Considerations for Successful Biopharmaceutical Product Development: Discovery to Proof of Concept

-A Panel Discussion

Stanley C. McDermott, PharmD, MS, RPh
Managing Director – Regulatory Sciences
Head, Clinical Research / Clinical Affairs
Cardinal Health Regulatory Sciences
Session Objectives

• Biopharmaceutical product development is a complex process, requiring extensive time and resources from sponsors and investors.

• Key concepts to consider during the development and approval processes for new drugs;
  – emphasis on how inventors and entrepreneurs can minimize the time to confirm clinical proof of concept (PoC)

• Better understanding of how to simplify this highly interesting, yet complicated process.
Expertise and credentials

- **Industry- and FDA-trained experts** providing regulatory science and product development consulting services required for product approval and product lifecycle management
  
  - 120+ NDA/BLA/ANDA approvals supported
  - 500+ INDs supported
  - 500+ approved products under maintenance (100+ countries)

40

Years of global experience

800+

Clients served

170+

Regulatory scientists in-house
Core service areas

- Global regulatory development
- Nonclinical development
- Chemistry, manufacturing and controls
- Clinical development and research
- Medical writing

Regulatory competencies and offerings

- Compliance
- Regulatory publishing
- Launch and post-approval
- Licensing and registrations
- Training
New Drug and Biologics Approvals and Research and Development Spending

The New Drug Development Process

Pre-Clinical Research

- Synthesis and Purification
  - Phase 1
  - Phase 2
  - Phase 3

Animal Testing

- Short-Term
- Long-Term

Institutional Review Boards

- IND Submitted
- Clinical Studies
- NDA Submitted
- Review Decision
- Sponsor answers any questions from review

Accelerated Development/Review

- Treatment IND
- Parallel Track

Effective use to accelerated PoC

For more information, visit: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm053131.htm
Target selection & validation

Discovery

Development

Studies of Disease Mechanisms

Target receptor; ion channel; transporter; enzyme; signalling molecule

Lead Search
- Develop assays (use of automation)
- Chemical diversity
- Highly iterative process

Animal Studies
- relevant species
- transgenic KO/KI mice
- conditional KOs
- agonists/antago
- antibodies
- antisense
- RNAi

Molecular Studies

Lead optimization
- selectivity
- efficacy in animal models
- tolerability: AEs mechanism-based or structure-based?
- pharmacokinetics
- highly iterative process

Drug Candidate safety testing

Human Studies Phases I, II, III

Drug Approval and Registration

Mapping Product Development Stages
Target Selection & Validation

- Define the unmet medical need (disease)
- Understand the molecular mechanism of the disease
- Identify a therapeutic target in that pathway (e.g. gene, key enzyme, receptor, ion-channel, nuclear receptor)
- Demonstrate that target is relevant to disease mechanism using genetics, animal models, lead compounds, antibodies, RNAi, etc.
Discovery through Nonclinical Development

- Develop an assay to evaluate activity of compounds on the target
  - \textit{in vitro} (e.g. enzyme assay)
  - \textit{in vivo} (animal model or pharmacodynamic assay)

- Identify a lead compound
  - screen collection of compounds (“compound library”)
  - compound from published literature
  - screen Natural Products
  - structure-based design (“rational drug design”)

- Optimize to give a “proof-of-concept” molecule—one that shows efficacy in an animal disease model
- Optimize to give drug-like properties—pharmacokinetics, metabolism, off-target activities
- Safety assessment, Preclinical Candidate!!!
Drug Product Design

- Selection Criteria for Dosage Forms
  - Clinical Needs
  - Dose/Onset/Duration of Action
  - Product Performance
  - Patient Compliance/Acceptance
  - Marketing Considerations
Clinical Development

• Submit Investigational New Drug (IND) Application
  – Provides exemption from a federal statute
  – Effective in 30 days if FDA does not object or request additional information

• Phase 1 Clinical Trials
  – Approximately 1 year in duration
  – Requires 20 to 80 subjects
  – Assess the safety profile, pharmacokinetic (PK) characteristics, and safe dosage range (SAD, MAD, MTD studies)*
  – Evaluate absorption, distribution, metabolism and excretion (ADME studies), and the duration of presence/action

*Single ascending dose (SAD), Multiple ascending dose (MAD), Maximum tolerated dose (MTD)

Modified based on information obtained from: www.fda.gov
Clinical Development

• Phase 2 Clinical Trials
  – Approximately 2 years in duration
  – Controlled studies composed of 100 to 300 patients
  – Dose ranging in the target patient population
  – Assess safety and efficacy of dosing and formulation variances

• Phase 3 Clinical Trials
  – Approximately 3 years in duration
  – Requires 300 to 3,000 or more patients (intended use population)
  – Compare new therapies with existing standard of care and assess safety and efficacy of final (commercial) formulation product

Modified based on information obtained from: www.fda.gov
Developmental Clinical Pharmacology: Emphasis on PoC

- Typically short, involving relatively few HVs/patients
  - FIH (SAD/MAD; with one patient cohort)
  - Phase 1 Biomarker
  - PK/PD
- Intelligent Go/No-Go endpoints
  - Proof of Mechanism
  - Proof of Efficacy
- Generally lack statistical significance
- High quality read-outs (PD, biomarker, etc.)
  - Clinical physiology
  - Adaptive designs
Discussion