Current Ethical and Regulatory Framework for Pediatric Product Development

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Introduction

• Over the past 15 years, we have evolved from a view that we must protect children *from* research to a view that we must protect children *through* research.

• We have an obligation to ensure that there are adequate data to support the safe and effective use of drugs, biologics and devices in infants, children and adolescents.

• The critical need for pediatric research underscores our shared responsibility to ensure that children are only enrolled in scientifically necessary and ethically sound research.

• Children are widely considered to be vulnerable persons who, as research participants, require additional protections beyond those afforded to competent adult persons.
Topics

• Basic Ethical Framework in Pediatrics
  – Principle of Scientific Necessity;
  – “Low Risk” and “Higher Risk” Pathways

• Four Key Concepts (with examples)
  – Prospect of Direct Benefit; Extrapolation
    • Enrollment of Adolescents in HIV Vaccine Trial
  – Component Analysis
    • Use of Central Venous Catheter
  – Disorder or Condition
    • “Over the Counter” (OTC) Cough & Cold Products

• Federal Public Panel Review
Basic Ethical Framework in Pediatrics

1) Children should only be enrolled in a clinical trial if the scientific and/or public health objective(s) cannot be met through enrolling subjects who can provide informed consent personally (i.e., adults).

2) Absent a prospect of direct therapeutic benefit to the children enrolled in a clinical trial, the risks to which those children would be exposed must be “low” (i.e., knowledge does not justify more than “low” risk).

3) Children should not be placed at a disadvantage after being enrolled in a clinical trial, either through exposure to excessive risks or by failing to get necessary health care.

Principle of Scientific Necessity

1) Children should only be enrolled in a clinical trial
   - to answer an important scientific and/or public health question about the health and welfare of children, and
   - the question cannot be answered through enrolling other subjects (e.g., competent adults, non-human primates)

   • Equitable selection (*prima facie* obligation)
     - Enroll subjects capable of consent (i.e., adults) before children
     - Do not enroll children unless essential (i.e., no other option)

   • Practical Applications
     - Use of Extrapolation of efficacy from adults to children (see below)
     - Use of FDA “Animal Efficacy Rule” (21 CFR 314.610)
       • Levofloxacin approved for treating pneumonic plague on April 27, 2012
Additional Protections for Children

✓ Need sufficient scientific data from animal models or adult human clinical trials to conclude that:

2) “Low Risk” Pathway: Absent sufficient prospect of direct benefit to the child, administration of investigational product presents an acceptably “low” risk, or…
   • 21 CFR 50.51 (“minimal risk”)/50.53 (“minor increase over minimal risk”)

3) “Higher Risk” Pathway: Administration of investigational product to children presents a sufficient prospect of direct benefit to justify “higher” risks, and the balance of risk and potential benefit is at least as favorable as any available alternatives.
   • 21 CFR 50.52 (“greater than minimal risk”)
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Prospect of Direct Benefit (PDB)

• A “benefit” is “direct” if it accrues to the enrolled child; and results from the research intervention being studied.
• PDB is based on the “structure” of an intervention (i.e., dose, duration, method of administration, etc.)
• The level of evidence needed to support PDB (“proof of concept”) lower than that required to establish efficacy.
• Whether PDB sufficient to justify risks, given the clinical context, is a complex judgment similar to clinical practice
• Given the intervention, the enrolled child should have “as good a chance for benefit as the clinical alternatives”
Extrapolation of Efficacy

• Conditions for Extrapolation: “If the course of the disease and the effects of the drug are sufficiently similar…”
  – Requires understanding of disease pathophysiology and mechanism of therapeutic response to the investigational product
  – Confirmatory studies may be used to support extrapolation

• Evidence needed for efficacy:
  – Data from two adequate and well-controlled clinical investigations
  – Data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation)

• Typology of Extrapolation:
  – Full: No clinical trials of efficacy required; safety and dosing only.
  – Partial: One “confirmatory” trial required; also safety and dosing.
  – None: Two adequate and well-controlled clinical investigations.
Enrollment of Adolescents in HIV Vaccine Trial

