



## **Regulatory Framework for Conducting Phase I Studies: a Comparison Between U.S., European Union and Canada**

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- Applications for clinical trials
  - What are the differences between Canada, US and Europe?
  - Content of the IND vs CTA
  - Review process and timelines
- Preclinical work requirements
- Phase I studies
- Clinical pharmacology and biopharmaceutics information required during drug development

- CFR: Code of Federal Regulations
- CTA: Clinical Trial Application/Authorisation
- EMEA: Europe Medicines Agency
- EU: European Union
- FDA: Food and Drug Administration
- HPFB: Health Products and Food Branch
- IB: Investigator's Brochure
- ICF: Informed Consent Form
- IND: Investigational New Drug Application
- NDA: New Drug Application
- REB: Research Ethics Board

## CANADA (HPFB)

### Health Canada

- **Health Products and Food Branch (HPFB)**
- ▶ **16 directorates/offices** including:
  - ✓ Therapeutic Products Directorate (TPD)
  - ✓ Biologics and Genetic Therapies Directorate (BGTD)
  - ✓ Natural Health Products Directorate (NHPD)
  - ✓ HPFB Inspectorate

## USA (FDA)

### Department of Health and Human Services

- **Food and Drug Administration (FDA)**
- ▶ **8 centers/offices**, including:
  - ✓ Center for Drug Evaluation and Research (CDER)
  - ✓ Center for Biologics Evaluation and Research (CBER)
  - ✓ Center for Devices and Radiological Health (CDRH)
  - ✓ Office of Regulatory Affairs (ORA)

## CANADA (HPFB)

### Food and Drugs Act

### Food and Drug Regulations

Part C: Drugs

Division 5: Drugs for Clinical Trials involving Human Subjects

Division 8: New Drugs

## USA (FDA)

### Food, Drug and Cosmetic Act

### Code of Federal Regulations (CFR)

Title 21: Food and Drugs

Part 312: Investigational new drugs (IND)

Part 314: New drug applications (NDA)

## EUROPE (EMA)

### Directive 2001/83/EC

(medicinal products)

### Directive 2001/20/EC

(clinical trials)

Each country must adopt laws and regulations to comply with the EU Directives

e.g. UK Medicines for Human Use (Clinical Trials) Regulations 2004

# *Application for an Investigational Trial Introduction*

- Sponsors must receive authorisations from regulatory authorities prior to conducting a Phase I study with an investigational product
- The IND (in the U.S) is the means through which the sponsor technically obtains an exemption from the FDA to ship an investigational drug to clinical investigators
- In Canada, a CTA must be submitted by a sponsor in order to obtain an authorization to sell or import a drug for the purposes of a clinical trial
- Authorisation to conduct a clinical trial in the European Union requires submission of a CTA to the Competent Authority of the Member State(s) where the clinical trial will be conducted (e.g., MHRA for the UK)

- Not mandatory
- Written request sent to the appropriate division in CDER or CBER
- Review division should respond within 14 days of request
- Information package should be submitted at least 4 weeks prior to formal meeting
- Information package should include:
  - Product name, chemical name/structure, dosage form/regimen  
Information about the product and indication
  - brief statement of purpose of meeting, specific objectives/outcome
  - proposed agenda
  - list of specific questions grouped by discipline
  - clinical/preclinical data and CMC information as appropriate

- Not mandatory
- Opportunity for the sponsor to present relevant data, discuss concerns and resolve issues regarding drug development
- Opportunity for Health Canada to provide guidance on the acceptability of the proposed trial(s)
- Written request
- Information package should be provided to the appropriate Directorate 30 days prior to the meeting date
- Information package should include:
  - a brief summary of all data
  - a proposed global clinical plan
  - details of the proposed clinical trials to be conducted in Canada
  - a summary of significant Quality aspects of the drug

