OPP Policy Decisions Regarding Insect Repellent Efficacy Testing

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Policy Issues

- Objective of repellent efficacy testing
- Choice of endpoint for repellent efficacy studies
- Statistics & handling of censored data

General Considerations

- Consistency of approach
- History of testing methods/implementation

Issue 1: Objective of Repellent Testing

- Preferred objective is to measure duration of complete protection
- Consistent with market research by both EPA and registrants: Repellent users expect and demand complete protection

Issue 2: Choice of Endpoint

- Preferred study endpoint is first confirmed failure event
- Failure events vary depending on species:
  - Landing (or bite) for mosquitoes and flies
  - Crossing for ticks and chiggers
- Choice of confirmed events as endpoints reduces variability

Issue #3: Statistics & Data Censoring

- Preferred summary statistic is Kaplan-Meier median Complete Protection Time with 95% c.i.
- If K-M median is not calculable, mean CPT with 95% c.i. is acceptable
- Underestimates of mean and variance resulting from treating censored data points as confirmed failure events are acceptable for regulatory purposes

Product Performance Test Guidelines OPPTS 810.3700: Insect Repellents to be Applied to Human Skin

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Role of Guidelines

- Data requirements
  - Defined by regulation
  - Interpreted and applied case-by-case
- Test guidelines
  - Advisory, not mandatory
  - If a particular data requirement is imposed, here's how we recommend you address it
- Standard Evaluation Procedures (SEPs)
- Labeling standards

Assumptions Underlying Guideline

- OPP will continue to require laboratory and field tests of topical repellent efficacy
- Guideline should include standard methods for commonly required types of repellent efficacy testing
- Guideline should serve as a single source for all guidance directly relevant to sponsors and investigators conducting repellent efficacy tests

Events Since October 2008

- HSRB Comments
  - On guideline draft of September 2008
  - On subsequently reviewed protocols and completed studies
- Other Comments
- WHO Repellent Testing Guidelines
- Consumer Research

EPA Response

- Compile all HSRB and other comments
- Use multidisciplinary internal workgroup to analyze comments by topic and issue
- Consult with repellent scientists from USDA
- Identify and resolve policy questions
- Revise guideline within policy framework in response to comments

Scope of This Guideline

- Guideline includes
  - Technical guidance for commonly required standard performance tests for skin-applied repellents
  - What investigators need to know about the Human Studies Rule to prepare protocols and conduct studies likely to be reviewed favorably by EPA and the HSRB
- Guideline does not include technical guidance for
  - Non-standard or rarely performed tests
  - Tests of repellency of impregnated fabrics or clothing
  - Tests of products intended to repel insects from indoor or outdoor spaces

Overall Structure of Guideline

- Introduction and Definitions
- General guidance applying to all repellent studies
  - Developing a protocol
  - Review of protocols
  - Changes to approved protocols
  - Execution
  - Reporting
  - Records retention
- Guidance applying to commonly required tests
- References and Appendices

Commonly Required Standard Tests

- Lab tests to determine typical consumer dose
- Lab tests with mosquitoes
- Lab tests with biting flies
- Field tests with mosquitoes
- Field tests with biting flies
- Lab tests with ticks or chiggers

Changes in this Revision

- Reflection of policy decisions
- Streamlined organization
- Changes in general guidance
  - Study design
  - Statistics
  - Ethics
- Changes in specific guidance

General Guidance: Study Design

- Clarify limited appropriateness of multiple treatments per subject
- Recommend treated subjects not also serve as untreated controls
- Recommend positive controls in all studies (20% deet in ethanol at standard 1 g/600 cm^2 rate)
- Emphasize importance of representative samples
- Recommend testing attractiveness to target pests to qualify subjects

General Guidance: Statistics

- Recommend longer test duration and earliest practical treatment to reduce potential for data censorship
- Revise discussion of sample size
- Revise discussion of analysis plan

General Guidance: Ethics

- Clarify—
  - Prerequisite research
  - Risks of concern are only those associated with participation in research (*vice* background risks)
  - Regulations require benefits discussion and assessment of relation of benefits to risks
  - Subjects from potentially vulnerable populations should not be arbitrarily excluded if special care would provide adequate protection of their safety and welfare
  - Rationale for discouraging distant travel
- Cite Flesch-Kincaid Grade Level as measure of readability
- Call for specifying how investigators will confirm candidate understanding

Specific Guidance: Dose Determination

- Clarify methods—
  - For measuring subject skin area
  - For calculating standard dose
- Identify additional reporting elements

Specific Guidance: Mosquitoes & Flies

- Lab tests: Clarify rearing techniques, cage size, insect density
- Field tests: Clarify subject placement and behavior; revise site-selection criterion for pre-test absence of WNV
- Recommend standard positive control
- Discourage use of treated subjects as untreated controls
- Identify additional reporting elements
- Merge and harmonize M & F guidance

Specific Guidance: Ticks & Chiggers

- Clarify description of recommended method
- Recommend refining definition of "crossing" to suit species and life stage used in testing
- Accept concurrent testing with 2 species
- Clarify rearing techniques, number of ticks, test conditions, subject preparation
- Recommend standard positive controls

Next Steps

- Publish this guideline for immediate use
- Further refine this guideline in response to comments and new developments
- Continue development of additional guidelines:
  - Impregnated materials and space repellents
  - Exposure studies