A Life-cycle Approach to Dose Finding Studies

Rajeshwari Sridhara, Ph.D.
Director, Division of Biometrics V
Center for Drug Evaluation and Research, USFDA

This presentation reflects the views of the author and should not be construed to represent FDA’s views or policies
Outline

• Organization
• Drug approval pathways
• Role of Statisticians
• Dose finding studies
• Life-cycle approach
• Who
• What
• When

• Where
• How
• Why
Washington DC Metro Area
Organization

Office of the Commissioner

Office of Foods
And Veterinary Medicine

Office of Medical Products and Tobacco

Center for Food Safety & Applied Nutrition
Center for Veterinary Medicine
Center for Devices & Radiological Health
Center for Drug Evaluation & Research
Center for Biologics Evaluation & Research
Center for Tobacco Products
National Center for Toxicological Research

Office of Regulatory Affairs

Office of Chief Scientist

OCE
Center for Drug Evaluation and Research (CDER)

• CDER performs an essential public health task by making sure that safe and effective drugs are available to improve the health of people in the United States.

• CDER regulates over-the-counter and prescription drugs, including biological therapeutics and generic drugs. This work covers more than just medicines. For example, fluoride toothpaste, antiperspirants, dandruff shampoos and sunscreens are all considered "drugs."
Regulatory support for good statistical practices

• Substantial evidence of effectiveness

“...Evidence consisting of adequate and well-controlled investigations, including clinical investigations, by qualified scientific experts, that proves the drug will have the effect claimed by its labeling...”

Section 505(d) FD&C Act of 1962 as amended
Regulatory Evidence Standard

• Traditionally interpreted as:
  – Results observed in at least two independent studies
  – Probability of one-sided type I error controlled at 0.025 level in each study
  – Clinically meaningful treatment effect
  – Acceptable risk/benefit profile

* Section 505(d) FD&C Act of 1962 as amended
Multidiscipline Environment – Review Team

Clinical

Project Management

Statistics

Pharmacology & Toxicology

Product Quality (CMC)

Pharmacology & Biopharmaceutics
Communication Dynamics between FDA and Industry
Types of Applications Reviewed

• IND- Investigational New Drug Application
  – To conduct clinical investigations
  – Many submissions will be made to one IND
  ➢ Submitted for review as: (1) Special protocol assessment, (2) Protocol and its amendments, statistical analysis plan, or as (3) Pre-IND, End-of-phase 1, End-of-phase 2, or pre-NDA meeting packages

• NDA- New Drug Application and BLA – Biologic Licensing Application
  – To gain clearance for marketing
FDA-Industry Interactions During Drug Development

Basic Research → Prototype Design or Discovery → Preclinical Development → Clinical Development

- Phase 1
- Phase 2
- Phase 3

Industry - FDA Interactions During Development

- Pre-IND Meeting
- Initial IND Submissions
- End of Phase 2a Meeting
- End of Phase 2 Meeting
- Market Application Submission
- Ongoing Submission
- Pre-BLA or NDA Meeting

FDA Filing/Approval & Launch Preparation

IND Review Phase → Application Review Phase
Regulatory Approvals

• Regular Approval: based on Clinical benefit (Survival benefit/patient benefit, or benefit in validated or “accepted” surrogate markers)

• Accelerated Approval in serious or life-threatening disease: based on ”surrogate” endpoint reasonably likely to predict clinical benefit; improvement over available therapy; required confirmation of clinical benefit
Role of Statistical Reviewer
Protocol Review

Goal: An Adequate and Well Controlled Study

- Clear objectives
- Valid control
- Quantitative assessment of the drug effect
- Well-defined selection criteria
- Unbiased assignment of treatment
- Validated endpoints
- Reliable methods of analysis
- Detailed sample size consideration
- Limited input in the design of dose-finding Phase I oncology clinical trials from FDA statisticians
Marketing Applications

• Data from clinical trials answer the question – Is there a treatment effect? If so what is the magnitude of effect?
• Thorough review of the study report, protocol and its amendments, pre-specified analysis plan, and independent review committee charters including DMC charter, to understand the study conduct, impact of protocol violations and amendments, impact of deviations from pre-specified analyses and role of independent committees.
• Review of data (efficacy and safety) to ensure absence of systematic bias or any other potential bias in the conduct and analyses of the study
Pre-clinical or Non-clinical Studies

• Carcinogenicity Study Review
  – Consult to pharmacology-toxicology reviewers

• Stability Study Review
  – Consult to chemistry reviewers

Other clinical Studies

• QTc Study Review
  – Consult to clinical pharmacology reviewers
Non-Review Related Activities

• Regulatory research – present in conferences and publish
• Collaborative projects with academia and industry – methodological issues not specific to any product
• Outreach activities – educate non-statisticians, co-sponsored meetings with professional societies, etc.
Statisticians - Pharmacologists Interactions

• As needed
• Interaction process during NDA/BLA review draft policy established
• Exchange of ideas on selected review applications – MOOSE Rounds
ONCOLOGY DRUG DEVELOPMENT
Cancer Trials

