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Health Canada Santé Canada

Therapeutic Products Directorate

Direction des produits thérapeutiques

Health Products and Food Branch

Direction générale des produits de santé et des aliments

4.1 – Objectives of Clinical Trial Assessment

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

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Slide 1

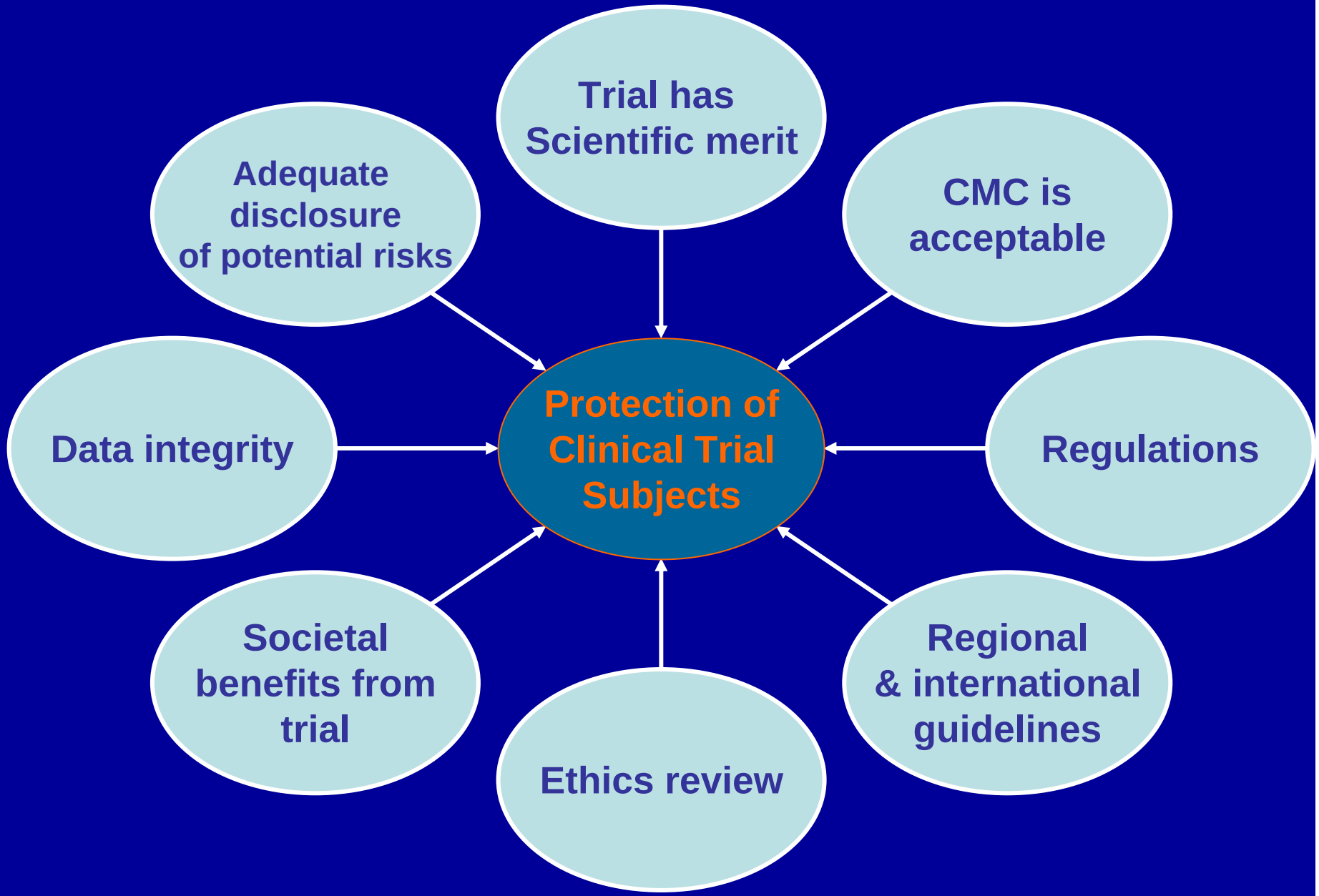
L1 Lourenco; 28.01.2008

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

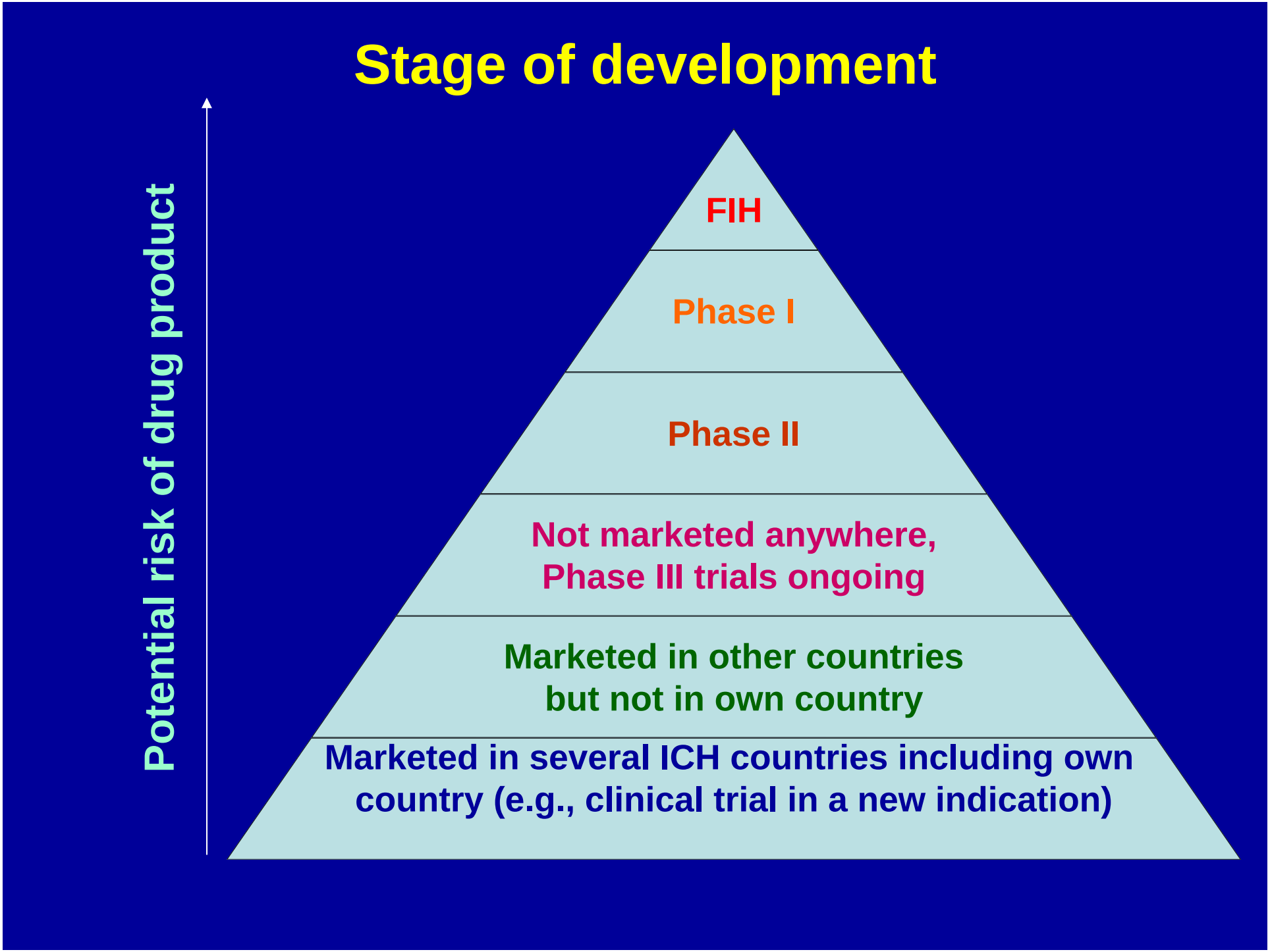
Objectives of Clinical Trial Assessment



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



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

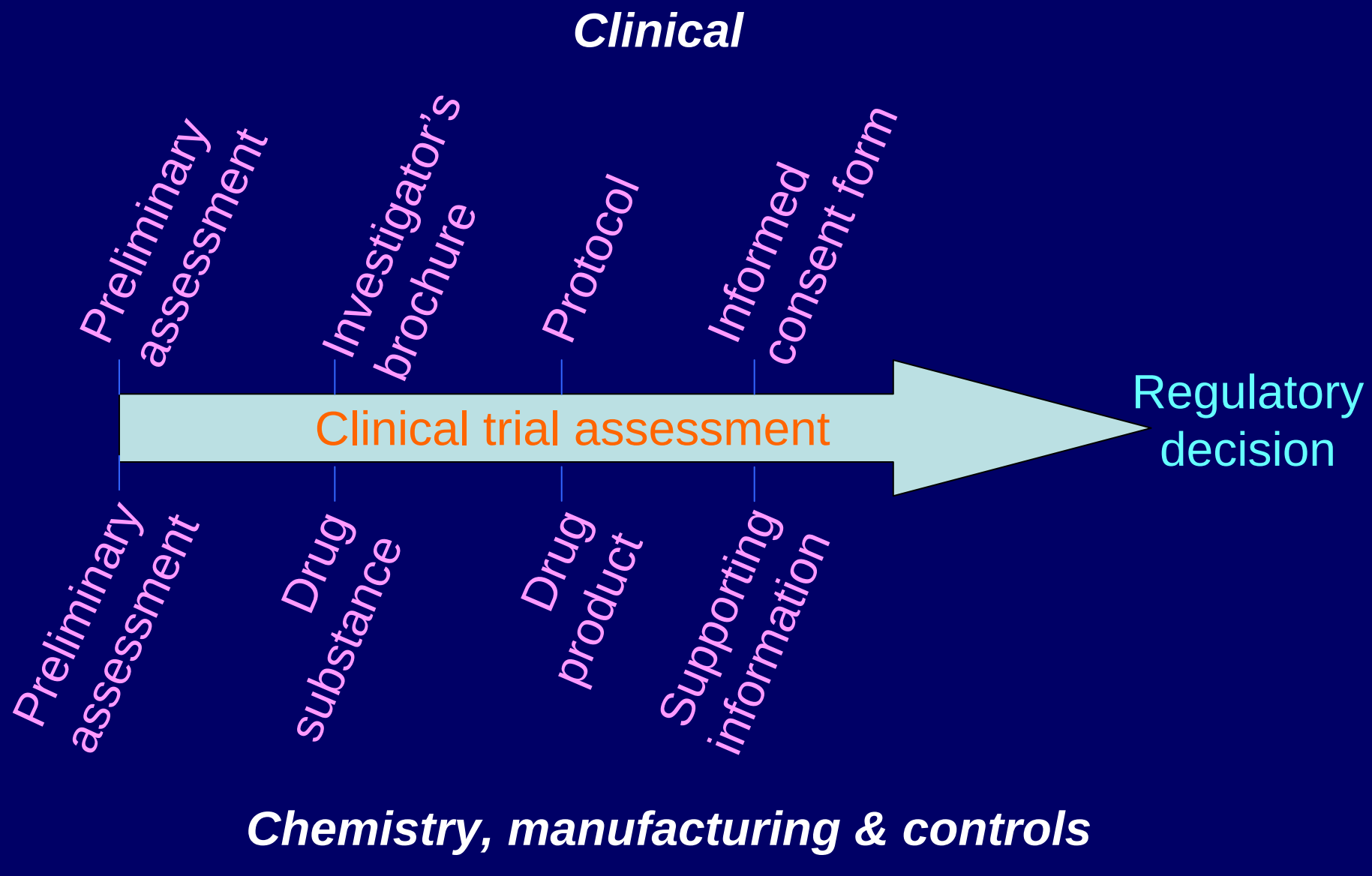
- Route of administration: oral, intravenous, intramuscular, subcutaneous, inhalation, intranasal, topical (local or systemic)
- Pharmaceutical, biologic, radiopharmaceutical: is it a novel class of drug substance/product? (e.g., nanosuspension, oligonucleotide, gene therapy)
- Potential risks with drug 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



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*