Selected Recommendations (August 14, 2007)

• Not enroll adolescents until after interim efficacy and cell-mediated immunity (CMI) analysis of adult data
  – Require trend in favor of experimental HIV vaccine (i.e., sufficient prospect of direct benefit to justify risks)

• If extrapolation appropriate, base adolescent sample size on descriptive CMI data from interim analysis
  – Descriptive comparison between adult and adolescent immune response data could serve as bridge for extrapolation of efficacy
  – Adjust adolescent sample to improve power to detect a significant safety signal at an incidence of <1-3%

• Extrapolation of efficacy may permit concurrent labeling

IND 13028/6: MRK Ad5 HIV Vaccine (NIH released RMN from confidentiality restrictions)
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Component Analysis

• “To determine the overall acceptability of the research, the risk and anticipated benefit of activities described in a protocol must be evaluated individually as well as collectively.”
  – The National Commission 1978

• Why is component analysis important?
  – Failure to distinguish components of a clinical trial may result in an intervention that does not hold out a prospect of direct benefit exceeding the allowable threshold of a minor increase over minimal risk (absent referral under 21 CFR 50.54).
Use of Central Venous Catheter

- Multinational, placebo-controlled, double-blind study of an investigational product, in children ≥ 7 years old
- Product (or placebo) administered by IV infusion over 4 hours each day for 14 days
- Insertion and use of central venous catheter (CVL) presented *more than* a minor increase over minimal risk
- CVL was justified in children receiving active product due to prospect of direct benefit from the infusion
- CVL was *not* justified in children receiving the placebo due to *no* prospect of direct benefit from the infusion
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“Low Risk” Pathway
Importance of disorder or condition

- Administration of an experimental drug/biological product is not “minimal” risk, and is not approvable under 21 CFR 50.51
- Research under the “minor increase” category (21 CFR 50.53) must be “likely to yield generalizable knowledge about the subjects’ disorder or condition that is of vital importance for the understanding or amelioration” of the disorder or condition
- Disorder or condition can be defined by “specific… characteristic(s) that an established body of scientific evidence or clinical knowledge has shown to negatively affect children’s health and well-being or to increase their risk of developing a health problem in the future.”
- Key Concept: “at risk” for disorder or disease.
Example: OTC† Cough & Cold Products

- Single-dose PK studies of OTC cough and cold products are necessary to establish the correct dose to be used in subsequent efficacy studies.
- Based on available data, a single dose of an OTC cough and cold product may not offer a prospect of direct benefit to the enrolled child, but can be considered “low” risk (but not “minimal” risk).
- Enrolled children must have a disorder or condition.
  - Children who are symptomatic from a cold have a condition (disease).
  - Asymptomatic children may be “at risk” for a cold based on empirical data that clearly defines an “at risk” population (using US data).
    - Frequency Criterion: >6 infections per year for children aged 2 to <6 yrs and >4 infections per year for children aged 6 to <12 yrs.; AND,
    - Crowding Criterion: ≥4 persons living in the home OR ≥3 persons sleeping in one bedroom; AND,
    - Exposure Criterion: another ill family member in the home OR a child in the family who is attending preschool or school with ≥6 children in the group.

† OTC = "over the counter" (i.e., non-prescription)
Developing an “Escape Hatch”

• The National Commission was concerned that the standard categories for IRB approval may exclude important research.

• Key aspects of the discussion
  – “Public review and comment”
    • Should not be an administrative procedure absent oversight by “society”
  – “Sound ethical principles”
    • Should apply (not suspend) the ethical principles of respect for persons, beneficence and justice to a “new and unanticipated state of affairs”
  – “Serious health problem”
    • Not limit to “national emergency” but restrict to research of “major significance”

• “National Advisory Board” not established until FDA Pediatric Advisory Committee chartered (in 2003) to do these reviews
Required Public Panel Findings

• The clinical investigation in fact satisfies the conditions of 50.51, 50.52, or 50.53, as applicable, or
• All of the following conditions are met:
  – The clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
  – The clinical investigation will be conducted in accordance with sound ethical principles; and
  – Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians
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Thank you.