# *Types of IND submissions in the U.S.*

- **Investigator IND**
  - submitted by a physician who initiates and conducts an investigation
  - a physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population
- **Emergency Use IND**
  - allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND
  - also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist
- **Treatment IND**
  - submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place

# *FDA Exploratory IND*

## *(Guidance posted in January 2006)*

- Guidance for Industry, Investigators, and Reviewers – Exploratory IND Studies (FDA, CDER, January 2006)  
<http://www.fda.gov/cder/guidance/7086fnl.pdf>
- Existing regulations allow flexibility in the amount of data that needs to be submitted with an IND application, depending on the goals of the proposed investigation, the specific human testing proposed, and the expected risks
- Exploratory IND study describes a clinical trial that involves very limited human exposure
- Early phase I clinical studies that assess feasibility for further development of the drug or biological product

- Exploratory IND study can help sponsors:
  - Determine whether a mechanism of action defined in experimental systems can also be observed in humans (e.g., a binding property or inhibition of an enzyme)
  - Provide information on pharmacokinetics (PK)
  - Select the most promising lead product from a group of candidates designed to interact with a particular therapeutic target in humans, based on PK or pharmacodynamic (PD) properties
  - Explore a product's biodistribution characteristics using various imaging technologies (microdose study)

- Since they present fewer potential risks, exploratory INDs require less, or different, preclinical support as compared with traditional IND
  - No need for full clinical trial program; requires rationale for selecting a compound and for the single trial or related trials
  - CMC information can be provided in a summary report to enable the Agency to make the necessary safety assessment
  - More limited toxicology evaluation

# Application for an Investigational Trial

## CANADA (HPFB)

### Clinical Trial Application (CTA)

Usually one CTA for each individual study

- Possibility of combining protocols within the same CTA
- Cross-references between applications

## USA (FDA)

### Investigational New Drug Application (IND)

**Open IND:**

- Single initial application
- New protocols sent as amendments to the IND

## EUROPE (EMA)

### Clinical Trial Authorisation (CTA)

Usually one CTA for each individual study

- More or less similar to Canada

### EudraCT

- Sponsors must register (database of trials occurring in Europe)

# CTA/IND requirements

## Bioequivalence (BE) studies

### CANADA (HPFB)

#### CTA

**Required for all studies, including bioequivalence**

Exception: Phase IV studies or studies that involve drug products that are marketed in Canada

### USA (FDA)

#### IND

**Not required for BE studies\***

Exception: IND is needed for BE studies involving:

- cytotoxic compounds
- When maximum daily recommended dose is exceeded

### EUROPE (EMA)

#### CTA

**Required for all studies, including bioequivalence**

\* IRB approval is still needed

## CANADA (HPFB)

- **Informed Consent Form (ICF)**
- N/A: Information updated in each CTA
- N/A: Safety and efficacy data limited to that in the IB

## USA (FDA)

- ICF only required to be submitted to the REB
- **Investigational Plan and Annual Reports**
- **Extensive Pre-clinical and Human Experience** (in addition to the IB)

## EUROPE (EMA)

- ICF only required to be submitted to the REB
- N/A: Information updated in each CTA
- **Extensive Pre-clinical and Human Experience** (in addition to the IB)

- 
- **Investigator's brochure (IB)**
  - **Study protocol**
  - **Chemistry, Manufacturing, and Control (CMC)**
- } **ICH E6 (Good Clinical practices)**

## CANADA (HPFB)

- ✓ **30-day** review period (default system)
- ✓ Phase 1 in **healthy volunteers**:
  - **7-day review target**
  - possibility of faster revision for subsequent submissions

## USA (FDA)

- ✓ Initial IND: **30-day** review period (default system)
- ✓ IND Amendments: study could legally begin right away, but **sponsors usually wait 30 days for potential issues**

## EUROPE (EMA)

- ✓ EU Directive: **maximum of 60-day** review period
- ✓ Each country may set shorter delays. e.g., 30 days in UK

