occasions the reactions may spread beyond the patch. A reaction may result in localized lightening or darkening of the skin, which may persist. . . . Reactions may be due to either skin irritation or allergy to either study materials or patch materials."

There is potential social benefit in establishing the irritation potential of proposed repellent products intended for direct and repeated application to the skin. Such products should be essentially non-irritating. Because this test method may not identify weak irritants, its adequacy to substitute for the normally required animal testing is unclear. Although there is a small risk of lasting effects on the subjects, including allergenicity, this type of study is commonly conducted for cosmetics and other consumer products, and if this research is determined to satisfy the registration requirement for irritation testing, it is probably justifiable. A new proposal for similar research would require stronger justification than is documented for this completed research, which was initiated before the effective date of EPA's rule.

5. **Independent Ethics Review**: This work was overseen by the Allendale Investigational Review Board of Allendale NJ. This IRB is registered with OHRP, but is not known to be accredited. Compliance with FDA rules essentially equivalent to the Common Rule was asserted with respect to "clinical research studies performed by TKL," but not specifically with respect to this study. The documentation submitted concerning the IRB review meets regulatory requirements.

6. **Informed Consent**: Written informed consent was reported to have been obtained from all subjects. Although it could have been much clearer and more informative, the informed consent document was approved by the IRB before subjects were recruited. The process described for soliciting interest among "subjects that were completing a study at TKL Research" suggests over-reliance on habitual test subjects, and a primary concern of both subjects and investigators with establishing subject eligibility, rather than informing them.

7. **Respect for Potential and Enrolled Subjects**: Subject privacy was respected in study reports. Subjects were told they were free to withdraw, but were also told they would only be paid if they completed the study. Subjects were also encouraged in the telephone script to refer others to the laboratory as potential candidates, with a promise of a finder's fee if the referral completed a study at the lab. Tying payment to completion compromised subject freedom to withdraw.

Applicable Ethical Standards

Because this research was initiated before April 7, 2006—the effective date of EPA's rule governing third-party human research for pesticides—prior submission of the protocol and supporting materials to EPA was not required. Because this research was submitted to EPA after the effective date of the rule, the requirement of 40 CFR §26.1303 for documentation of ethical conduct did apply.

Again because this research was initiated before the effective data of the rule, the general standard for acceptance is that of 40 CFR §26.1704, which provides in pertinent part:

> EPA shall not rely on data from any research initiated before April 7, 2006 if there is clear and convincing evidence that the conduct of the research was fundamentally unethical (*e.g.*, the research was intended to seriously harm participants or failed to obtain informed consent), or was significantly deficient relative to the ethical standards prevailing at the time the research was conducted.

In addition, without regard to when the research was initiated, §26.1703 of the final rule, 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.

I have applied the standards in sections 26.1704 and 26.1703 in arriving at the conclusions below.

Compliance with Ethical Standards Prevailing when the Research Was Conducted

Prevailing ethical standards for this type of research when it was conducted in 2005 were the Common Rule (45 CFR Part 46; 40 CFR Part 40, subpart A) and the essentially equivalent rules of the US Food and Drug Administration (21 CFR Parts 50 and 56). The latter are cited in the protocol and the study reports. The fundamental requirements of these rules are for independent ethics oversight by an Institutional Review Board and fully informed, fully voluntary consent of subjects.

This research was reviewed and approved in advance by the Allendale Investigational Review Board of Allendale NJ. The AIRB is registered by OHRP. It is not known to be accredited by AAHRPP or another accrediting organization.

Notwithstanding the oversight and approval by the AIRB, some ethical concerns arise when this research is reviewed against Common Rule standards:

- The population from which subjects were drawn appears to have been identified entirely for the convenience of the investigators.

- The level of compensation was so low as to likely make participation attractive only to economically disadvantaged subjects.

- Compensation was provided only to subjects who completed the research, compromising subjects' freedom to withdraw.

- The possibility of lasting effects—including changes in skin coloration or allergenicity—was acknowledged in the informed consent document, but only "appropriate and

reasonable medical treatment . . . to relieve the immediate problem" was promised, and then only for undefined "significant reactions."

- The possibility that participation could induce allergy was acknowledged, as well as that "you can expect to react to this material if you encounter it at a later date," but the commitment to tell subjects what they'd reacted to was qualified by the words "whenever possible."

- The discussion of HIPAA information in the informed consent document includes mention of identification of subjects by Social Security Number; this is not health information, and no reason for collecting it is offered.

- Given that the test materials were intended for frequent and repeated skin contact, it would be expected that they would be unlikely to cause significant skin irritation. Yet the protocol states that the method, while able to screen "strong irritants", is not appropriate to identify weaker irritants. This calls into question the appropriateness of the method for the stated purpose.

