HSRB Criteria for Review of Pre-Rule Intentional Dosing Studies

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June 24, 2009

Background - Science

- At its May 2006 meeting, the HSRB established the following points of consideration for scientific review of pre-Rule studies:
  - Justification;
  - Dose Selection;
  - Endpoint Selection;
  - Participant Selection;
  - Methodology; and
  - Statistical Analyses.

Background - Science (2)

- HSRB definition of single dose level studies:

  An individual study that uses one dose level irrespective of the number of subjects, frequency of dosing or inclusion of a control or placebo.

- The Board concluded that single dose level studies have limited utility.
- Single dose level studies cannot be used in isolation to establish a NOAEL or LOAEL.

Background - Science (3)

- A single dose level study may be useful if it:
  - Is interpreted within the context of additional studies that provide information at other dose levels *under analogous conditions*.
  - Provides evidence of adverse effects observed at lower levels than other studies have indicated.
- Its utility will depend upon the robustness and rationale of study design.

Background - Ethics

- 40 CFR 26 Subpart Q - Ethical Standards for Assessing Whether To Rely on the Results of Human Research in EPA Actions:

  § 26.1703 Prohibition of reliance on research involving intentional exposure of human subjects who are pregnant women (and therefore their fetuses), nursing women, or children.

  § 26.1704 Prohibition of reliance on unethical human research with non-pregnant, non-nursing adults conducted before April 7, 2006.

  § 26.1705 Prohibition of reliance on unethical human research with non-pregnant, non-nursing adults conducted after April 7, 2006.

  § 26.1706 Criteria and procedure for decisions to protect public health by relying on otherwise unacceptable research.

Background - §26.1704

§26.1704 prohibits the reliance on data from studies initiated prior to April 7, 2006 if there is clear and convincing evidence that:

1. The conduct of the research was fundamentally unethical; or
2. The study was significantly deficient relative to the ethical standards prevailing at the time.

Background - Ethics (3)

HSRB-established approaches for ethics review:

1. Did the study fail to fully meet specific ethical standards prevalent at the time the research was conducted?

   Examples:

   FIFRA Section 12(a)2(P).

   Declaration of Helsinki or other accepted International Codes of Research Ethics.

   The Common Rule (40 CFR 26).

Background - Ethics (4)

2. If the study did not meet the ethical standards of the time, was the conduct of the study:

   A. Fundamentally unethical?

      Was the research intended to seriously harm participants or failed to obtain informed consent?

   B. Significantly deficient?

      Could have resulted in serious harm to participants, based on knowledge available at the time?

      The informed consent process was impaired?

40 CFR 26.1706: Should the Agency Rely on Unethically Acquired Data?

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Background - §26.1706

§26.1706 allows the EPA to consider data that fails to meet the standard established by §26.1703 through §26.1705 under certain circumstances, including:

- The EPA has determined that relying on the data is crucial for establishing a more stringent regulatory restriction that will improve public health protection.
- The EPA obtains the views of the HSRB concerning the proposal to rely on otherwise unacceptable data.

Question Posed to the Board

Should the HSRB recommend the use of scientific data that may have been obtained using methods that violated established norms of medical and research ethics?

- Precedent?
- Criteria?
- Existing guidance?

Issues to Consider

- Not all “unethical” studies are conducted in such an egregious manner as the examples most often debated publicly.
- Many studies fall into grey zones of established ethical standards.
  - Experiments that contain a single bad component (e.g. breast cancer study)?
  - Experiments using methods which do not conform to contemporary ethical standards.

Case Example

Value of prophylactic radiotherapy after radical surgery for esophageal carcinoma: report on 495 patients. *Ann Thorac Surg* 2003.

- The study was conducted in China from 1986 to 1997.
- RCT of postoperative radiotherapy in the treatment of squamous cell esophageal cancer
- Largest study to date, and showed a clear benefit of postoperative radiation.
- Participants were not informed that they were part of a research study and did not consent to participation.