Early Phase Clinical Studies in China

Pei Hu, MD

Phase I Unit
Clinical Pharmacology Research Center
Peking Union Medical college Hospital
Beijing China

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

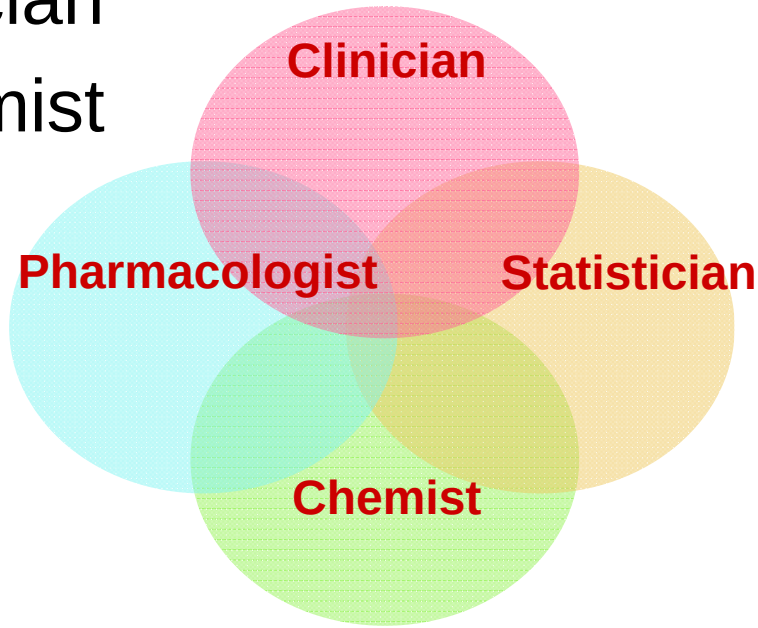
What We Can Do at Early Drug Development

- 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

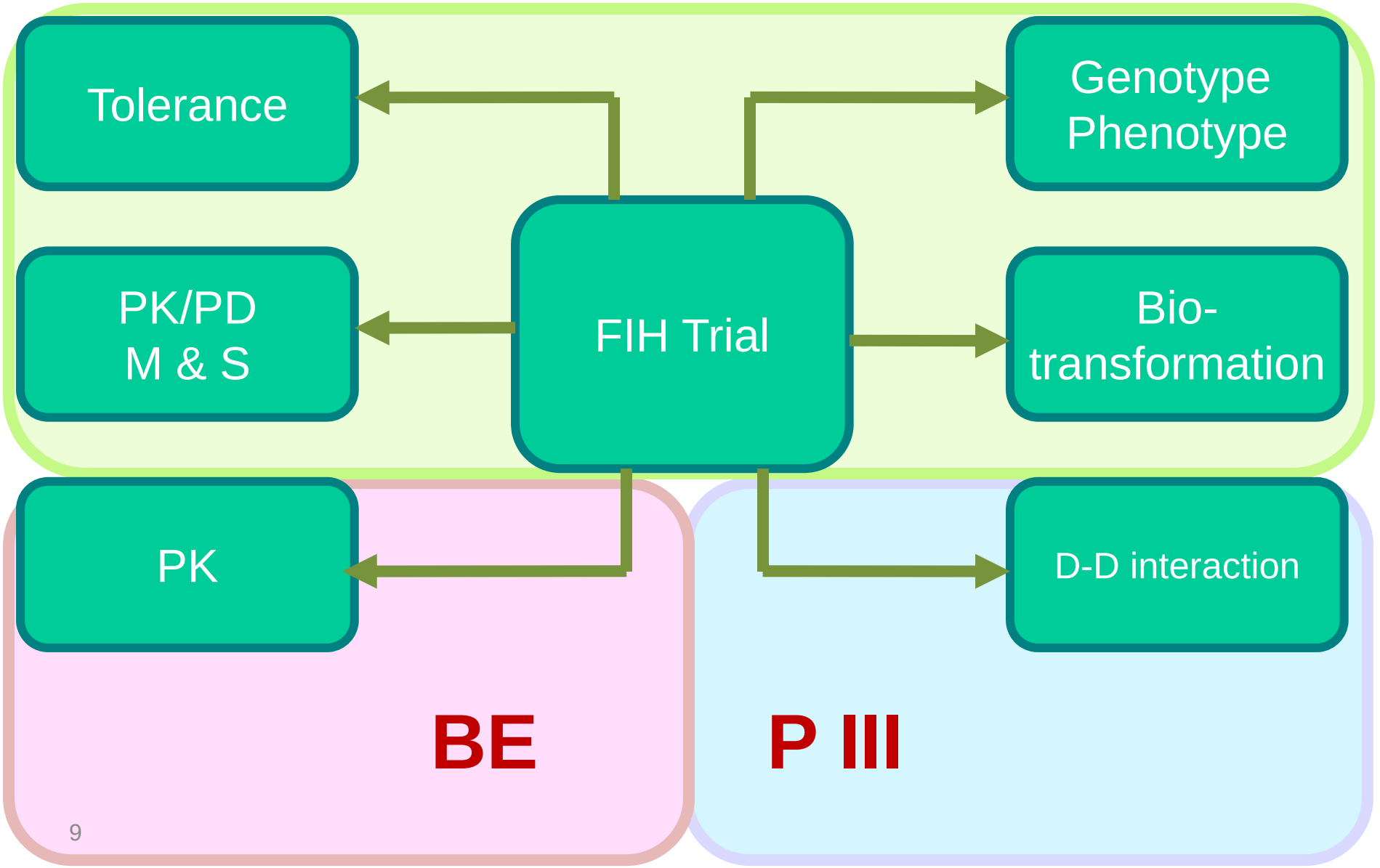
*: System is compliant with 21 CFR part 11 and has been validated by IQ, OQ and PQ.

