Prospect of Direct Benefit based on Animal Studies

Robert M. Nelson, MD PhD
Pediatric Ethicist, Office of Pediatric Therapeutics, Food and Drug Administration

Pediatric Ethics Subcommittee of the Pediatric Advisory Committee, June 9, 2008

Pediatric Drug Development

Preclinical Animal Models → Healthy Human Adults

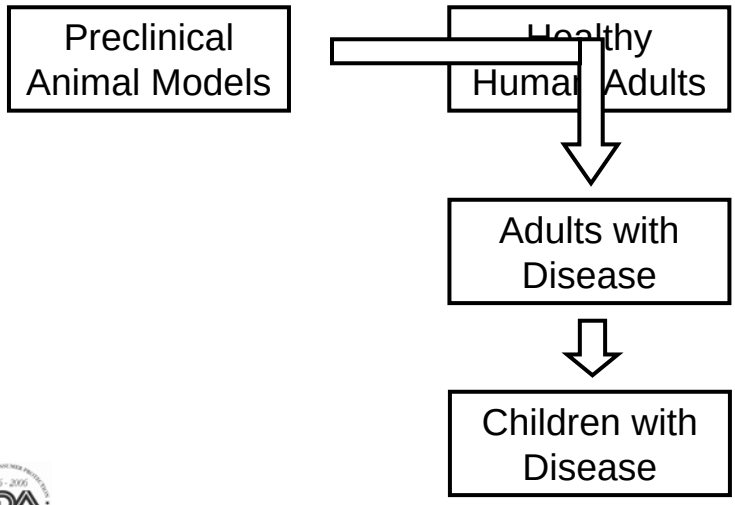
↓

Adults with Disease

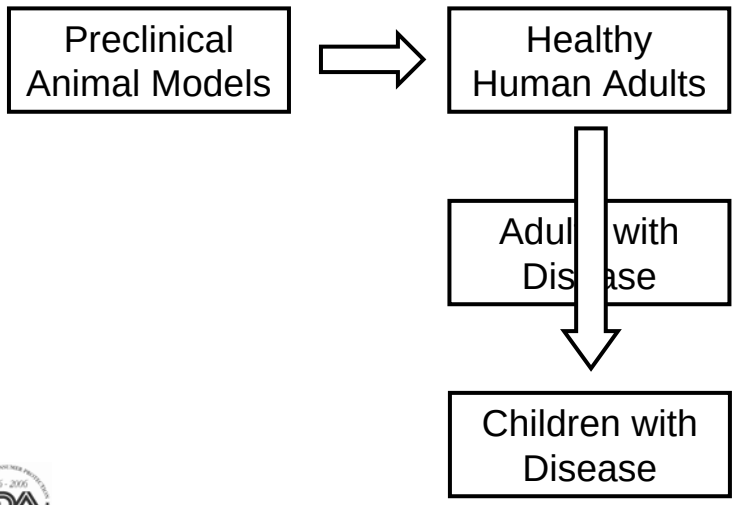
↓

Children with Disease

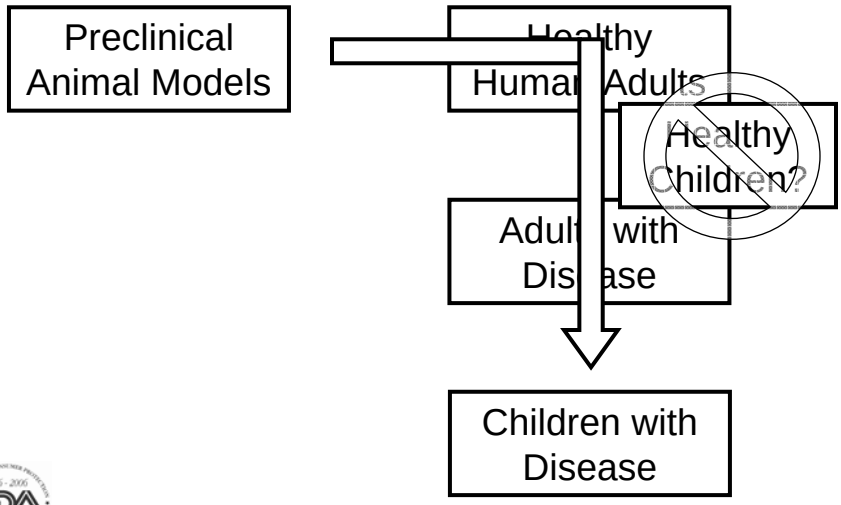
Pediatric Drug Development



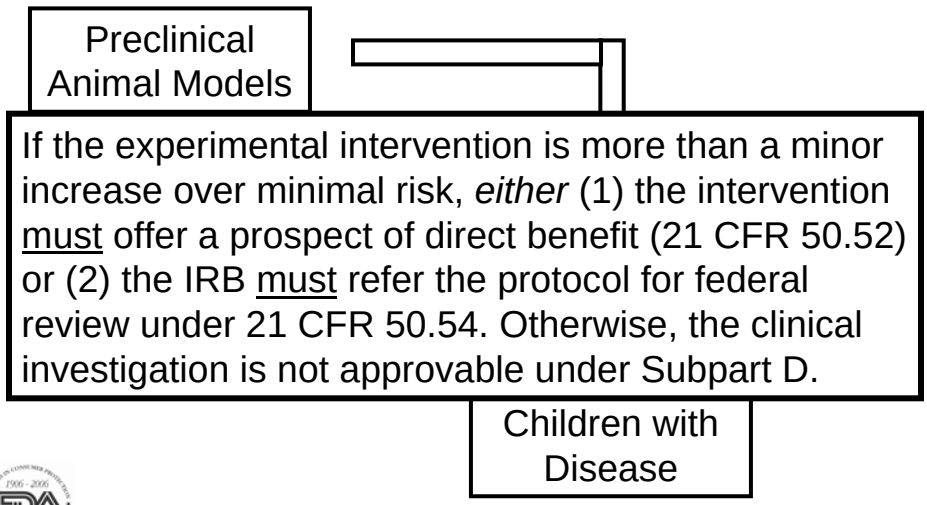
Pediatric Drug Development



Pediatric Drug Development



Pediatric Drug Development



“First-in-Children” under 21 CFR 50.52

- Any clinical investigation [presenting] more than minimal risk to children… by an intervention [with] the prospect of direct benefit… may involve children as subjects only if:
  - risk justified by anticipated benefit to subjects;
  - relation of anticipated benefit to risk as favorable to subjects as… available alternative approaches.
- Absent a suitable adult human population, the challenge is to establish a sufficient prospect of direct benefit from animal studies alone to justify a “first-in-children” clinical trial.

Prospect of Direct Benefit (PDB)?

- A “benefit” is “direct” if it:
  - Accrues to individual subject enrolled in clinical trial, and
  - Results from research interventions required to answer scientific questions posed by trial (i.e., not from other interventions included in protocol, but unrelated to the research question).
  - The word “benefit” often preceded by “clinical” to indicate that “direct benefit” relates to the health status of the enrolled subject.

Prospect of Direct Benefit (PDB)?

- Based on "structure" of intervention (i.e., dose, duration, method of administration, etc.), and not an investigator's intent.
- Evidence for PDB should be "weaker" than evidence supporting "efficacy" - otherwise one needs to know the answer to the research question prior to doing the research.

Justification of Risk

- Need empirical evidence of sufficient "prospect of direct benefit" to justify exposure to the risks.
  - Complex quantitative and qualitative judgment
  - Risk/benefit evaluation similar to clinical practice
- Justification of risk by PDB can include:
  - Importance of "direct benefit" to subject
  - Possibility of avoiding greater harm from disease
  - Risks of experimental intervention can only be justified by benefits to be expected from that same intervention
  - Justification set in context of disease severity (e.g., degree of disability, life-threatening) and availability of alternative treatments.

Drugs Intended to Treat Life-threatening and Severely-debilitating Illnesses

