Early Drug Development: A Regulatory Perspective

4th PQRI/FDA Conference on Advancing Product Quality
April 9-11, 2019

Ramesh Sood, Ph.D.
Senior Scientific Advisor (acting)
ONDP, OPQ
Outline

• Background
• Drug development process
• Investigational New Drug Applications (INDs)
• Interaction opportunities
• Expedited development/review programs
• Conclusions
CDER Mission

CDER’s mission is to protect and promote public health by helping to ensure that human drugs are safe and effective for their intended use, that they meet established quality standards, and that they are available to patients.
CDER Mission

• Promote public health by ensuring the availability of safe and effective drugs
  • Oversight of new drug development and review of drug marketing applications
    • Development-phase consultations with drug innovators
    • Development of regulations and guidance to industry
    • Oversight of the conduct of clinical trials

• Protect public health by promoting the safe use of marketed drugs

• Protect public health by ensuring the quality and integrity of marketed drug products
Office of Pharmaceutical Quality

Pharmaceutical quality is our shared goal of assuring consistently safe and effective drugs are available to patients and consumers.

Pharmaceutical quality is what gives them confidence in their next dose.

**OPQ Mission**
OPQ assures that quality medicines are available to the American public

**ONDP Mission**
Leveraging knowledge and expertise to collaboratively link product performance to the patient and communicating risk-based recommendations effectively to all internal and external stakeholders

**ONDP Vision**
Linking pharmaceutical quality to the patient in a meaningful way

**Motto**
One Quality Voice
Outline

• Background
• Drug development process
• Investigational New Drug Applications (INDs)
• Interaction opportunities
• Expedited development/review programs
• Conclusions
Drug Discovery Phases

PRE-CLINICAL RESEARCH
- SYNTHESIS AND PURIFICATION
- ANIMAL TESTING
  - Short-term
  - Long-term

CLINICAL STUDIES
- Phase 1
- Phase 2
- Phase 3

NDA REVIEW
- Accelerated Development/Review
- Treatment IND
- Parallel Track

IND SUBMITTED
- FDA Time
- Industry Time

IND SUBMITTED
- FDA Time
- Industry Time

NDA Submitted
- FDA Time
- Industry Time

Review Decision

Source: FDA/Center for Drug Evaluation and Research
Drug Discovery Phases

**Drug Development**
- Drug sponsor develops a new drug compound and seeks to have it approved by FDA for sale in the United States.

**Pre-Clinical Phase**
- **Drug Sponsor’s Discovery and Screening Phase**
  - **IND Application**
    - The sponsor submits an Investigational New Drug (IND) application to FDA based on the results from initial testing that include the drug’s composition and manufacturing, and develops a plan for testing the drug on humans.

**Clinical Phase**
1. **Phase 1**
   - The typical number of healthy volunteers used in Phase 1; this phase emphasizes safety. The goal here in this phase is to determine what the drug’s most frequent side effects are and, often, how the drug is metabolized and excreted.
   - **IND Review**
     - FDA reviews the IND to assure that the proposed studies, generally referred to as clinical trials, do not place human subjects at unreasonable risk of harm. FDA also verifies that there are adequate informed consent and human subject protection.

2. **Phase 2**
   - The typical number of patients used in Phase 2; this phase emphasizes effectiveness. This goal is to obtain preliminary data on whether the drug works in people who have a certain disease or condition. For controlled trials, patients receiving the drug are compared with similar patients receiving a different treatment—usually a placebo, or a different drug. Safety continues to be evaluated, and short-term side effects are studied.
   - **Phases 2 & 3**
     - At the end of Phase 2, FDA and sponsors discuss how large-scale studies in Phase 3 will be done.

3. **Phase 3**
   - The typical number of patients used in Phase 3. These studies gather more information about safety and effectiveness, study different populations and different dosages, and uses the drug in combination with other drugs.
Investigational New Drug Application (IND)

• “A sponsor shall submit an IND to FDA if the sponsor intends to conduct clinical investigation with an investigational new drug that is subject to section 312.2(a).”
  – There are certain exemptions

• Section 312.2(2) states: “....this part applies to all clinical investigations of products that are subject to section 505 of the FD&C act or to the licensing provisions of the Public Health Services Act”
General Principles of IND Submission

• CFR 312.22 (a):
• “FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety”.
  – Phase 1: safety of the phase 1 investigations
  – Phase 2 and 3: Also includes assessment of the scientific quality of the investigation and likelihood that the data will meet standards for supporting marketing approval
IND Content and Format