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



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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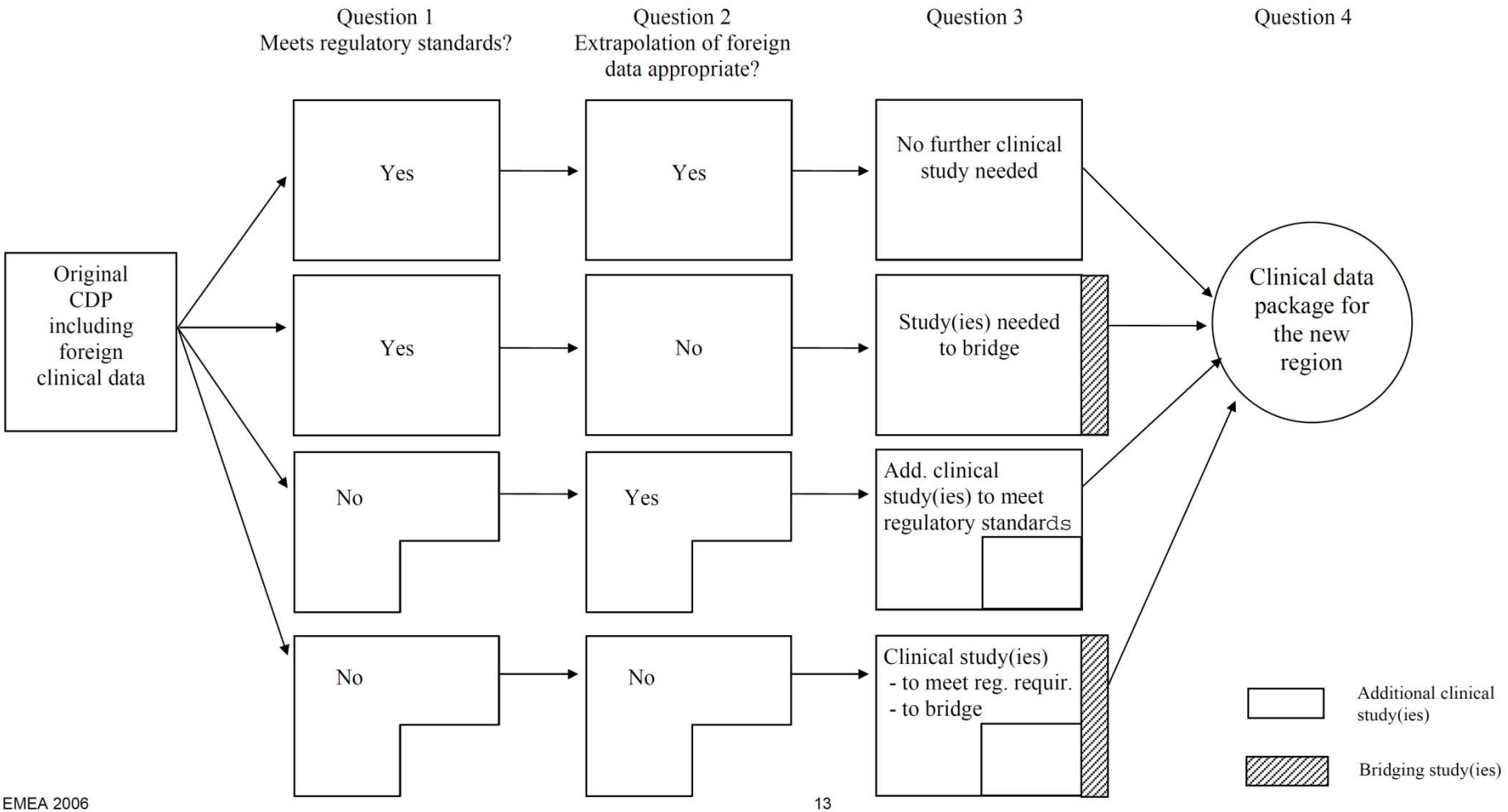
ICH Topic E 5 (R1)
Ethnic Factors in the Acceptability of Foreign Clinical Data