• Phase I Dose-finding Trials: Clinical Pharmacology and Toxicity
  – To establish MTD, Study basic pharmacology of the drug
• Phase II Trials: Initial Clinical Investigation
  – Investigate effectiveness and safety of the drug
• Phase III Trials: Confirmatory Trials
  – Full scale evaluation of drug compared to a control Tx
• Phase IV Trials: Post-marketing surveillance
  – Monitoring long term effects on morbidity and mortality
Design of Phase I Cancer Trials

• Algorithm based – most commonly used, example, 3+3 designs
  – No memory of the previous dose cohort
  – Inefficient

• Model based designs
  – Builds on information from previous cohort
  – Allows to characterize uncertainty in the estimates
  – Limitations due to model assumptions
  – More efficient

• Generally no randomized dose cohorts

• Dose-response relationship limited by confounding factors that are unknown or not collected
Current Product Development Process

- **Pre-Clinical**
  - Assess DLT within 28-day cycle
  - Cumulative Toxicity Unknown

- **Phase I**
  - Assess DLT within 28-day cycle
  - Determine MTD
  - Cumulative Toxicity Unknown

- **Phase II**
  - Use MTD
  - Multiple cycles of treatment
  - Frequent dose modifications
  - Soft efficacy endpoint (ORR)

- **Phase III**
  - Use MTD or a modified MTD
  - Multiple cycles of treatment
  - Frequent dose modifications
  - Clinical endpoint (OS)

- **Phase IV**
  - Dose Finding
Current Product Development Process – Outdated

- Dose-finding uses old cytotoxic therapy paradigm
- Cytotoxic paradigm:
  - 28-day cycles, finite number of treatment cycles
  - Dose based on BSA, a substitute for exposure based dosing
  - Toxicity observed in short time
  - More is better
  - Good animal models
  - Well characterized toxicities (hematologic, GI, neurologic, etc.) with CTCAE grading criteria
  - DLT defined based on these toxicities
Current Products

• Example: Kinase Inhibitors
  – Oral formulation of fixed doses
  – Administered beyond 28-day 6 cycles – until disease progression
  – Cumulative toxicity
  – Delayed toxicity, that is not observed in pre-clinical or dose-finding studies
  – Type of toxicities different from typical cytotoxic products: example, rash
Phase III Cancer Clinical Trials

• Frequent:
  – Dose modifications
  – Dose interruptions
  – Dose discontinuations

• Recommended dose in the product label?
• Post-marketing studies to evaluate optimal dose
AACR-FDA Dose-finding Workshops

• 2015 – focus on small molecule oncology products – kinase inhibitors

• 2016 – focus on immunotherapy

• 2017 (TBD) – focus on combination therapy
Questions

• Do we have adequate animal model?
  – Maybe not. Current study design unable to predict some toxicities
  – Replication in different animal models useful

• Is the definition of DLT appropriate for non-cytotoxic targeted or other immunotherapies?
  – Define BED (Biologically effective dose) or minimum effective dose (MED)?

• Are we using all the data we have?

• How can we learn from past observations?

• How can we account for limitations and uncertainties?
Can We Be More Efficient?
Product Life-cycle Adaptive Process

- In-vitro Data
- Pre-clinical Data
- Phase III Trial Data
- Phase II Trial Data
- Phase I Dose Finding Trial Data

Stanford University Symposium 2017
What can we do now?

- Review data from Phase III studies in a particular drug class-disease to:
  1. Characterize ‘unacceptable’ toxicities
     - Go back to pre-clinical testing
  2. Redefine DLT based on this information
     - Go back to dose-finding trial
  3. Record when these toxicities occurred
  4. Estimate exposure – how long treatment was received
  5. Develop statistical model based on observed dose modifications
What can we do now? – Contd.

➢ Review data from Phase II studies to:
  1. Understand limitations and uncertainties in the PK-PD modelling
  2. What is the missing piece of information that we should have assessed in order to make better decisions?

➢ Review data from Phase I studies
  1. What happened to patients beyond the first cycle?
  2. What dose modifications were made?
  3. What toxicities were observed beyond the first cycle?
  4. Do we have the right PD marker?

➢ Any in-vitro data that were not used in the pre-clinical or Phase I studies
What can Statisticians do?

• Incredible amount of data is generated
  – Can be used for priors in the statistical models
• Simulate multiple clinical trial scenarios
• Think beyond 28-day cycle
• Use new definition of DLT
• MTD? May be use BED or MED
• Model both toxicity and efficacy?
• Model with dose as a function of time?
• Use what you learn
Product Life-cycle Adaptive Process

- In-vitro Data
- Pre-clinical Data
- Phase I Dose Finding Trial Data
- Phase II Trial Data
- Phase III Trial Data
Summary

• There are best practices to improve efficiency
  – Use pre-clinical models and phase I results to make go/no-go decisions
  – Pre-clinical models to manage toxicity post-hoc
  – Randomized phase II with two or more doses, to explore schedule and sequencing of drugs, food effect, combinations, etc.

• Continuous learning and improvement is essential – product life-cycle process

• Informed clinical trial designs

• Sharing data and experience among sponsors would greatly improve efficiency – more importantly patients will benefit