Commercialization Milestones & Regulatory Considerations For Developing a New Therapeutic

June 23, 2015

Robert Schumacher, PhD
Scientific Director, Center for Translational Medicine
University of Minnesota Academic Health Center
Commercialization Milestones

- Discovery
- Securing resources
- Securing intellectual property
- Licensing
- Marketing approval

- Validation & optimization
- Preclinical proof of concept
- Pre-IND meeting
- IND enabling studies
- IND application
- Clinical development

Commercialization
Critical Steps

Research & Discovery

Validation & Optimization

Proof of Concept

Clinical Trial Enabling

Clinical Testing

Commercialization
Validation & Optimization

Key questions:

• Is the potential therapeutic having the desired pharmacological effect?
• Does the drug candidate have sufficient bioavailability and reasonable metabolic stability?
• What are the metabolites and are they active?
• Are there species differences in metabolism? Gender differences?
• Is the drug mutagenic or cytotoxic in vitro?
• Can the drug be formulated to use in animal toxicology studies?
• Can it be synthesized/prepared at a reasonable cost?
Preclinical Proof of Concept

Key questions:
• Can efficacy be demonstrated in at least one validated animal model?
• Is the route of administration and dosing schedule acceptable?
• What is the ADME profile: how is the drug metabolized and eliminated; how long does it take; what enzymes are involved in drug metabolism?
• What is the maximum tolerated dose (MTD) and dose-limiting toxicities?
• What tissues and organs are most sensitive; do they recover after dosing is stopped?
• Are there biomarkers that can be used to monitor safety and/or efficacy?
• Is there an acceptable therapeutic index (TI)?
• Can sufficient drug be made for pivotal toxicology studies; is it stable; what impurities are present?
Pre-IND meeting with FDA

• First of several meetings that coincide with critical steps in the development process – along with end of phase 2 (EOP2), pre-NDA/pre-BLA.
• Pre-IND meeting is opportunity to get FDA review of preclinical development plan prior to initiation of more expensive and resource intensive pivotal program (preclinical development).
• Value and timing of pre-IND meeting will be impacted many factors, including: therapeutic, indication, development strategy, risk tolerance, available resources and team’s experience.
IND-Enabling Program

Key questions:
• What are the appropriate species to use in the pivotal toxicology studies?
• What toxicities need to be monitored in the FIH clinical trial?
• Any affects on reproduction or evidence of teratogenicity, mutagenicity, or embryo toxicity?
• Are there effects on behavior (CNS), pulmonary function, or CVS?
• Are there drug-drug interactions of potential concern?
• Can exposure, dose-response and toxicities be extrapolated to humans?
• What is the recommended starting dose and dose escalation for the FIH clinical trial?
• Can drug be reliably prepared and formulated under GMP?
• Do the API and product have adequate stability?
Investigational New Drug (IND) Application

• Request submitted to FDA to authorize administration of an investigational therapeutic (drug or biologic) to humans.
• FDA reviews IND within 30 days.
• If FDA has concerns about the application they will put a ‘clinical hold’ on the proposed clinical trial until the issues are resolved.
• Clinical trial can begin after IND is approved and the clinical protocol has been reviewed and approved by the Institutional Review Board (IRB).
Studies Needed to Move Into Clinical Testing

Generally, minimum requirements to open a standard IND are:
- Pharmacology studies – e.g. efficacy/proof of principle in animal model(s)
- General toxicology study in a rodent model
- General toxicology study in a non-rodent model
- Absorption, distribution, metabolism and elimination (ADME) studies
- Genotoxicity studies
- Safety pharmacology studies
- Analytical assays – e.g. to quantify API, plasma levels of drug (and major metabolites) and impurities
However…

• There are differences between requirements for small molecules, large molecules/biotechnology derived pharmaceuticals, and cellular and gene therapy products.

• Oncology and life threatening diseases for which there are limited treatment options are exceptions.

• Guidances are more important than past examples to understand how FDA will regulate a potential therapeutic.

• Guidances describe what data is needed but don’t tell you how to interpret the data or what additional data you need to make strategic and/or business decisions.
Clinical Development

• Phase I
  – Primary focus is to assess safety profile; also determine dose limiting toxicities and pharmacokinetics and aide in dose selection
• Phase II
  – Primary goal is to demonstrate efficacy - clinical proof of concept
  – Help design pivotal clinical trials
• Phase III
  – Demonstrate safety and efficacy in intended population
  – ‘Gold standard’ is randomized controlled trial (usually at least two)
• Phase IV / post-marketing
  – Post-approval requirements
  – Monitor safety in the population that actually uses it
Development Challenges

- Risky
- Expensive
- Highly regulated
- Research environment
- Requires different expertise

Clinical Trial

Research & Discovery

Validation & Optimization

POC – efficacy, ADME/PK, toxicology

Clinical Trial – Enabling
Translation at the University of Minnesota

• In addition to OTC, University has unique resources, expertise and capabilities available to support the translation of discovery based technologies into commercial products and clinical applications.
Translating Triptolide

Triptolide:
• Diterpenoid triepoxide extract from Chinese herbal plant;
• Potent antitumor agent in preclinical pancreatic cancer studies but solubility, narrow TI and lack of IP limit clinical & commercialization potential.

Key milestones:
• CTM partnership to develop triptolide for pancreatic cancer (2007)
• Minnelide, a highly water-soluble analog, synthesized by ITDD (2008)
• Minnelide characterization & POC studies completed, selected as lead (2009)
• Pre-IND meeting (2009)
• Comprehensive development plan designed and executed (2010)
• Pivotal toxicology studies initiated (2011)
• Preclinical studies needed for IND completed (2011)
Minnelide Preclinical Development

Outcomes:

• Minnelide licensed to a University start-up (Minneamrita), which plans to complete clinical development

• Minneamrita used University-generated data to file an IND for a FIH clinical trial.

• Clinical trial for patients with advanced GI tumors ongoing at Masonic Cancer Center and TGen/Virginia Piper Cancer Center; 33 patients enrolled thus far.
Translating Success

University of Minnesota

Clinical Testing

Clinical Trial Enabling

Proof of Concept

Validation & Optimization

Research & Discovery
Thank You & Good Luck!