• Information needed in the IND (CFR 312.23):
  – Cover Sheet
  – Table of Content
  – Introductory statement and general investigational plan
  – Investigators brochure
  – Protocols
  – Chemistry, Manufacturing and Controls information (CMC)
  – Pharmacology and toxicology information
  – Previous human experience with the investigational drug
  – Additional information (e.g., abuse potential, pediatric study, radioactive drug, etc.)
CMC Content

- 21CFR 312.23(a)(7)(i)
- “Although in each phase of the investigation sufficient information is required to be submitted to assure the proper identification, quality, purity and strength of the investigational drug, the amount of information needed to make that assurance will vary with the phase of investigation, proposed duration of investigation, dosage form and amount of information otherwise available...”
Drug Substance

- Description
- Physicochemical and biological characteristics
- Name and address of manufacturer
- General method of preparation
- Analytical procedures and limits to assure identity, strength, quality and purity
- Stability of DS to support its use during toxicological studies and planned clinical studies
- Impurity profile of toxicological and clinical batches
Drug Product

- Components and composition
- Name and address of the manufacturer
- Description of manufacturing and packaging processes
- Analytical procedures and limits to assure identity, strength, quality and purity
- Stability information to support the product stability during clinical studies duration
Additional Information

• Description of the composition, manufacture and control of placebo when used
• Information about any comparator being used
• Labeling information
• Claim for categorical exclusion under section 25.31 (e)
Outcome of Initial Review

• FDA has 30 calendar days to review the initial IND
• Safety is the main consideration at this stage
• Interdisciplinary team reviews the initial IND for their respective sections
• Any additional information needed to make a decision may be requested
• Based on the review
  – IND may be safe to proceed
  – Or may be put on hold, if there are pending safety related concerns
Major Reasons for Clinical Hold

• Subjects are or would be exposed to an unreasonable and significant risk or illness or injury
• Clinical investigators named not qualified by reason of scientific training and experience
• Investigators brochure misleading, erroneous, or materially incomplete
• IND does not contain sufficient information required under section 312.23
Examples of CMC Reasons or Clinical Hold

- CMC information to ensure safety of the subjects is not provided or the information provided presents safety concerns
  - Product made with unknown and impure components
  - Synthesis/manufacturing information provided is insufficient to evaluate safety attributes of the material to be used
  - Presence of impurities with known or likely toxicity which have not been adequately evaluated in preclinical safety studies
  - Insufficiently defined impurity profile of clinical material
  - Lack of sterility assurance or endotoxin control for sterile products
  - Product not stable through the clinical study duration or information to make this assessment not provided
  - Poorly characterized master or working cell banks
Additional Information During Clinical Development

• Protocol amendments (section 312.30)
  – Change in protocol, new protocol, new investigator

• Information amendments (section 312.31)
  – New toxicology, CMC or other technical information
    • Change in dosage form, major formulation change, change in API source, new impurities etc.

• IND safety reports (section 312.32)

• Annual reports (section 312.33)
  – Within 60-days of anniversary date
  – E.g., Summary of studies in progress/completed
  – Summary of significant manufacturing changes, stability data
Treatment INDs

• Purpose:
  – To facilitate the availability of the promising new drugs to desperately ill patients early in the drug development before marketing approval

• Treatment IND can be submitted for
  – The drug intended to treat serious or immediately life threatening disease
  – There is no comparable or satisfactory alternative drug or therapy available to treat that stage of disease in the intended patient population
  – The drug is under investigation under an IND or all clinical trials have been finished
  – The sponsor of the controlled clinical trial is actively pursuing marketing approval of the investigational drug with due diligence
Treatment IND/Protocol

- Treatment protocol can be submitted by the IND sponsor
- Treatment IND can be submitted by a licensed practitioner if the IND sponsor does not want to submit a treatment protocol but will give drug under investigation to the practitioner
  - CMC information mentioned before under section 312.23 will be needed
  - However, if IND sponsor agrees to provide investigational drug to the licensed practitioner in support of his/her treatment IND is deemed to authorize the incorporation-by-reference of the technical information contained in the sponsor’s IND into the medical practitioner’s treatment IND
- Treatment can start 30-days after receipt of the IND/protocol or earlier notification by FDA
Outline

• Background
• Drug development process
• Investigational New Drug Applications (INDs)
  • Interaction opportunities
  • Expedited development/review programs
• Conclusions
Meetings with FDA

Meetings may be face to face, teleconference, or written response
FDA generates official non-binding meeting minutes