# CTA review performance Health Canada

Class/ Catégorie Target Review 1 Objectifs Examen 1	CTA/DEC			CTA-A/ MDEC		
	2003	2004	2005	2003	2004	2005
PH1 BIOEQUIVALENCE-7 <i>PH1 debioéquivalence-7</i>	n= 736 Avg= 5	n= 937 Avg= 5	n= 997 Avg= 7 Mdn= 7	n= 37 Avg= 4	n= 46 Avg= 4	n= 51 Avg= 5 Mdn= 5
PH1 HEALTH HUMAN-7 <i>PH1 des humains en santé-7</i>	n= 48 Avg= 6	n= 82 Avg= 9	n= 79 Avg= 11 Mdn= 8	n= 3 Avg= 4	n= 22 Avg= 6	n= 19 Avg= 7 Mdn= 7
PH1 Other-30 Days <i>PH1 Autre- 30 jours</i>	n= 53 Avg= 22	n= 60 Avg= 27	n= 60 Avg= 27 Mdn= 29	n= 27 Avg= 15	n= 43 Avg= 14	n= 57 Avg= 22 Mdn= 24

**From Therapeutic Products Directorate (TPD) – 2005 Annual  
Drug Submission Performance Report - Part I**

[http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/docs/perform-rendement/ar-ra/tpd\\_dpt\\_annual\\_annuel\\_05\\_e.html](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/docs/perform-rendement/ar-ra/tpd_dpt_annual_annuel_05_e.html)

### **Average review time for CTAs submitted by Anapharm**

- **2004**
  - **5 days** for BE studies
  - **10 days** for Phase I studies
- **2005**
  - **7 days** for BE studies
  - **11 days** for Phase I studies

# Application for Investigational Trial Summary Table

	Canada (HPFB)	USA (FDA)	Europe (EMA)
<b>Investigational Trial Application</b>	<b>Clinical Trial Application CTA</b>	<b>Investigational New Drug Application IND</b>	<b>Clinical Trial Authorisation CTA</b>
<b>Application Process</b>	<b>Multiple CTAs</b>	<b>Open IND</b>	<b>Multiple CTAs</b>
<b>Differences in Content</b>	<ul style="list-style-type: none"> <li>▪ Investigator's Brochure (IB)</li> <li>▪ Study protocol</li> <li>▪ Chemistry, Manufacturing, and Control (CMC)</li> </ul>		
	<ul style="list-style-type: none"> <li>▪ N/AP</li> <li>▪ N/AP</li> </ul>	<ul style="list-style-type: none"> <li>▪ General Investigational Plan</li> <li>▪ Toxicology and Human Experience sections</li> </ul>	<ul style="list-style-type: none"> <li>▪ N/AP</li> <li>▪ Toxicology and Human Experience sections</li> </ul>
<b>Review Time</b>	<ul style="list-style-type: none"> <li>▪ 30 days default</li> <li>▪ 7-day review target for Phase I studies in healthy volunteers</li> </ul>	<ul style="list-style-type: none"> <li>▪ 30 days default for initial IND</li> <li>▪ N/AP</li> </ul>	<ul style="list-style-type: none"> <li>▪ Maximum of 60 days</li> <li>▪ N/AP</li> </ul>
<b>Annual Reports</b>	<b>N/AP</b>	<b>Required</b>	<b>N/AP</b>

**Absence of Toxicology and Human Experience sections**

**Possibility of shorter review periods**

# *Toxicology studies needed prior to the conduct of clinical trials*

- **Single dose (acute) toxicity studies (extensive 14-day observation)**
  - Two mammalian species (rats and dogs are often used)
  - Needed prior to first human exposure (Phase I)
  - A dose escalation study is an acceptable alternative
- **Repeated dose (sub-acute) toxicity studies**
  - Two mammalian species (rodent and non-rodent)
  - Two-week repeated studies are needed to support phase Ib studies that would involve dosing for up to 2 weeks