Conclusions

There are some gaps in the documentation of the ethical conduct of this study, especially with respect to thoughtful consideration of risks and benefits of the research. Yet there is no clear and convincing evidence that the research was intended to harm participants, or that it was fundamentally unethical in other ways. Deficient documentation does not itself constitute evidence that the ethical conduct of this research was deficient, and this research was conducted before these discussions were required by regulation.

From the documentation available I have concluded that the research did not involve intentional exposure of any subjects who were pregnant or nursing women or children. Reliance on it is therefore not prohibited by §26.1703. I have also identified several concerns relative to ethical standards prevailing when it was conducted. Without question, a proposal for similar new research involving a pesticide would require much clearer justification than is provided here. Nonetheless, primarily because this type of testing is widely used for consumer products not regulated as pesticides, if it is deemed to be scientifically acceptable, in my judgment there is not clear and convincing evidence that the ethical conduct of this research was significantly deficient relative to the ethical standards prevailing at the time it was conducted.

Attachments:

1. Framework for Ethical Assessment
2. §26.1303 completeness check

Framework for Ethical Assessment

March 13, 2007

Georgeian, K.; Dosik, J. (2005) Primary Irritation Patch Study Supplemented with Additional Supporting Materials Satisfying 40 CFR §26.1303 for [Repellent Code] 1000718-008, concentrate of 1000718-009. Unpublished study prepared by TKL Research, Inc. under Project No. DS200105-1. 100 p. MRID 47077101.

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1. Value to Society: The purpose of the research was "[t]to determine the ability of [two] experimental insect repellent product[s] . . . to cause an immediate irritation by topical application to the skin of humans under controlled patch study conditions." The sponsor of this research, as a matter of corporate policy, avoids "unnecessary use of animals in testing," and has submitted this as a substitute for animal testing of dermal irritation as is normally required by EPA. If it is considered scientifically acceptable, this work could provide a basis for classification and labeling of the tested products.

a. What was the stated purpose of the research?
"[t]to determine the ability of [two] experimental insect repellent product[s] . . . to cause an immediate irritation by topical application to the skin of humans under controlled patch study conditions." (p. 11)

b. Does it evaluate a diagnostic or therapeutic intervention that could lead to improvements in health or well-being?
No.

c. Does it test a hypothesis that can generate important knowledge about human biology?
No explicit hypothesis is stated. "This evaluation method will screen out strong irritants. It will not, however, detect weaker irritants that require multiple exposures to produce a positive reaction." (p. 11)

d. How will society benefit from the knowledge gained from this research?
If deemed scientifically acceptable, the results of this research may serve as the basis for classification and labeling of the tested products.

e. What government, organization, company and/or institution(s) funded the research?
The Sponsor has asserted a claim of confidentiality covering its identity, to guard against potential disclosure to competitors of its product development and marketing plans.

2. Scientific Validity: I defer to others for this assessment. If the study is concluded not to be scientifically valid, it would not be ethically acceptable.

a. Did the research have a clear scientific objective?
See 1(a) above

b. Was the research designed using accepted principles, methods, and reliable practices?
The design is generally consistent with Safety Testing Guidelines of the Cosmetic, Toiletry, and Fragrance Association. (See pp. 39-44). EPA does not have a guideline for human testing of acute dermal irritation.

c. In what way were human subjects exposed in this research, and what endpoints were identified or measured?
"Study material was applied to patch as instructed. Patches were applied to the infrascapular area of the back, either to the right or left of the midline. . . . Material evaluated under occlusive patch conditions was applied to a 2-cm x 2-cm Webril pad attached to a non-porous plastic film adhesive bandage (3M medical tape). The patch was secured with hypoallergenic tape (Micropore) as needed." (p. 14) "The study extended over a 4-day period. On Day 1, the patches were applied to the designated sites. Forty-eight hours after application the patches were removed. The sites were evaluated 48 and 72 hours after application. A subject with a response at patch removal was required to wait . . . for re-evaluation." (p. 12) Observations were made for erythema, edema, and vesiculation.

d. Did the research design have sufficient statistical power to definitively test the objective?
I defer to others for this assessment

e. To what purpose is the study used, or proposed for use?
To satisfy the requirement for an acute dermal irritation study for each product for which registration is sought.