- "FDA's application of the statutory standards…shall recognize the need for a medical risk-benefit judgment in making the final decision on approvability. As part of this evaluation,…FDA will consider…the severity of the disease and the absence of satisfactory alternative therapy."
  - 21 CFR 312.84 (Revised April 1, 2006)
- "The IRB should evaluate research protocols…in the same way that comparable decisions are made in clinical practice. It should compare the risk and anticipated benefit of the [study] intervention [with] available alternative methods for achieving the same goal, and should also consider the risk and possible benefit of attempting no intervention whatsoever."
  - The National Commission Research Involving Children 1978

Proposal: Sliding Threshold

- Animal data necessary to establish sufficient justification for the prospect of direct benefit (PDB) varies with the severity of the disease and the adequacy of alternate treatments.
- Structure (generally insufficient for PDB)
- Function (based on mechanism of action)
  - Molecular target (receptor); Biomarker (RNA/protein); Physiologic pathway (metabolic product)
  - Transgenic Technology (human target + mouse)
- Clinical Disease Model
  - Surrogate endpoints
  - Clinical endpoint (e.g., survival)

Sliding Threshold for Approval

- It is not the “evidence” that varies, but rather the “threshold” at which we have a sufficient basis for approving proposed research.
- This “threshold” involves the evidence in support of direct benefit, the severity of the condition or disease, the presence or absence of alternative treatments, the importance of the scientific knowledge, and the provision of informed consent.

Dosing Considerations

Maximum Recommended Starting Dose (MRSD) for “first-in-human” clinical trials

- MRSD frequently based on “no observed adverse effect levels” (NOAEL) in the tested animal species, and conversion of NOAELs to a human equivalent dose with the application of a safety factor
- Assessment of risk/potential benefit for “safe starting dose” using NOAEL may not be equivalent to MRSD dose associated with greatest efficacy in animal studies

Some limitations of animal studies

- Methodological biases in animal experimentation (lack of randomization and blinding, small sample sizes)
- Animal models may not adequately mimic human pathophysiology (e.g., TGN1412 study)
- Variability of animal modeling from one lab to another (need standardized predictive preclinical animal model)
- Animal data may diverge from human outcome data collected in other settings leading to difficulties in assessing the prospect of direct benefit
- Laboratory environment can lead to stressed animals which may effect test results
- Use of anesthesia to diminish suffering may alter physiologic state and affect endpoints