Regulatory Update on Worker Exposure Studies:

Impact of Expanded Protection for Volunteers in Human Research Studies

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Protection of Human Rights

- The Nuremburg Code (1949)
- Declaration of Helsinki (1964)
- The Belmont Report (1974)

Since 1991, all studies conducted by or supported by the government must comply with the Common Rule.

Studies by third parties should adhere to established ethical guidelines.
Purpose of the “Final Rule”

- Strengthen and expand safeguards on human studies research
- Expand provisions of the Federal Policy for the Protection of Human Subjects of Research (the Common Rule) to cover third party (i.e. registrants) intentional dosing studies submitted to EPA under the pesticide laws
Dec, 2001 – EPA seeks advice from NAS regarding science and ethics issues

May, 2003 – EPA issued plan for developing standards for human research

Aug, 2005 – Legislation passed by Congress appropriating funds to EPA

Sept, 2005 – EPA released draft rules for 90-day public comment

Feb 6, 2006 – Final Rule is published
Feb 6, 2006 Final Rule
Summary

- Added protection in intentional dosing studies
- Prohibits use of children, pregnant and nursing females in intentional dosing studies
  - By third parties submitting data to EPA
  - By EPA
- Established a Human Studies Review Board (HSRB):
  - Provide advice and recommendations to EPA on decisions whether to rely on or reject a human study
  - Review study design and protocols before any new studies are generated
The HSRB: an advisory panel

- ~16 independent ethicists and scientists
- Provide advice, information and recommendations on:
  - Research protocols and proposals
  - Final reports of completed research
  - How to strengthen EPA’s programs for protection of human subjects of research
- Meets approximately 4 times per year
- Public meetings
- Review of science & ethics
**Intentional Dosing Study**

- Exposure to the subject that would not have occurred if the subject were not participating in the study
- Most worker exposure studies fall into this category (scripted)
- "Observational Studies"
  - Exposure or activities or environment are not modified or scripted
  - Data collection does not require any changes
    - Ex: behavioral analysis, activity patterns, surveys
  - No HSRB review, but EPA review
Observational Study

- Cannot change or influence activities:
  - Cannot ask him to use a specific product
  - Cannot ask him to spray more/less acres
  - Cannot ask him to spray at a different rate
  - Cannot ask him to wear/not wear PPE
  - Cannot tell him what day to spray
- Find growers using product
- Timing based on grower’s schedule
- Sampling duration may not be optimum
- Data interpretation may be more difficult
So, what is the impact of the revised Final Rule on our “worker exposure” studies?
New Aspects to Exposure Studies

- Societal value of proposed research
- Study design – justified scientific objective, justified study parameters, statistics
- Subject selection – representativeness, focus groups, define the population, random selection and recruitment
- Risk/benefit analysis*
- Independent ethics review*
- Informed consent* – literacy, language
- Spanish-speaking researcher
- Respect for subjects* – privacy, withdraw, medical care, reimbursement
- Ethics training for all study researchers & SD

*done prior to Feb, 2006
Submissions to HSRB

- **Protocols and supporting materials:**
  - Reports from completed studies
    - At least 75 days before HSRB meeting
  - Submission of documents must be made to EPA for preliminary review prior to going to HSRB
  - EPA must prepare written reviews of the scientific and ethical aspects of the research and provide this to the HSRB along with the protocols & supporting documents
HSRB Meetings

- Public forum, open to public
- Typically last 2 to 4 days
- Overview presentations are made by EPA
- Board deliberations and discussions are based on submitted materials and EPA’s review documents
- Registrants and consultants can only provide information when asked or during public comment periods
Organization of the Submission:

- One submission per study
- Table of contents and continuous pagination

Sections:
  - Scientific research: protocol, SOPs
  - Informed consent process: recruitment process, consent form, recruitment flyer, product risk statements including Spanish translations
  - Ethical oversight: IRB approval, minutes from IRB meetings, IRB & registrant correspondence
  - Reference materials: copies of scientific information cited

- 5 page submission check list (40 CFR 26.1125)
Unique Aspects for Task Forces

- Scenarios (work function or application method) = multiple studies
  - Example: Closed-cab airblast applicator exposure scenario* = 5 studies
    1. Citrus, FL – 5 MUs
    2. Nuts, GA – 5 MUs
    3. Stone fruit, MI – 5 MUs
    4. Pome, WA – 5 MUs
    5. Grapes, CA – 5 MUs
  - One protocol for each site = 5 protocols
  - “Governing document” ties all 5 protocols

*Source: HSRB web site, June 24-25, 2008 Public Meeting
June 24-25, 2008 HSRB Meeting