3. Fair Subject Selection: 54 subjects were enrolled in the study. One was lost to follow-up; 53 completed the study. Subjects included 8 males and 46 females, ranging in age from 19-71. Pregnant or nursing women were excluded. Three subjects were Hispanic, one was Black, and the rest were White. The sampling frame from which subjects were selected included prior subjects in tests conducted by this laboratory and others referred to the lab by prior or current subjects. Recruiting focused on subjects just completing a previous test, who were already at the laboratory; this served the convenience of the investigators but does not appear to have been related to the goals of the study. Compensation was low enough to attract primarily economically disadvantaged subjects. Otherwise there is no indication that subjects were from susceptible groups.

a. Were the groups and individuals recruited and enrolled determined solely on the basis of the scientific goals of the study?
Subjects were recruited from among prior subjects of the testing laboratory, as they completed a previous test. (p. 61) Candidates were also encouraged to refer others, and were promised a finder's fee for any subjects they referred who completed a study. (p. 64) The scientific goals of the study were not considered in choosing these methods for recruitment. Inclusion and exclusion factors were generally appropriate, and excluded pregnant or nursing women and anyone under 18.

b. Were any subjects from susceptible groups, such as children, prisoners, the infirm, or impoverished? Did the burden of participation fall disproportionately on a particular group?
All subjects made three visits to the laboratory over a period of four days, for a total "financial incentive" of $30. They could earn $25 more as a finder's fee for referral of a new subject who completed the test. This level of compensation appears to be low enough to be attractive only to economically disadvantaged candidates/subjects.

c. Were any subjects under 18? Pregnant? Nursing?

Children and pregnant or nursing women, or women who planned to become pregnant, were excluded. (p. 34)

d. What compensation was paid to the participants?

"You will be paid a sum of $30.00 dollars upon completion of the study. If in the judgment of the investigative personnel it is best to discontinue your participation in this study due to an adverse experience or severe reaction you will be paid in full for your participation. If you are dismissed for refusal to obey rules or follow instructions you will not be paid." (p 27)

4. Risks and Benefits: Subjects were told that "Some of the materials may be irritating under certain conditions, but the degree of irritation is not expected to be greater than . . . . redness, swelling, itching, cracking, peeling, or in rare cases, small blisters or sores. . . . On rare occasions the reactions may spread beyond the patch. A reaction may result in localized lightening or darkening of the skin, which may persist. . . . Reactions may be due to either skin irritation or allergy to either study materials or patch materials."

There is potential social benefit in establishing the irritation potential of proposed repellent products intended for direct and repeated application to the skin. Such products should be essentially non-irritating. Because this test method may not identify weak irritants, its adequacy to substitute for the normally required animal testing is unclear. Although there is a small risk of lasting effects on the subjects, including allergenicity, this type of study is commonly conducted for cosmetics and other consumer products, and if this research is determined to satisfy the registration requirement for irritation testing, it is probably justifiable. A new proposal for similar research would require stronger justification than is documented for this completed research, which was initiated before the effective date of EPA's rule.

a. What were the risks to subjects?
Subjects were told that "Some of the materials may be irritating under certain conditions, but the degree of irritation is not expected to be greater than . . . . redness, swelling, itching, cracking, peeling, or in rare cases, small blisters or sores. . . . On rare occasions the reactions may spread beyond the patch. A reaction may result in localized lightening or darkening of the skin, which may persist. . . . Reactions may be due to either skin irritation or allergy to either study materials or patch materials." (p. 26)

b. How were the risks to individual subjects minimized?

Subjects with visible skin disease, who were using systemic or topical drugs that might interfere, who had psoriasis or atopic dermatitis or eczema, or who were pregnant, nursing, or planning to become pregnant, or who were known to be sensitive to cosmetics, skin care products, insect repellents, or topical drugs related to the materials being evaluated were excluded. (pp. 11-12)

c. What are the societal benefits in terms of knowledge to be gained from the study, and do these justify the excess risk to individual subjects?
There is social benefit in establishing the irritation potential of proposed repellent products intended for direct and repeated application to the skin. Such products should be essentially non-irritating. Because this test method may not identify weak irritants, its adequacy to substitute for the normally required animal testing is unclear. Submitters note that "[a]voidance of the unnecessary use of animals in testing is specifically included in this registrant's corporate policy and consistent with the EPA's position. . . . This type of human patch test is very common and is used regularly to confirm the non-irritant nature of substances intended for direct application to skin." (p. 49) Although there is a small risk of lasting effects on the subjects, including allergenicity, the risk to subjects is relatively low, and if this research is determined to satisfy the registration requirement for irritation testing, it is probably justified. A new proposal for similar research would require stronger justification than is documented for this pre-rule completed research.