# Toxicology studies needed prior to the conduct of clinical trials (cont'd)

## Duration of repeated dose toxicity studies to support Phase I and II trials in EU and Phase I, II and III in the U.S. and Japan\*

Duration of Clinical Trials	Minimum Duration of Repeated Dose Toxicity Studies	
	Rodents	Non-rodents
Single Dose	2 Weeks**	2 Weeks
Up to 2 Weeks	2 Weeks**	2 Weeks
Up to 1 Month	1 Month	1 Month
Up to 3 Months	3 Months	3 Months
Up to 6 Months	6 Months	6 Months***
> 6 Months	6 Months	Chronic***

\*\* In the US, as an alternative to 2 week studies, single dose toxicity studies with extended examinations can support single-dose human trials (4).

Based on *Maintenance of the ICH Guideline on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals M3(R1)*, Nov 2000

# *Toxicology studies needed prior to the conduct of clinical trials (cont'd)*

- **Safety pharmacology** (central nervous, cardiovascular and respiratory systems) needed prior to Phase I
- **Toxicokinetic studies** (absorption, distribution, metabolism and excretion) needed prior to Phase I
  - Toxicology studies performed according to current good laboratory practices (cGLPs)
- **Genotoxicity studies**
  - In vitro tests for the evaluation of mutations and chromosomal damage generally needed prior to first human exposure
  - Standard battery of tests for genotoxicity should be completed prior to Phase II studies
- **Local tolerance studies** (for IV/SC/IM dosage forms)

## **Reproduction toxicity studies**

- Studies with men and women of non childbearing potential
  - Reproduction toxicity studies not required
- Studies including women of childbearing potential
  - in Japan
    - assessment of female fertility and embryo-fetal development is needed
  - in Europe
    - assessment of embryo-fetal development required before Phase I
    - assessment of female fertility required prior to Phase III
  - In U.S.
    - Not required before Phase I with appropriate precautions
    - Female fertility and embryo-fetal development must be assessed before Phase III

## **Drug substance and drug product**

- Has to be synthesized according to cGMP (ICH Q7)
- Quality should be tested according to ICH Q1 (stability), Q2 (\*analytical validation) and Q3 (impurity: solvents and degradation products)
- Need to have a **retest** or **expiry** date

# *Transition to Phase I*

## *Determination of starting dose*

How should we select the starting dose in Phase I?

- In the past, it was common to administer empirically 1/50 to 1/100 of the NOAEL (No-Observed-Adverse-Event Level)
- *Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers* (FDA, CDER, July 2005)  
<http://www.fda.gov/cder/guidance/5541fnl.pdf>
  - provide common conversion factors for deriving a human equivalent dose (HED)
  - delineate a strategy for selecting the MRSD for adult healthy volunteers, regardless of the projected clinical use
- alternative approaches could be proposed (e.g., use of animal pharmacokinetics and modeling rather than dose administered)

## **Phase Ia: First in Human study**

**Study design: No clear written guidance or requirements from regulatory agencies**

- Primary objective: To assess safety and toxicity profile
- Assess PK and PD (when appropriate)
- Single-dose, double-blind, placebo control
- Ascending single doses administered to different cohorts of subjects until MTD is reached
- Examples of dose escalation schemes
  - 1N, 2N, 4N, 8N, 16N, etc.
  - Fibonacci sequence: 1N, 2N, 3N, 5N, 8N, etc.
  - Escalation scheme may be adjusted according to PK data

## **Phase Ia: First in Human study (cont'd)**

- Usually conducted in healthy volunteers
- Some sponsors still prefer to include male subjects only, but regulatory agencies recommend inclusion of females as early as possible in drug development process
- Limited number of subjects per cohort (e.g., 6-8 subjects)
  - Special considerations based on the nature of the drug
- Formulation may not be the final one (e.g., oral solution)

