Preliminary Course

Refresher

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.
If you don't read the newspaper, you are uninformed; if you do read the newspaper, you are misinformed.

~ MARK TWAIN ~
(Samuel Langhorne Clemens)
Refresher Topics

- ICH
- Global Factors
- CT Oversight
- ICF
- Good Regulatory Practices
- Drug Development
- Bioequivalence
- Lifecycle Approach
- Pharmacogenomics
- Elements in CT Assessment

ICH

- Progress in the Global Cooperation Group (GCG) promoting knowledge of ICH guidelines

- Learning from each other in a climate of trust and cooperation, can greatly increase the strength of all harmonization efforts

- Helps to move us toward efficient and effective regulatory systems and increased availability of safe, efficacious pharmaceuticals of high quality on a global level
Global Factors on R&D

• Multinational clinical trials
• Harmonization
• Decreased number of blockbuster drugs
• Personalized medicine, pharmacogenomics
• Exponential rise in generics
• Rising costs and emerging markets
• In choosing to place a clinical trial, companies will look for countries with the appropriate laws, along with the required population, disease prevalence, health care system, qualified investigators and staff, with high standards of professional integrity and ethics

CT Oversight

• Origins
• Roles and Responsibilities
• Good Regulatory Practices
• Regulations and Guidelines
Origins of CT Oversight

Lessons from the Past
- Tuskegee Syphilis Experiment (1932 – 1972)
- WWII experiments
- Thalidomide disaster (early 60's)
- Diethylstilbestrol and vaginal cancer in female offspring (1971)
- 20 healthy volunteers infected with tuberculosis in bioequivalence drug trial (2006)

Summary
- Lessons learned from the past and present
- International movement for the protection of human rights and research volunteers
- Incorporation of human rights principles into regulations
- Research in humans must be conducted with the highest level of scientific and ethical standards
- There is public trust in the regulator, and as regulators, we have a duty to protect
- In moving forward: life-cycle of drug product, pharmacogenomics

CTs: Roles and Responsibilities

Major Groups involved in CTs
- Regulator
- Sponsor
- Institutions/Clinical Trial Sites
- Qualified Investigators (QI) & Staff
- Research Ethics Boards
- Clinical trial subjects or legal guardians
- Data safety Monitoring Board (DSMB)
- Contract Research Organization (CRO)
- Site Management Organization (SMO)

Summary
- Regulator has the legal authority, therefore, has responsibility and accountability
- All have legal and ethical responsibilities and accountabilities
- By signing the consent form, subjects do not forfeit their legal rights
Informed Consent

A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

Consent in Vulnerable Populations

(Defined in E6 - GCP and relevant to E7 - Geriatrics and E11 - Pediatrics)

- Those not capable of consenting (minors or incapacitated)
  - Consent given by a legal representative
  - Subjects should be informed to the extent compatible with the understanding

- Those unable to read or make their mark
  - Use an impartial witness

- In Emergency situations
  - When not possible to get consent from a legal representative or impartial witness, the subject can be enrolled if provisions for such are stipulated in the protocol
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Vulnerable Subjects

- Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate.

- Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

Impartial Witness

A person, who is independent of the trial,

who cannot be unfairly influenced by people involved with the trial,

who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and

who reads the informed consent form and any other written information supplied to the subject.
Good Regulatory Practices

- Develop regulations that are flexible
- Use risk management principles
- Be consistent in guidance and decision-making
- Be efficient in information and records management
- Measure and maintain performance and transparency
- Be reachable and reach out to stakeholders
- Be aware of changing regional and global factors in R&D and access to drugs

Risk Management Principles

- Science-based risk management, with risk-based decision-making

- Precautionary principle: “absence of full scientific certainty shall not be used as a reason to postpone decisions when faced with the threat of serious or irreversible harm”

- Proactive – take initiative to address and prevent public health & safety concerns:
  - Safety of Canadian blood system
  - Bovine spongiform encephalopathy / Creutzfeldt-Jakob disease
  - Pandemic influenza

- Know own strengths and weaknesses:
  - Consult with experts on complex scientific, medical, or regulatory issues
  - Implement and make use of scientific advisory committees
Consistency (both in Guidance and Decisions)

- Adopt international guidelines when appropriate
- Develop SOPs:
  - Good guidance practices
  - Good review practices
- Develop and implement guidelines to address regional issues
- Be aware of drivers, such as globalization

Drug Development

- Phases of clinical trials
- Life of drug as seen by the regulator
- Common drug targets and future directions
- Current and future challenges and drivers for the regulator
Drug Molecule Life as Seen by Regulator

- Exploring other applications
  - New disease indications
  - New route of administration
  - New population

Continuous monitoring and assessment of safety

Phase I
Phase II
Phase III
1st Regulatory approval
1st Generics

Years since patent first filed by innovator

Small scale
Larger scale
Commercial scale
Impact of generics

Non-clinical testing

Objectives of Clinical Trial Assessment

- Trial has Scientific merit
- CMC is acceptable
- Protection of Clinical Trial Subjects
- Adequate disclosure of potential risks
- Data integrity
- Societal benefits from trial
- Ethics review
- Regulations
- Regional & international guidelines
Regulations and Guidelines (for C&M and Non-clinical data)