Type A  Stalled development or dispute
Type B  Pre-IND, pre-NDA, pre-BLA, Breakthrough/RMAT
Type B(EOP)  End of phase meeting
Type C  All other meetings

<table>
<thead>
<tr>
<th>Meeting Type</th>
<th>Meeting Scheduling or Written Response Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>30 calendar days from receipt of meeting request</td>
</tr>
<tr>
<td>B</td>
<td>60 calendar days from receipt of meeting request</td>
</tr>
<tr>
<td>B(EOP)</td>
<td>70 calendar days from receipt of meeting request</td>
</tr>
<tr>
<td>C</td>
<td>75 calendar days from receipt of meeting request</td>
</tr>
</tbody>
</table>
FDASIA (2012)

• Section 901—Fast Track Drug Products
  – Facilitate development and expedite the review of drugs for the treatment of a serious or life-threatening disease or condition that demonstrates the potential to address unmet medical need

• Section 902—Breakthrough Therapy Drugs
  – Expedite the development and review of a drug for serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies
    • Provide timely advice and interactive communication with the sponsor regarding the development of the drug
    • Provide a collaborative cross disciplinary review utilizing senior managers and experienced review staff, as appropriate
## Comparison of FDA’s Expedited Programs

<table>
<thead>
<tr>
<th>Qualifying criteria</th>
<th>Breakthrough</th>
<th>Fast Track</th>
<th>Accelerated Approval</th>
<th>Priority Review</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Qualifying criteria</strong></td>
<td>• Treat serious condition. • Preliminary clinical evidence indicates drug may demonstrate substantial improvement on a clinically significant endpoint over available therapies</td>
<td>• Treat serious condition. • Non-clinical or clinical data demonstrate the potential to address unmet medical need • OR • Drug designated as Qualified infectious disease product</td>
<td>• Treats serious condition. • Provides meaningful advantage over available therapies • Demonstrates an effect on surrogate end point that is likely to predict clinical benefit</td>
<td>• Application for drug that treats serious condition. • If approved, will provide significant improvement in safety or effectiveness • Drug qualified infectious disease product.</td>
</tr>
<tr>
<td><strong>When to submit request</strong></td>
<td>With IND or after Ideally no later than EOP2 meeting</td>
<td>With IND or after Ideally no later than the pre-NDa or pre-BLA meeting</td>
<td>Discuss with review division</td>
<td>With original BLA, NDA or efficacy supplement</td>
</tr>
<tr>
<td><strong>Features</strong></td>
<td>• Intensive guidance on drug development. • Organizational commitment • Rolling review • Other actions to expedite review (e.g. priority review)</td>
<td>• Actions to expedite development and review • Rolling review</td>
<td>• Approval based on effect on surrogate endpoint</td>
<td>Shorter review clock</td>
</tr>
</tbody>
</table>
Quality Expectations

- Are safe, efficacious, performs consistently over shelf-life and available
- Quality expectations not based on the approval process (accelerated vs standard)
- Willing to accept inherent potential risk as long as benefit outweighs the inherent risk
- US Prescribing Information has no section to include quality related risk
- Shared responsibility to meet these expectations
Regulators Challenges for Expedited Development and Assessment

• Accelerated manufacturing development likely to have less information than typically available
  – Challenging to establish/evaluate control strategy
  – Setting product specifications
  – Setting commercially viable expiration period
• Makes it challenging to do a risk-benefit assessment regarding risk of less CMC information vs. patient benefit
• Require innovative risk-mitigation strategies to ensure product quality and reduce quality related product risk to an acceptable level
Regulators Challenges for Expedited Development and Assessment

- Lack of sufficient data from
  - Commercial manufacturing site
  - Stability data to support long shelf-life
  - Data to bridge clinical and commercial materials
  - Commercial supply/availability considerations

- Procedural/Assessment challenges
  - Increased communication during pre-submission and assessment period
  - Usually have priority status with shortened time line
  - Needs to manage with existing high workload
  - Assessment timing constraints for inspections
Summary

• Most clinical investigations in humans require submission of an IND

• Sufficient CMC information should be provided in an IND to assure identity, quality, purity and strength of the study drug

• The level of CMC information increases as development progresses

• Safety concern is the primary reason for placing an IND on clinical hold based on CMC section in the initial phase 1 study

• Various resources (guidances, meetings) for interaction with FDA are available to sponsors during clinical development

• Expedited pathways are available for developing/getting approval for serious and life-threatening diseases
Thank you!

Questions?
The Office of Pharmaceutical Quality assures that quality medicines are available for the American public.