## **Phase Ib: Multiple, ascending dose study**

- Multiple doses, double-blind, placebo control
- Assessment of safety and tolerability under multiple dose conditions
- Assessment of PK under state conditions and of PK linearity
- Assessment of PD (when possible)
- Dose and dosing regimen based on results from Phase Ia
- Duration of dosing based on PK characteristics (steady-state achievement) and target indication (often 7-10 days)
- Limited number of subjects /cohort (e.g., 6-8 healthy subjects)
- Can go to Phase II after completion of Phase Ia and Ib studies

## **Some questions that need to be answered:**

- What the body does to a drug (absorption, distribution, metabolism, elimination): i.e., pharmacokinetics of the drug
- What the drug does to the body: pharmacodynamics
- Bioequivalence of to-be-marketed formulation
- Effect of food on the bioavailability of the drug
- Effect of concomitant medications on PK and/or PD
- Are plasma concentrations increasing proportionally with doses?
- Use in special populations (e.g., elderly, pediatric, etc.)
- Need for dose adjustment in patients with impaired renal or hepatic function?

## **Phase I studies typically required**

- First time in human, single- and multiple-dose
- Pharmacokinetics
- BA/BE studies
- Dose proportionality studies
- Drug-drug interactions
- Mass balance/metabolism
- Food effect study
- Effect of age
- Effect of gender
- Renal impairment study
- Hepatic impairment
- PK/PD studies
- Effect on biomarkers
- *Proof of concept* (when possible)

## **Food effect studies**

- Effect of food on bioavailability of a drug
  - Important labelling information
  - Required for the to-be-marketed formulation
- Guidance documents are available
  - Example: FDA Guidance on *Food-Effect Bioavailability and Fed Bioequivalence Studies* (Dec 2002)
- Study Design considerations
  - Typically two-way cross-over studies
  - Fasting state vs high-fat meal
  - Some sponsors may want to study the effect of different types of meals (e.g., high fat, low fat, “cardiac meal”, etc.)

## **Food effect studies (cont'd)**

- Sample size considerations
  - Label claim for no food effect
    - Study must be powered to meet the country specific standard BE criteria (e.g., 90% CIs between 80-125% for AUC and C<sub>max</sub>)
  - If significant food effect is expected
    - Sufficient number of subjects to reliably describe the magnitude (descriptive stats only) of the food effect on AUC, C<sub>max</sub> and T<sub>max</sub> (e.g., 12-24 subjects)

## **Drug interaction studies**

- New draft FDA Guidance: *Drug Interaction Studies - Study Design, Data Analysis, and Implications for Dosing and Labeling* (Sept 2006)
- Need for DI studies may depend on preclinical findings
- Study Design considerations
  - Study drug may be seen as the substrate or as the interacting drug
  - Cross-over approach usually preferred (1 or 2-sequence)
  - Single vs multiple dose
    - e.g., if effect of interacting drug is expected to be delayed, then multiple dose administration is required

## **Drug interaction studies (cont'd)**

- Examples of design
  - Single-dose, A vs A+B vs B (convenient but not optimal)
  - Effect of B on A:  
A vs A+B (B may be administered as multiple dose regimen)
  - Effect of A on B:  
B vs B+A (A may be administered as multiple dose regimen)

## **Drug interaction studies (cont'd)**

- Choice of substrate and interacting drugs
  - Examples of substrates if study drug is an inhibitor or inducer
    - Midazolam for CYP3A
    - Theophylline for CYP1A2
    - Warfarine for CYP2C9
    - Omeprazole for CYP2C19
    - Desipramine for CYP2D6
    - “Cocktail approach” possible

## **Drug interaction studies (cont'd)**

- Choice of substrate and interacting drugs
  - Examples of inhibitors or inducers if study drug is a substrate of CYP enzymes
    - CYP 3A inhibitor: ketoconazole
    - CYP1A2 inhibitor: fluvoxamine
    - CYP2C19 inhibitor: omeprazole
    - CYP 2C9/2C19/3A inducer: rifampin