- Closed-cab airblast applicator exposure
  - 2 protocols: pecans & citrus (5 MUs each)
  - 9 volumes - 2,000 pages
    - Volume I: AHETF Transmittal letter, 40 CFR 26.1125 check lists for both studies, scenario sampling plan for closed cab airblast applicator scenario (52 pages)
    - Volume II: Protocol and supporting documents for Study AHE55 for applications to citrus in Florida (107 pages)
    - Volume III: Protocol and supporting documents for Study AHE56 for applications to pecans in Georgia (108 pages)
    - Volume IV: AHETF revised Governing Document (153 pages)

- Huge time and resource effort!
Reviewed science and ethics of studies
Agreed existing exposure data for airblast applicators are inadequate
Agreed studies present minimal risks
Accepted revised statistical-based sampling design
  • “Hybrid” purposive sampling with random elements
Provided recommendations
Pending revision, protocols were accepted
June 24-25, 2008 HSRB Meeting

- Recommendations *(approx. 40)*
  - Characterization of non-responders
  - Training in survey implementation and cultural sensitivity
  - Use professional survey company
  - Only 1 worker per grower or facility
  - Minimize study restrictions
  - Exclusion of minor uses and crops
  - Explain how reading ability of test subjects will be assessed
Recommendations continued:

- Accuracy of Spanish translation
- Confidentiality regarding photographs
- Stratify by farm size
- Need for over-recruitment
- Simplify the informed consent form
- Counsel pregnant women
- More robust cost justification for departures from probability-based sampling needed
## Summary of HSRB Recommendations for 2 AHETF Protocols

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<th>Recommendation</th>
<th>Count</th>
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<tr>
<td>Address before executing AHE55 &amp; 56</td>
<td>10</td>
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<tr>
<td>Address in new CCAB/OCAB submissions</td>
<td>4</td>
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<tr>
<td>Incorporate in revised SOPs</td>
<td>14</td>
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<td>Address in future scenarios</td>
<td>6</td>
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<tr>
<td>No immediate action required</td>
<td>6</td>
</tr>
<tr>
<td><strong>Total:</strong></td>
<td><strong>40</strong></td>
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Recruitment of Volunteers

- Follows SOPs
- Occurs only after review and approval by IRB, EPA, HSRB, (& CDPR, if needed)
- Grower Universe List generated
  - USDA Census of Agriculture
  - Farm Market ID (farm subsidies)
  - Commercial List Providers
  - State and Local Government Entities
  - Grower Associations (crop and/or region specific)
  - Grower Publication Subscription List
  - Target is minimum of 300 names & phone numbers
- Master Grower List generated
  - 300 names selected randomly from GUL
Recruitment of Volunteers

- Develop the **Qualified Growers List**
  - Calls are made by professional calling company
  - Calls are made in order
  - Script is to determine qualification and interest
    - Crop, farm location, acreage, pesticides used, equipment, # acres per day, # employees
  - 15-20 attempts to reach each grower

- Initiation of contact with employees by SD:
  - Send an approved recruitment flyer
  - Contact by phone
  - On-site visit & recruitment meeting (English or Spanish)
Recruitment results based on systematic calling of 238 numbers from pecan master grower list
Volunteers in Pecan Study

- 21 out of 238 people were both eligible and willing to participate
  - Grew pecans commercially
  - Owned closed-cab airblast sprayer
- Site visits to discuss study, consent form, and study timing
  - Pool decreased from 21 to 9 growers
  - 5 of whom willing to spray week of Aug 18
- Impact of random grower selection!
Bottom-line...

- Approval is much more difficult
- Science and ethics are reviewed
- Justification for study is scrutinized
- Data generated and how it will be used must be defended
- Timeline is longer
- More steps in protocol development
- New SOPs
- Random elements increase expense
  - Identification, selection and recruitment
  - 1 worker per farm or facility
- More expensive – estimate 50% increase
**Bottom-line...**

- HSRB presents large hurdle
- **Human Volunteer Protocols Reviewed:**
  - AHETF (initial 5 protocols rejected 6/06; 8 protocols accepted, 6/08 & 10/08)
  - AEATF (2 protocols accepted, 4/08)
  - To date, no individual ag-chemical registrant has submitted WE protocols for HSRB review
  - **Other registrants:**
    - Avon Products (insect repellent study)
    - DermAegis, Inc. (insect repellent study)
    - Lanxess Corp. (insect repellent study)
Conclusions

- The obvious: less worker exposure studies!
- More likely to be **observational studies**
  - Impact on field CRO:
    - Likely longer field phase duration
    - Less structured timing of monitoring
    - More days in field; more down days
    - Closer coordination with sponsor field R&D and sales staff
    - Anticipate more sampling days to achieve goal
    - Many aspects of HSRB will be incorporated in study design
    - Flexibility required!
Thank-you!