5. Independent Ethics Review: This work was overseen by the Allendale Investigational Review Board of Allendale NJ. This IRB is registered with OHRP, but is not known to be accredited. Compliance with FDA rules essentially equivalent to the Common Rule was asserted with respect to "clinical research studies performed by TKL," but not specifically with respect to this study. The documentation submitted concerning the IRB review meets regulatory requirements.

a. Was the research asserted to have been overseen by an ethics review body?
Yes—by the Allendale Investigational Review Board of Allendale NJ.

b. Was the research subject to independent ethics review by individuals unaffiliated with the clinical research?
The members of the AIRB are unaffiliated with the sponsor or the performing laboratory.

c. Was the research asserted to comply with the Common Rule?
The QA unit of TKL Research, Inc., asserts (p. 6) that "[c]linical research studies are performed by TKL in accordance with federal regulations and proposed guidelines for good clinical practices which include: 21 CFR Part 312, . . . 21 CFR Part 50, . . . 21 CFR Part 56."

d. Does/did the research institution (or any institution participating in the research) hold a Federal Wide Assurance or Multi-Project Assurance during the period of the study?
No participating organization is listed on the OHRP website as holding a FWA

6. Informed Consent: Written informed consent was reported to have been obtained from all subjects. Although it could have been much clearer and more informative, the informed consent document was approved by the IRB before subjects were recruited. The process described for soliciting interest among "subjects that were completing a study at TKL Research" suggests over-reliance on habitual test subjects, and a primary concern of both subjects and investigators with establishing subject eligibility, rather than informing them.

a. Does the research assert that informed consent was obtained from participants?
Yes

b. How and under what circumstances was informed consent obtained?
"Subjects that were completing a study at TKL Research in Paramus were interviewed in private for eligibility. Subjects were then scheduled for an appointment for the start date of this study. Recruiting Services verified in the computerized system the subject's availability and eligibility by entering the subject's permanent TKL number. Anyone who did not meet the study requirements were telephoned and were told of their ineligibility, and canceled from the scheduled." (p. 61) "When potent ional subjects come into TKL Research they are checked-in by the receptionist, all subjects are given the informed consent to read in the waiting room. Then they are brought into the study room and the consent is reviewed with them. They are given the opportunity to ask questions regarding the study and consent. They are given the option of taking the consent home to read and return later if desired. The consent is then signed and dated. . . ." (p. 66)

7. Respect for Potential and Enrolled Subjects: Subject privacy was respected in study reports. Subjects were told they were free to withdraw, but were also told they would only be paid if they completed the study. Subjects were also encouraged in the telephone script to refer others to the laboratory as potential candidates, with a promise of a finder's fee if the referral completed a study at the lab. Tying payment to completion compromised subject freedom to withdraw.

a. Was information about individual subjects managed so as to ensure their privacy?
Yes. Subject privacy was not compromised in the submitted materials.

b. Were subjects free to withdraw from the research without penalty?
"Participation in the study is voluntary and you may refuse to participate or may withdraw at any time without penalty or loss of benefits, other than financial, to which you are otherwise entitled." (p. 26)

§ 26.1303 Submission of Completed Human Research for EPA Review
48-hour Human Irritation Studies

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 • all research proposals reviewed, • scientific evaluations, if any, that accompany the proposals, • approved sample consent documents, • progress reports submitted by investigators, and reports of injuries to subjects.	Y n/a Y Y	pp. 52-60 None pp. 97-98 p. 99
	§1115(a)(2): Minutes of IRB meetings which shall be in sufficient detail to show • attendance at the meetings; • actions taken by the IRB; • the vote on these actions including the number of • members voting for, against, and abstaining; • the basis for requiring changes in or disapproving research; • a written summary of the discussion of controverted issues and their resolution.	Y	p. 85
	§1115(a)(3): Records of continuing review activities.	n/a	
	§1115(a)(4): Copies of all correspondence between the IRB and the investigators.	Y	pp. 50-99
	§1115(a)(5): • 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; • 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	pp. 86-88
	§1115(a)(6): Written procedures for the IRB in the same detail as described in § 26.1108(a) and § 26.1108(b).	Y	89-93
	§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;	N	All these required "discussions" are asserted to be included in the telephone script used by recruiters (p. 62) and the approved ICD (pp. 97-98.) See also pp. 48-49 for additional comments.
	§1125(a) A discussion of: (2) The measures proposed to minimize risks to the human subjects;	N	
	§1125(a) A discussion of: (3): The nature and magnitude of all expected benefits of such research, and to whom they would accrue;	N	
	§1125(a) A discussion of: (4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and	N	
	§1125(a) A discussion of: (5) The balance of risks and benefits of the proposed research.	N	
	§1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.	Y	ICD as submitted to AIRB pp. 67-68; as approved pp. 26-27 and 97-98. Additional information for subjects appears on p. 69.
	§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.	Y	p. 61-69
	§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	p. 66
	§1125(e): All correspondence between the IRB and the investigators or sponsors.	Y	See entry above for §1115(a)(4)
	§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	p. 45, 83-84
(c) Copies of sample records used to document informed consent as specified by §26.1117, but not identifying any subjects of the research		Y	pp. 26-27; 97-98
(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	