## **Drug interaction studies (cont'd)**

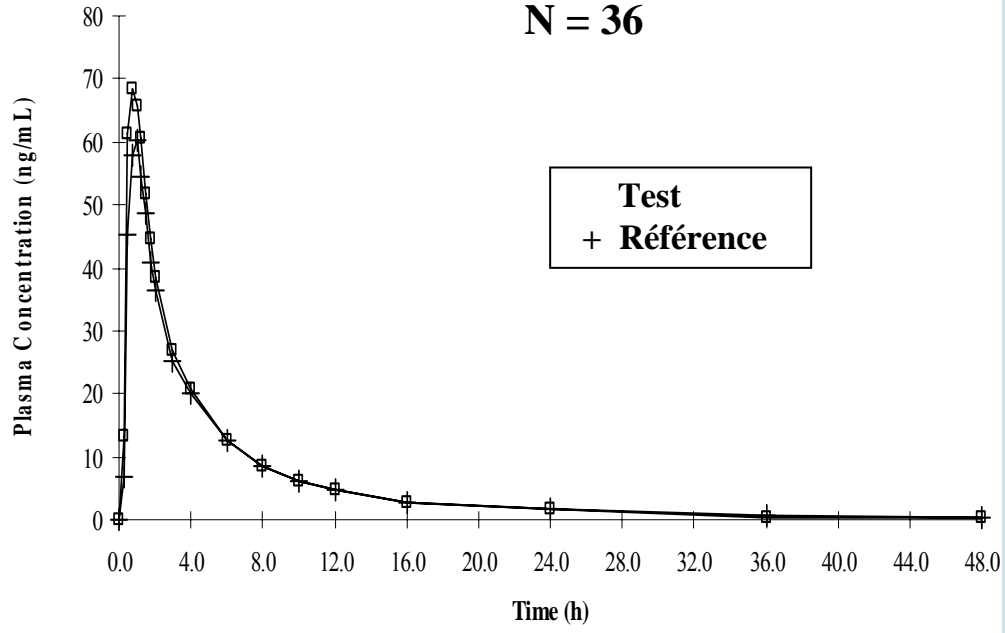
- Study endpoints
  - PK endpoints (AUC, C<sub>max</sub>, T<sub>max</sub>, Cl, T<sub>1/2</sub>, etc.) usually sufficient
  - PD endpoints may sometimes be useful
- Sample size considerations
  - Primary goal is to determine if there is any increase or decrease in exposure to the substrate
  - 90% CIs approach should be used
  - No effect boundaries
    - May be based on PK/PD information (e.g., 70-143% may be acceptable in some cases)
    - In absence of PK/PD justification, default 80-125% limits should be used

- Regulatory requirements do not vary significantly from one country to another with regards to the conduct of most clinical pharmacology studies
- However, there are major differences in bioequivalence requirements when comparing Canada vs US vs EU
  - Number of studies required (e.g., fasting and fed conditions; single and multiple-dose conditions)
  - Study design recommendations
  - Statistical criteria to establish bioequivalence

# Comparison in BE Requirements BE criteria

## Example of a study with different possible outcomes

**Mean Concentration – Time profile**  
N = 36



**Not acceptable for FDA**  
**May be acceptable for EMEA**  
**Acceptable for HPFB**

	AUCinf	Cmax
<b>Ratio</b>	<b>108.7%</b>	<b>117.6%</b>
<b>90% CI</b>	<b>104.1 - 113.6%</b>	<b>106.4 - 129.9%</b>

- **Clinical trial applications (Canada vs U.S. and EU)**
  - Information needed is similar but presentation is different
  - Less extensive toxicology and human experience sections for Canadian CTA
  - Competitive review timelines in Canada (but no “open CTA”)
- **Preclinical development**
  - Different regulatory requirements for toxicology studies
- **Clinical pharmacology studies**
  - Represent a significant portion of the clinical development
  - Critical information for product labelling

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