Designing and Conducting Clinical Trials of Drugs in Children

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PAS
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Has documented that she has no financial relationships to disclose or Conflicts of Interest (COIs) to resolve.
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Goals of Drug Development

• Protect the public health by assuring that drugs to be marketed are safe and effective.
• Bring new drugs that are safe and effective to market in a timely manner.
• Speed therapeutic innovations to advance public health.
Drug Development

• A complex, lengthy, multidisciplinary, stepwise process involving evaluation of animal and human safety and efficacy data.
Pediatrics is another layer of complexity

• One must deal with all the “usual” steps but also address the following questions for pediatrics:
  - What adult or animal data applies
  - What is the “benefit” or minor increase over a minimal risk to justify the trial
  - What level of text and how many assent and consent forms need to be addressed
  - What facilities can do these studies
  - What calculations are necessary for blood sampling and non-invasive vs invasive testing
Drug Development Stepwise Process

• Laboratory, animal, then human studies
• Small studies before large ones
• Short studies before long ones
• Low dose before high dose
• Single dose before multiple dose
• Each step builds on preceding experience.
Product Applications

- **IND**: Investigational New Drug Application
  - Allows initiation of clinical studies in humans.

- **NDA**: New Drug Application
  - Submission of information needed for marketing approval.

- **sNDA**: supplemental NDA
  - Application to change manufacturing, patient population or formulation of the product.

- **ANDA**: abbreviated new drug application
  - Application for marketing approval of a generic drug.
Stages of New Drug Development

• Pre-IND
• IND
  – Phases 1, 2 and 3 clinical development
• NDA
• Post-marketing
  – Phase 4 clinical development
Pre-IND
(for Pediatrics may already have this data in adults)

• Objective: Determine drug’s toxic and pharmacologic effects before first time use in humans through *in vitro* and *in vivo* animal testing.

• Discuss chemistry and pharmacology/toxicology

• Discuss clinical development plan (including statistics)

• Prior to human exposure
  – Chemical identification, characterization and purification
  – Animal studies
    • Drug must be reasonably safe for use in initial Phase 1 clinical trials
Getting a Starting Dose

• Determine the NOAEL
  – Highest dose level that does not produce adverse effects

• Convert NOAEL to HED (Human equivalent)

• Safety factor applied to the HED.
  – In general, safety factor of 10 is recommended.

• MaxRecommendedStartingDose: obtained by dividing the HED by the safety factor.
IND Submission

• Allows initiation of clinical studies in humans.
• Phase 1, 2 and 3 clinical studies
• 30-day clock for initial submission to determine if clinical study is reasonably safe to proceed.
• No review clock for subsequent submissions.
Clinical Hold

• An order to delay or suspend an investigation.
  – No new patients may be enrolled
  – Patients already in study should be taken off drug (unless discontinuation not in interest of patient safety).

• May be imposed anytime during review cycle

• Criteria: examples
  – Unreasonable risk to human subjects
  – Insufficient information to assess risk to human subjects
General Interactions During Review Process

- **Meetings**
  - EOP2 with sponsor
    - Lowest effective or maximum tolerated dose known; preliminary evidence of efficacy and reasonable evidence of safety
    - Potential claims
    - Discussion of Phase 3 trials
  - pre-NDA with sponsor
    - Phase 3 trials almost complete or completed
    - Format and content of to be submitted NDA
    - Adequacy of components
      - Clinical: Will trial data support filing of the NDA?
    - Reviewer needs
      - Clinical: Data tabulations and Case Report Forms
NDA Submission

• 74-day letter
  – states if application will be filed and any requests for additional information
• Site inspections
• Advisory Committee meeting if needed
• Labeling review
• Written reviews by all disciplines
• Regulatory decision
  – Risk/benefit analysis based on totality of information
  – includes any Phase 4 commitments
Supplemental NDA (sNDA)

• A supplement is an application to allow a company to make changes in a product that already has an approved new drug application (NDA)
• Most preclinical, clinical work performed in initial NDA
• Most pediatric studies are submitted as supplements
ANDA (Generic Drug)

• “Copy” of approved drug
• Safety and efficacy already established for the approved reference drug.
• Must contain same active drug in the same amount and acceptable inactive ingredients.
• Must be bioequivalent to reference drug.
• Must have the same labeling as the reference drug.
• Even if studying a “generic”, changes must go into the originator label. This means negotiations with the originator.
Review Disciplines in Division:
(within the Center for Drugs there are 18 product development divisions)

- Chemistry
- Pharmacology/Toxicology
- Clinical Pharmacology/Biopharmaceutics
- Clinical
- Statistics
- Microbiology
- Project Manager
References

• Code of Federal Regulations
  – 50 Human Subject Protection
  – 54 Financial Disclosure
  – 56 Institutional Review Boards
  – 201 Labeling
  – 312 IND
  – 314 NDA

• Legislation (for example, FD&C Act, PDUFA, FOIA, FDAAA, BPCA, PREA, FDASIA).