Early Phase Clinical Studies in China

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China Clinical Pharmacology Trials and Ethnic Differences in PK and PD” symposium, March 16, 2012
Outline

• Introduction of Phase I Facilities in China
• Inspection and Accreditation for Phase I Facilities
• Bridging Studies
Outline

• Phase I Facilities
  – Phase I Unit mainly focus on FIH trial for Innovative Drug, which with better infrastructure
  – Phase I Unit mainly focus on BE trials for generic Drug
  – An Example of Phase I Unit
    • Clinical pharmacology team
    • Clinical experts
    • Operation team
    • Data management & Statistical analysis

• Inspection and Accreditation
• Bridging Studies
Where our experience is to date

What We Can Do at Early Drug Development

- Multi-functional Phase I platform Architecture
  - Research ward
  - Lab
  - Team
- Biotransformation/Genotype & Phenotype (P450s, transporters)
- Biomarker selection and development
Research Team

- Specialist in certain therapeutic area: Clinician
- Clinical pharmacology knowledge: Pharmacologist
- Statistical skills: Statistician
- Analytical method: Chemist

Team Work
An Example of Phase I Unit
How PUMCH-Phase I Unit is developing

• Since 1995
• Operation model
  – Clinical Unit + Bioassay Lab
  – “One stop shop” (from protocol to CSR)
• Famous general hospital based
• International view
  – ICH-GCP
  – GLP
  – Bilingual communication
Standard Operation Procedure

- SOP for Phase I Research Ward
- SOP for Laboratory

Information Management System

- *Promasys system for clinical data
- *Watson-LIMS for Laboratory data

*: System is compliant with 21 CFR part 11 and has been validated by IQ, OQ and PQ.
International Quality Accreditation

- 2005: Passed the evaluation of China National Accreditation Service (CNAS) for Laboratory and obtained the Accreditation Certificate of ISO-IEC17025.
Phase I clinical research platform

- Tolerance
- PK/PD
- M & S
- FIH Trial
- Genotype
- Phenotype
- Bio-transformation
- PK
- BE
- P III
- D-D interaction
- Bio-transformation
Phase I clinical research platform

• Now our unit has 40 beds with a well-equipped bioassay lab attached. During the last 19 years, we have conducted than 200 phase I clinical trials.

• In recent years, FIH study design and dose selection is much more rely on modeling and simulation.

• By taking advantages of having a bioassay lab attached, it is possible for PUMCH investigators to guide dose selection according to the PK exposure or PD response of previous dose group. Quick response from lab is important since it will make FIH trials safer.
Outline

• Introduction of Phase I Facilities in China
• Inspection and Accreditation for Phase I Facilities
  – Organization
  – Personnel
  – Equipment
  – QA/QC
  – Training
• Study Capabilities
Inspection and Accreditation

- GUIDELINE FOR PHASE I CLINICAL TRIAL, SFDA, Effected on Dec. 02, 2011
- GUIDELINE FOR CLINICAL TRIAL BIOANALYTICAL LABORATORY PRACTICE MANAGEMENT, SFDA, Effected on Dec. 02, 2011
Two New Guidelines

• **GUIDELINE FOR PHASE I CLINICAL TRIAL, SFDA, Effected on Dec. 02, 2011**
  – Based on GCP, and the current situation of domestic Phase I trials
  – Referred to the relevant international regulations.
  – The guideline covers the purpose, foundation and scope of phase I trial. And it,
    • explains the overall requirements for phase I trials.
    • describes the principle of the management of contracts, protocol, subjects, IMP, bioassay of study samples, study data, statistical analysis and final report.
Two New Guidelines

• GUIDELINE FOR CLINICAL TRIAL BIOANALYTICAL LABORATORY PRACTICE MANAGEMENT, SFDA, Effected on Dec. 02, 2011

– to enhance the study quality management of analytical laboratory.
– the main specific requirements were proposed as following:
  • Requirements for organization and personnel
  • Requirements for hardware and software of bioanalytical laboratory
  • Management on experiment process and study quality are emphasized.
  • The system of study quality management is defined and required by this guideline
Organization, personnel and training

Requirements for organization and personnel are important parts of this guideline. Responsibilities of Laboratory leader, quality assurance unit manager, project leader and the laboratory staff are defined.