At the clinical trial stage:
- Do not require that sponsors follow ICH guidelines
- Do not inspect manufacturing sites against the Annex 2 of the GMP
- Expect that sponsors work towards meeting the guidelines by improving the manufacturing and control of the drug substance and drug product as the product progresses through clinical development
- Guidelines are applied at the marketing stage
- Generally require that sponsors follow all applicable ICH guidelines for the non-clinical program

Arriving 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
Clinical Trial Assessment
(at the different phases of development)

- Regulator and Applicant or Sponsor must identify
- What information has been collected
- What are the unclear issues
- Lack of Data
  - Good reason for increasing the # of Asian Studies
- Economic
- Motivation high for both patients and investigators
- Less ethnic differences within Asia
- From Canadian/global perspective increase ethnic data improves safety especially in multicultural societies

Continuous Assessment of Risk - Benefit

- Assessing benefit / risk involves:
  - Analysis of unmet medical need and disease characteristics
  - Analysis of data accumulated through product development

- Both the regulator and the sponsor should assess benefit / risk continuously
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Benefit / Risk

Spectrum of Proof of Concept (PoC)
- Target
- Mechanism
- Efficacy
- Commercialization

Translational Medicine approach with 2 phases:

Exploratory Phase
- FIM: SD safety and tolerability in Healthy volunteers
- PoC (may require SD and MD in patients in preparation of)
- Validation

Confirmatory Phase
- Human ADME, multiple PK studies (bioavailability, special populations, drug-drug interactions), mechanistic (biomarker, imaging studies), phototox, Abuse liability studies.

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Life-Cycle Approach

Pharmacovigilance and Benefit-Risk Management

- Druggability
- Favorable PK profile
- Important indications
- Technology

CLINICAL TRIAL DESIGN
- Clinical Trial Objectives
- Described ADRS Reporting

CONFIRMATORY PHASE
- Human ADME, multiple PK studies (bioavailability, special populations, drug-drug interactions), mechanistic (biomarker, imaging studies), phototox, Abuse liability studies.

EXPLORATORY PHASE
- FIM: SD safety and tolerability in Healthy volunteers
- PoC (may require SD and MD in patients in preparation of)
- Validation

EVALUATION
- Understanding of Human and Animal Kinetics
- Evaluation of Efficacy
- Evaluation of Safety
- Evaluation of Utility
- Evaluation of Use in Special Populations
Bioequivalence Studies

- Objective & characteristics
- Study designs
- Essential components in the review

Objective & Characteristics

**Objective**
- To test the formulation of a subsequent-entry pharmaceutical product as compared to a reference

**Characteristics**
- Healthy adult volunteers
- Canadian reference product or product that is marketed in US, EU, Australia, or Switzerland
- Single or total daily dose does not exceed that specified in the labelling of the reference drug product
- The study does not include the simultaneous administration of a radioactive labelled and unlabelled drug product
### Study Designs

- Single dose with a two period cross-over design
- Conducted in fasted and fed state (if indicated to be taken with food)
- Three and four-period cross-over for modified-release formulations
- Some studies involve parallel group designs
- Steady-state studies for formulations likely to accumulate (e.g., delayed release drug products)

### Quality Review

- Information on Canadian Reference Product or Non-Canadian Reference Product
- Drug substance:
  - Attestations (GMP, ICH organic solvents, TSE/BSE)
  - Batch analyses
- Drug product:
  - Composition of dosage form
  - Attestation (non-medicinal ingredients consistent with reference product, prohibited excipients, GMP)
  - Batch analyses
  - Excipients of human or animal origin (information may be submitted later, but 2 days prior to starting the study)
### Clinical Review

- Use a Reviewer’s check-list
- Dose as labelled
  - Consider titration and tapering at end of dosing (“critical dose” drugs - abrupt discontinuation can lead to withdrawal symptoms)
- Wash-out period
  - Should consist of at least 10 terminal elimination half-lives; should not exceed 3 to 4 weeks
- Sample size usually >12 and depends on the estimated intra-subject variability
- Eligibility criteria
  - Should take into consideration the contraindications, warnings and precautions for the drug
  - TB screening for drugs with immunosuppressant properties (medical history and skin test)
- Pregnancy testing if females of child-bearing potential included; acceptable contraceptive methods defined
- Total blood volume collected should not exceed 500 mL within a 4 week period
- Intravenous catheter for multiple blood draws in early time points
- Risks related to the drug are listed in the informed consent form and acceptable contraceptive methods defined

### Summary Bioequivalence Studies

- Choice of Comparator is important
  - Not all studies for local registration
  - Canada allows use of non-local reference product from another ICH region, Australia, or Switzerland
- Health Canada has several guidance documents on the requirements for registration
- Review of comparative bioavailability studies focuses on safety
Pharmacogenomics (PGx)