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
1: Chen X, Shen G, Jiang J, Liu H, Hu K, Darstein C, Lasher J, Hu P. Pharmacokinetics and Safety of Subcutaneous **Pasireotide** and Intramuscular Pasireotide Long-acting Release in Chinese Male Healthy Volunteers: A Phase I, Single-center, Open-label, Randomized Study. Clin Ther. 2014 Aug 1;36(8):1196-210.

Inhaled drug, similar PK between population
2: Jiang J, Li L, Yin H, Woessner R, Emotte C, Li R, Khindri S, Pei H. Single-and multiple-dose pharmacokinetics of inhaled **indacaterol** in healthy Chinese volunteers. Eur J Drug Metab Pharmacokinet. 2014 Apr 6.

Oral drug, similar PK and PD between population
3: Chen X, Wang H, Jiang J, Chen R, Zhou Y, Zhong W, Liu H, Hu P. The pharmacokinetic and safety profiles of **blonanserin** in healthy Chinese volunteers after single fasting doses and single and multiple postprandial doses. Clin Drug Investig. 2014 Mar;34(3):213-22.

Fixed-dose combination oral drug, PD between population
4: Chen X, Hu P, Jiang J, Liu T, Zhong W, Liu H, Zhao Q. Pharmacokinetic and pharmacodynamic profiles of a fixed-dose combination of **olmesartan** medoxomil and amlodipine in healthy Chinese males and females. Clin Drug Investig. 2012 Dec;32(12):783-90.

Oral drug, similar PK and PD between population
5: Chen X, Jiang J, Liu T, Liu H, Zhong W, Hu P. Pharmacokinetics of single and repeated oral doses **prucalopride** in healthy Chinese volunteers. Int J Clin Pharmacol Ther. 2012 Nov;50(11):797-804.

Oral drug, similar PK between population
6: Chen X, Kosoglou T, Statkevich P, Kumar B, Li J, Dockendorf MF, Wang G, Lowe RS, Jiang J, Liu H, Wang Z, Cutler DL, Hu P. Pharmacokinetics of **vorapaxar** and its metabolite following oral administration in healthy Chinese and American subjects. Int J Clin Pharmacol Ther. 2014 Aug 20.

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

7: Jiang J, Zhang J, Jacobsen LV, Hu P. The pharmacokinetics, pharmacodynamics, and tolerability of **liraglutide**, a once-daily human GLP-1 analogue, after multiple subcutaneous administration in healthy Chinese male subjects. J Clin Pharmacol. 2011 Dec;51(12):1620-7.

Oral drug, similar PK between population

8: Hu P, Bartlett M, Karan RS, Jiang J, Zhang S, Zhang J, Howard D, Yeh CM, Al-Fayoumi S, Jarugula V, Dole WP. Pharmacokinetics, safety and tolerability of single and multiple oral doses of **aliskiren** in healthy Chinese subjects: a randomized, single-blind, parallel-group, placebo-controlled study. Clin Drug Investig. 2010;30(4):221-8.

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

9: Jiang J, Hu Y, Zhang J, Yang J, Mueck W, Kubitza D, Bauer RJ, Meng L, Hu P. Safety, pharmacokinetics and pharmacodynamics of single doses of **rivaroxaban** – an oral, direct factor Xa inhibitor - in elderly Chinese subjects. Thromb Haemost. 2010 Jan;103(1):234-41.