- GCP, SOP, Guidance
- Clinical Pharmacology
- Pop Approach
- Software for PK, PK/PD, Modeling & Simulation
Facility Management

Specific requirements on contract management, SOPs, experiment conducting and data management are put forward.
Quality Assurance

The system of quality management must be established and independent quality assurance personnel should be designated to ensure quality control and quality assurance in the process of study.
Equipment

Requirements for hardware and software of bioanalytical laboratory are specified. Basic requirements for laboratory facilities, archive facilities, waste disposal, instruments and equipments, materials and reagent management are proposed.

- Well-equipped Phase I Unit (e.g. First aid instruments)
- Instruments for collecting PD data (holter-ECG, EEG)
- EDC system
- Lab for bioassay
- Software for PK, PK/PD, Modeling & Simulation
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ICH Topic E 5 (R1)
Ethnic Factors in the Acceptability of Foreign Clinical Data

Question 1
Meets regulatory standards?

Yes

Yes

No further clinical study needed

No

No

Clinical data package for the new region

Question 2
Extrapolation of foreign data appropriate?

Yes

Yes

No

Study(ies) needed to bridge

No

Yes

Add. clinical study(ies) to meet regulatory standards

No

No

Clinical study(ies)
- to meet reg. requir.
- to bridge

Original CDP including foreign clinical data

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Questions to be answered

• What percentage of drugs exhibit significant pk or pd differences? (what is significant/)
• What magnitude of difference exists?
• Are there patient characteristics that increase this risk? (e.g., age, disease, nutrition)
• Do pk/pd differences have clinical consequences? (e.g., adverse events)
Questions to be answered

• What kind of methodologies will be used for testing ethnic differences?
• What kind of methodologies will be used for analyzing bridging study data?
Most studies showed similar PK with a few exceptions

Peptide drug, im and sc formulations, similar PK and PD between population

Inhaled drug, similar PK between population

Oral drug, similar PK and PD between population

Fixed-dose combination oral drug, PD between population

Oral drug, similar PK and PD between population

Oral drug, similar PK between population
GLP-1 analogue, sc formulation, similar PK between population

Oral drug, similar PK between population

Oral drug, similar PK between elderly subjects in different ethnic population

Oral drug, similar PK and PD between population

Intravenous drug, similar PK between population

Oral drug, similar PK between population

Oral drug, similar PK between population
Ethnic difference exist for PK

Comparison of plasma concentration of drug X between Chinese and Caucasian healthy volunteers (Single dose)

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Ethnic Differences on PK Exist:

Comparison of plasma concentration of drug X between Chinese and Caucasian healthy volunteers (Multiple dose)

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Methodologies for analyzing bridging studies data

• Small sample size
  PK study design: Descriptive statistics

• Parallel study design: relative bioequivalence

• Small sample size
  PK/PD study design: M&S Pharmacometrics

PK profile of Drug Y at steady state
Methodologies for analyzing bridging studies data

- Application of population approach
- Modeling & Simulation
Summary

- The new guidelines will have profound influences on the study quality of Phase I Units in China.
- In order to extrapolate clinical data across populations, it is necessary in certain conditions to study inter-ethnic differences in drug response and toxicity, ethnic diversity in pharmacokinetics and clinical outcomes.
- Methodologies employed should be clinical relevance.
- Modeling/simulation and the population approach will be applied more in the future.
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• All the volunteers who participated the studies
• The staffs at PUMC Hospital for providing the medical care to the subjects.
Thank you for your attention!
• How can the export of a subset of imported (from country A) clinical study samples into country B be managed?

• 血样出口流程.docx
• Experiences with interactions between clinical and bioanalytical site.
• Does the CFDA accept the bioanalysis of clinical samples from a study performed in China outside China under OECD-GLP/GCP
• How can the export of a subset of imported (from country A) clinical study samples into country B be managed?
The traditional Chinese medicines (TCM) are essential components of alternative medicines in China. Many TCMs are known to alter the expression of hepatic drug-metabolizing enzymes and transports.