Pharmacogenomics is the identification and study of genes and their corresponding products which influence individual variation in the efficacy and/or toxicity of therapeutic products, and the application of genomic information to help inform therapeutic product development and/or clinical application. This may include:

- Choosing the most appropriate therapeutic product for a patient;
- Selecting optimal dose; and/or
- Identifying those at risk for unexpected or more frequent adverse drug reactions

Informed Consent and PGx

Very important in all following scenarios:

- PGx testing carried out within the context of the main clinical trial
- PGx testing as a sub-study that is not linked, but may be indirectly related to the main clinical trial
- For future use (banking) as in exploratory studies

The informed consent form should explain:

- That PGx testing will be conducted and the purpose of such testing (i.e., how the PGx data will be used)
- The sample and data coding strategy, and the storage, destruction, and security measures used for sample and data preservation to ensure confidentiality to the extent possible
- The rights of the subject with regards to the PGx testing and the study overall
PGx Regulatory Guidance

- FDA: Guidance for Industry - Pharmacogenomic Data Submissions
- EMEA: Reflection Paper on Pharmacogenomic Samples, Testing and Data Handling
- ICH Topic E15: Definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data and sample coding categories
  - To ensure consistency in the terminology used by the different regions
- Japan
- Health Canada Guidance: Submission of Pharmacogenomic Information

Examples of PGx

**Drug Metabolism**
- CYP2C19 and CYP2D6 Variants – Poor vs extensive metabolizers
- N-acetyltransferase - slow and fast acetylators
- Deficiency of dihydropyrimidine dehydrogenase (DPD) activity - Capecitabine
- Glucose- phosphate dehydrogenase (G6PD) deficiency - Rasburicase
- Thiopurine methyltransferase deficiency or lower activity - Azathioprine
- Homozygous UGT1A*28 allele - Irinotecan

**Drug Target**
- C-KIT expression in GIST - Imatinib
- CCR5 -Chemokine C-C motif receptor on human T-cell - Maraviroc
- EGFR expression - Erlotinib, Cetuximab, Vectibix
- Her2/neu expression – Trastuzumab, Herceptin
- Philadelphia (Ph1) chromosome – Busulfan
- ApoE4 carriers– Vasculitis – Alzheimer’s Rx Anti-Amyloid Antibody
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PGx Summary

• PGx is not a new topic but facilitated by new tools
• Several Guidance documents have been developed by different regions
• We are now seeing CTAs with a PGx component
• Co-approval of an ITA for the PGx test may be required
• Informed consent is one of the most important aspects of PGx testing

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Essential Elements in Clinical Trial Assessment

Sufficient evidence

Sufficient evidence signifies a positive benefit-to-risk ratio based on the sum of the following:

• Acceptable Quality (CMC) for the phase of development
• Acceptable supporting nonclinical and clinical data (as applicable) for the phase of development
• Acceptable protocol and informed consent form for the proposed trial
• Maintenance of the positive benefit/risk ratio during the conduct of the trial through safety monitoring of the trial as well as other ongoing trials with the drug (‘product life-cycle’ approach)
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Regulations Development

When developing regulations, consider:

- What are the disease areas of interest (what can your population offer)?
- What can your health care system offer?
- What is the status of investigator/institution-driven research in your country?
- What frameworks are in place for ethical review of human research and protection of clinical trial subjects?
- What are sponsors looking for in your country?

Prepare your regulatory framework, and scientific expertise accordingly.

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Regulatory Frameworks

- Regulations must aim to protect clinical trial subjects and enable sound benefit / risk assessment, without unduly restricting research and access.
- Regulatory requirements should take into consideration the global context.
- Globalization: adopt international guidelines where possible.
- Address regional-specific issues by developing region-specific guidelines.
- Guidance documents on process, format, and content, of clinical trial applications should be available.
Good Review Practices - Overview

- Regulatory expertise
- Scientific expertise
- Time management
- Documentation
- Systematic approach to review
- Review of subsequent information
  - Life cycle approach

Challenges

- A small group of clinical reviewers have to cover a broad knowledge base on different disease areas
  - Has the potential to lead to ill-informed decisions: “ignorance of ignorance”

- Always approach a review with a perspective of safety
  - Regulatory requirements must be met
  - Challenge sponsors if there is inconsistency with international guidelines

- Do not review in isolation
Thank You

APEC
Linnus Teo Siew Yan

Health Canada
Mike Ward and Dr's (Agnes Klein MD, Celia Lourenco, Will Stevens

ICH

Novartis
Susan D'Amico, Dr. Namrata Bahadur, Dr. Sudhichai Chokekijchal

PMDA
Dr. Junko Sato

Thai FDA
Akanid Wapeewuthikorn

Norman Viner, MD
Chief, Clinical Trials Division
Centre for Biotherapeutics and Genetic Therapies
Biologics and Genetic Therapies Directorate