Oral drug, similar PK and PD between population

10: Jiang J, Liu D, Hu P. Pharmacokinetic and safety profile of olmesartan medoxomil in healthy Chinese subjects after single and multiple administrations. Pharmazie. 2009 May;64(5):323-6.

Intravenous drug, similar PK between population

11: Cheng YF, Jiang J, Hu P, Reinholdsson I, Guo W, Asenblad N, Nilsson D. Pharmacokinetics of 8-hour intravenous infusion of **NXY-059**: a phase I, randomized, double-blind (within dose panels), placebo-controlled study in healthy Chinese volunteers. Clin Ther. 2008 Dec;30(12):2342-53.

Oral drug, similar PK between population

12: Zhao Q, Jiang J, Li X, Lu ZS, Hu P. Single-dose pharmacokinetics of **levetiracetam** in healthy Chinese male subjects. Br J Clin Pharmacol. 2007 May;63(5):614-7.

Oral drug, similar PK between population

13: Hu P, Jiang J, Wang H, Pietropaolo K, Chao GC, Brown NA, Zhou XJ. Single-dose and multiple-dose pharmacokinetics and safety of **telbivudine** after oral administration in healthy Chinese subjects. J Clin Pharmacol. 2006 Sep;46(9):999-1007.

Ethnic difference exist for PK

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

	Chinese	Japanese	Caucasian
$AUC_{0\text{-}24hr}$ (hr·μg/mL)	20	17	7
$AUC_{0\text{-}t}$ (hr·μg/mL)	22	NA	NA
C_{max} (μg/mL)	8	7	2
T_{max} (hr)	4	1	4

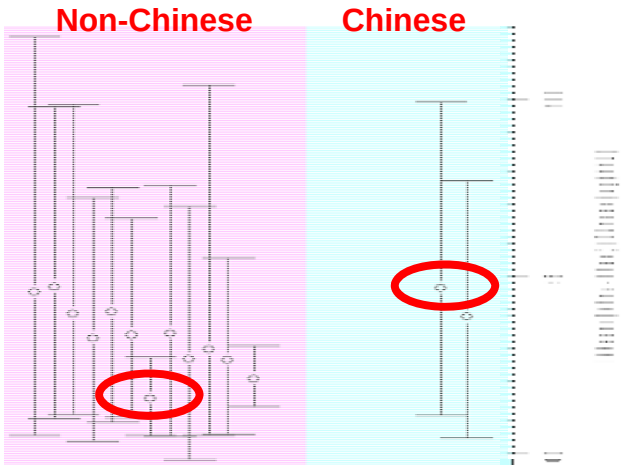
Ethnic Differences on PK Exist:

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

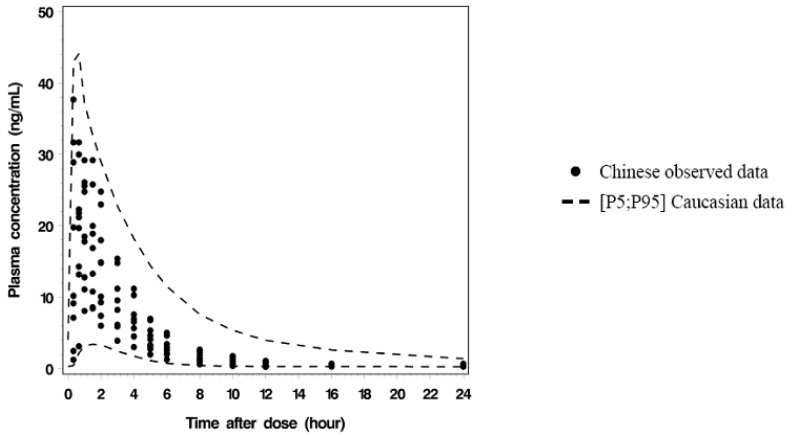
	Chinese	Japanese	Caucasian
$AUC_{0\text{-}24hr}$ (hr·μg/mL)	36	9	7
AUC_{0-t} (hr·μg/mL)	38	NA	NA
C_{max} (μg/mL)	15	6	3
T_{max} (hr)	4	1.5	4

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 cross populations, it is necessary in certain condition 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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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 Effects of TCMs on DMPK

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.