Translational Medicine Symposium 2013: The Roller Coaster Ride to the Clinic
TRANSLATIONAL MEDICINE SYMPOSIUM 2013

CLINICAL DEVELOPMENT AND TRIALS

Bench to Business to Bedside: The Roller Coaster Ride to the Clinic
Introductions

• Moderator:
  – Michael Spigarelli (Clinical Trials Office)

• Panelists:
  – Sunil Sharma (Huntsman Cancer Institute)
  – Carrie Byington (CCTS, University of Utah)
Goals

• To discuss Clinical Development and Trials in the context of the afternoon’s sessions
• To facilitate audience asking questions and leading the discussion
• To use slides to set the basis for discussion not for a lecture based lesson
Design a Clinical Trial: Drug

- You have a new potentially useful drug.
- You have screened library of compounds and discovered this drug.
- You have interested a company in developing these types of drugs for patient use.
- The company has conducted animal safety studies and other things needed to enter clinical trials.
- Now what?
Design a Clinical Trial: Device

- You have discovered a novel device/technology that will be used in/with humans.
- You have an interested company in getting this device/technology approved.
- You have approached the FDA and have permission to test in a clinical trial.
- Now what?
Considerations in Clinical Trial Development

- **Audience**
  - Disease
  - Patient
  - Drug/Device

- **Clinical Trial design**
  - What does phase have to do with it?

- Is there a drug or device already on the market?
Audience: Disease

- Chronic vs. Acute
- Life Threatening vs. Disease Modulating
- Cure vs. Palliation
- Rare or Orphan Disease
- Major market vs. developing world
- Diagnostic vs. Therapeutic
Audience: Patient

- Patient vs. Normal Volunteers
- Special Populations
- Informed Consent and Ethical Considerations
- ‘Do no harm’ vs. risk in trials
- Quantifying risk: role of review committees
- Legal considerations
Do No Harm Considerations

- Scientific Merit
- Animal Safety Studies
- Investigational New Drug (IND/IDE) filings
- Food and Drug Administration (FDA) review
- Institutional Review
- Trial Monitoring
- Principal Investigator Responsibilities
- Conflict of Interest
- Analysis of Results and transmittal of Data
- Follow up studies
Audience: Drug/Device

- Drug vs. Device
- Small molecule vs. Protein
- Designer Drug vs. Natural Product
- Systemic (oral, IV) vs. Topical
- Already approved vs. Never in man
- Target known vs. unknown
- Minimally risk
- More substantial risk
Clinical Development Path

- **Discovery**
  - High-throughput screening
- **Pre-clinical**
  - Laboratory & animal testing
- **Phase I**
  - 20-100 volunteers: safety & dosage
- **Phase II**
  - 100-500 volunteers: efficacy & side-effects
- **Phase III**
  - 1,000-1,500 volunteers: long-term use study
- **FDA review**
- **Production**

- Compounds
- Cost/trial

- $1-5 \times 10^6$
  - 40-60% success rate
- $5-20 \times 10^6$
  - 50-70% success rate
- $80-400 \times 10^6$
  - 60-80% success rate
Clinical Development Path

- Pre-Clinical Research
  - Synthesis and Purification
  - Animal Testing
    - Short-Term
    - Long-Term
  - Institutional Review Boards
- Clinical Studies
  - Phase 1
  - Phase 2
  - Phase 3
  - Accelerated Development/Review
  - IND Submitted
  - Parallel Track
- NDA Review
  - NDA Submitted
  - Review Decision
  - Sponsor Answers Any Questions From Review
- Sponsor/FDA Meetings Encouraged

Source: FDA/Center for Drug Evaluation and Research
Clinical Development Path

Product Design

- Financial Plan
- Business Strategy
- Drug discovery
- 5,000–10,000 compounds screened
- 250 under preclinical testing
- Enter clinical testing
- Patents
- Approved as marketed drug
- Clinical Need
Drug Development: Expense

DiMassi et al 2003
Good Clinical Practice (GCP)

- Clinical Trial Guidelines: International Conference on Harmonization (ICH)
- Defines standard, ethical clinical research practice
- Defines operational conduct and ethical practice
- Regulatory Agencies Provide Additional Rules
Clinical Trials: Phase 1 Trials

- **Phase 1**: dose escalation in healthy volunteers or patients
  - Assess safety & maximum tolerated dose in 20-80 normal subjects
- Testing the safety of an agent in humans
- More complicated if FIRST IN HUMAN
- Main endpoints: Safety, pharmacokinetics (PK) and pharmacodynamics (PD)
- Secondary endpoints are: Efficacy
- Is the drug/device safe? Small number of subjects to decide, also what is the correct dose/schedule?
Clinical Trials: Phase 2

- Now we know the dose that is tolerable for your drug or drug/device combo, we have some idea of its PK/PD
- Phase 2 trials are testing EFFICACY in a defined population
- Can be single-arm or randomized to known treatment
- Statistical models to generate a power calculation and confidence intervals to estimate true efficacy
Clinical Trials: Phase 3

- Phase 3: Studies usually required for filing New Drug Applications
  - Large global, randomized, controlled trials for registration
  - Primary endpoint: Comparative efficacy vs Standard of Care
  - Secondary endpoints: Safety
Clinical Trials: Phase IV

• Your Drug/Device meets IND/IDE goals
  FDA gives you an approval

• Phase 4 – Extra studies, post-marketing commitments

• Does approval means that your drug is safe?

• Statistically safe or is it ‘real life’ safe?
Determining the First in Human (FIH) Strategy

• How do we determine the trial design and starting dose moving into humans?

• What is the statistical design and does it answer the initial questions?
Doing More in Early Clinical Trials

• Drug/Device Development is expensive and it is critically important to fail early.

• Pure safety endpoints are being stretched to include other considerations
  – Does the drug hit the intended target?
  – Does it have a meaningful biological effect?
  – Is there a specific patient population that will benefit to alter enrollment strategy to improve response rates in early trials?
DISCUSSION TOPICS

- Product Design
- Financial Plan
- Clinical Trial
- Business Strategy
- Regulatory Path
- Preclinical Plan
- Patents
- Clinical Need
- Reimbursement
Role of Academic Institutions

• What is CTSA and how does it help with clinical trial development and execution?
• What are the challenges to doing effective clinical trials?
• What is the infrastructure needed in academic centers to conduct effective clinical trials?
Drugs vs. Device

• How are device trials different?

• What are special considerations for device trials that are dependent on operator performance?
Industry Role in Clinical Trials

• What is the role of industry/device companies in clinical trials?

• How does industry fund clinical trials and maintain an arm's length from the outcome?

• Can some drugs/devices be developed outside of industry?
General Issues in Clinical Trials

- Clinical Research as a viable career path
- Is it difficult to do clinical trials globally?
- How do patients find out about clinical trials?
- Is there patient benefit from clinical trials?