4.1 – Objectives of Clinical Trial Assessment

Presentation to APEC Preliminary Workshop on Review of Drug Development in Clinical Trials

Celia Lourenco, PhD, Manager, Clinical Group I
Office of Clinical Trials
Therapeutic Products Directorate
Disclaimer: the information within this presentation is based on the presenter's expertise and experience, and represents the views of the presenter for the purposes of a training workshop.
Overview

- Overarching objectives of clinical trial assessment
- Preliminary considerations
- Process in clinical trial assessment
- Chemistry, manufacturing, and controls
- Clinical component
- Regulatory decision
Objectives of Clinical Trial Assessment

- Protection of Clinical Trial Subjects
  - Adequate disclosure of potential risks
  - Data integrity
  - Societal benefits from trial
  - Trial has Scientific merit
  - CMC is acceptable
  - Regulations
  - Regional & international guidelines
  - Ethics review
  - Scientific merit
  - CMC is acceptable
  - Regulations
  - Regional & international guidelines
  - Ethics review

Objectives of Clinical Trial Assessment:

- Adequate disclosure of potential risks
- Data integrity
- Societal benefits from trial
- Trial has Scientific merit
- CMC is acceptable
- Regulations
- Regional & international guidelines
- Ethics review
- Scientific merit
- CMC is acceptable
- Regulations
- Regional & international guidelines
- Ethics review
Preliminary Considerations

- Carry out a quick scan of the application to determine if there could be major gaps

- This helps in prioritization, obtaining information and mobilizing expertise for decision-making:
  - Stage of development / phase of trial?
  - Disease target?
  - Subject population?
  - Potential safety concern(s) in drug class?
  - Sponsor?
Stage of development

- **FIH**
- **Phase I**
- **Phase II**
- Not marketed anywhere, Phase III trials ongoing
- Marketed in other countries but not in own country
- Marketed in several ICH countries including own country (e.g., clinical trial in a new indication)
Disease Target

- Morbidity and mortality of the disease
- Prevalence of the disease
- Availability of current therapies
- Current clinical practice guidelines
- Potential for exaggerated pharmacodynamic effects
Subject Population

• Healthy adults
• Adult patients
• Pharmacogenomic subpopulation
• Elderly patients
• Pregnant women
• Pediatric
• Vulnerable patients
Drug Product Type or Class

- Route of administration: oral, intravenous, intramuscular, subcutaneous, inhalation, intranasal, topical (local or systemic)
- Pharmaceutical, biologic, radiopharmaceutical: is it a novel class of drug substance/product? (e.g., nanosuspension, oligonucleotide, gene therapy)
- Potential risks with drug product or class, such as:
  - immunogenicity (e.g., PRCA)
  - hypersensitivity
  - human-sourced excipients (e.g., risk of BSE, viruses, etc.)
  - immunosuppression
  - birth defects
  - QT-prolongation
  - drug-dependence
  - liver toxicity
  - other…
Sponsor

- Large pharmaceutical company
- Small pharmaceutical or biotech
- Domestic or international
- Academic

Protection of clinical trial participants always prevails, regardless of who the sponsor is
Process in CT Assessment

Clinical

- Preliminary assessment
- Investigator's brochure
- Protocol
- Informed consent form

Drug substance
Drug product
Supporting information

Chemistry, manufacturing & controls

Regulatory decision
Chemistry, Manufacturing, and Controls

- Drug substance
- Drug product
- Impurities
- Manufacturing facilities
- Manufacturing process
- Quality control
- Supporting information
Drug Substance

• Nomenclature & chemistry
• Manufacture
• Characterization
• Impurities
• Control of drug substance
• Container closure system
• Stability
Drug Product

- Description and composition
- Pharmaceutical development
- Manufacture
- Control of excipients (e.g., human or animal origin)
- Control of drug product
- Container closure system
- Stability
Clinical

- Investigator’s brochure
- Protocol
- Informed consent form
Investigator’s Brochure

• Sufficient information on the following, as applicable:
  – Affinity/activity at target
  – Pharmacological activity in disease models
  – Pharmacokinetics, pharmacodynamics, and drug metabolism in two animal species
  – *In vitro* metabolism using human liver microsomes
  – Single and repeat dose toxicity and toxicokinetics in two animal species, one rodent and one non-rodent
  – Genotoxicity
  – Safety pharmacology (cardiovascular, CNS, respiratory)
  – Reproductive toxicity
  – Immunotoxicity
  – Local tolerance
  – Carcinogenicity
  – Clinical studies in humans, if available
Protocol

• Rationale
• Study design & objectives
• Population & sample size
• Drug dosage regimen and administration
• Eligibility criteria
• Study procedures and assessments
  – Safety variables
  – Efficacy variables
• Risk mitigation measures
• Subject withdrawal and trial discontinuation criteria
• Statistical analysis
Informed Consent Form

• Ensure that the following are adequately explained:
  – Objectives of the trial, number of subjects and duration of the trial
  – Trial procedures and subject’s responsibilities
  – Aspects that are experimental
  – Potential risks and anticipated benefits
  – Other available therapies
  – Medical records may be accessed by regulatory authorities
  – Subject’s participation in the trial is voluntary and subject may refuse to participate or withdraw at any time
To Arrive at the Regulatory Decision

• Approach the CT application with Safety as the foundation
• Use a systematic, step-by-step approach, integrating all information submitted in the CT application and other information that is available publicly
• Quality is linked to clinical and clinical is linked to quality
• Identify any major gaps, and seek resolution through discussion with the sponsor
• On a case-by-case basis, there can be flexibility in data requirements as long as safety is preserved
• Ensure that the decision is science/evidence-based
For a Positive Regulatory Decision

• Both CMC and clinical components comply with:
  – Regulatory requirements
  – Quality standards, as applicable
  – Acceptable risk mitigation measures in quality and clinical aspects
  – Commitments requested by regulator

• Societal benefit from the trial is considered to outweigh the risks to clinical trial subjects