Phase 1 Clinical Trials in Mainland China

Opportunities and Challenges

Q. David Yang
CEO
MicroConstants China Inc

HKU CRC April 2013

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Presentation Outlines

- Clinical Trial Approval in China
- CFDA Guidance/Policy on Phase I Studies
- Opportunities
- Challenges
- Finding Solutions

CLINICAL TRIAL APPROVAL IN CHINA

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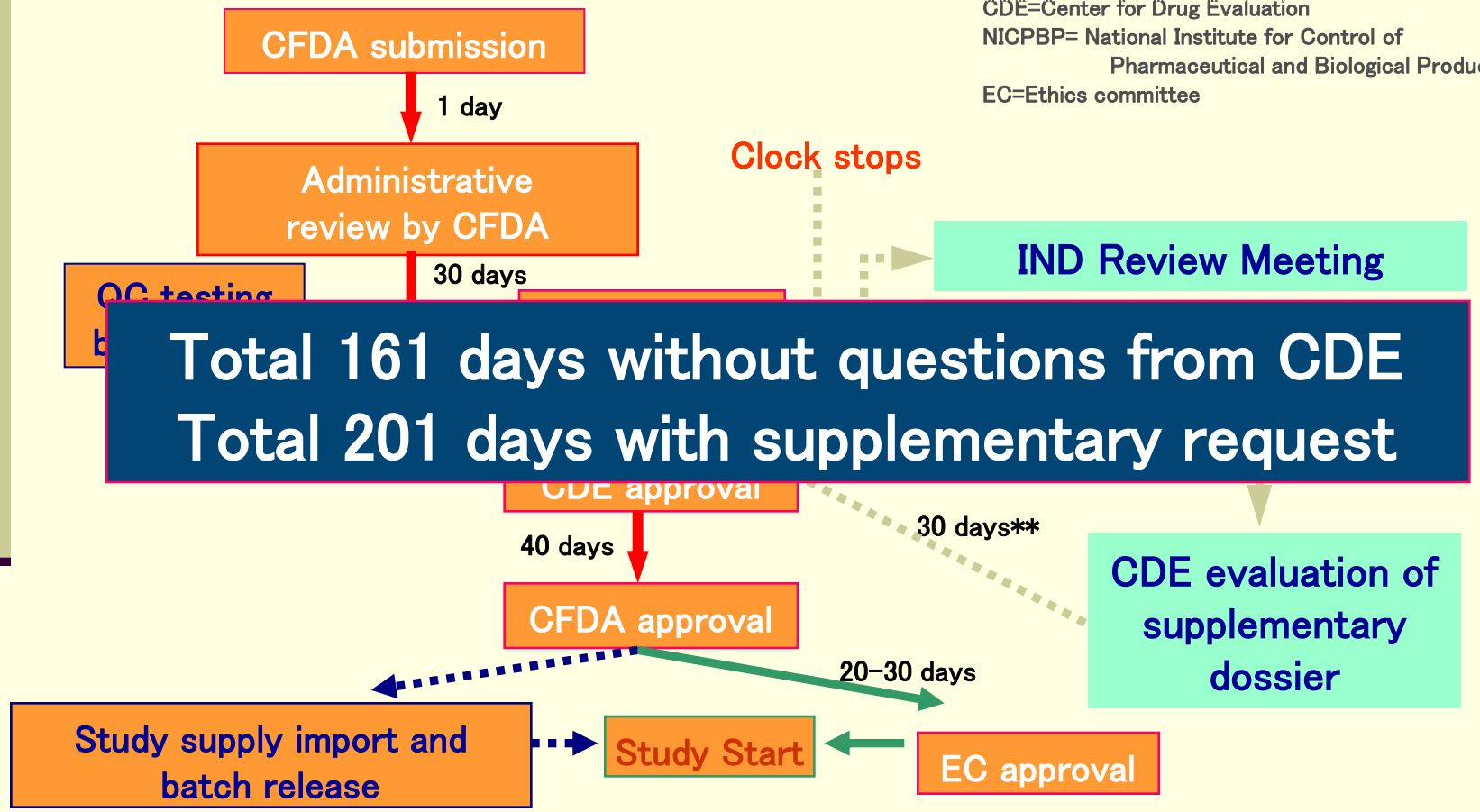
Types of Clinical Trial Approval in China

- IND in China
  - FIM
  - Product in clinical stage outside China
  - Green channel for oncology/infectious disease drugs
- For Imported Drug (Approved outside China)
  - PK study + abbreviated Phase III
- For Global Trials
  - PK study + number of patients desired
  - If the patients population is large enough, sponsor can apply for NDA directly in China after product approval outside China

China CTA Approval Process

CFDA= State Food and Drug Administration
CDE=Center for Drug Evaluation
NICPBP= National Institute for Control of Pharmaceutical and Biological Product
EC=Ethics committee



Anfan Wu: Clinical Trials Partnerships 2013

* All days are working days

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Actual CTA Approval Time

- IND of Class I drugs/biologicals 6-9 M
- Global trials application 12-18 M
- Imported drug application 12-18 M
- Special Review and Approval Procedure (Green Channel) 3-5 M

If no additional data submission is required

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CFDA on Import Drug IND/NDA

- CFDA now accept IND for oversea manufactured products
- CFDA doesn't accept NDA for products without CPP
- Except for treatment of public diseases (TB, HIV) case by case for NDA submission without CPP

CFDA GUIDANCE/POLICY FOR PHASE I STUDIES

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Phase I Unit in China Overview

- >130 Phase I Units
- Out of 500+ CFDA GCP certified CTC
- All affiliated with government hospitals
- 24-72 beds
- Most, if not all, have bioanalytical labs

Guidance on Phase I Unit Operation

- **CFDA, Effective Dec. 02, 2011**
  - Covers all areas of Phase I activities
  - Endorsed third party independent labs
  - With emphasis on
    - Quality system
    - Qualification of staff
    - **No subcontracting without sponsor approval**

Guidance on Bioanalytical Lab Operation

- **CFDA, Effective Dec. 02, 2011**
  - Define requirements for
    - organization/facility/hardware/software
  - With emphasis on
    - Quality system
    - Qualification of staff
    - Audit of data
  - No mentioning of certification system

Phase I Unit Re-certification Process

- **CFDA, Ongoing (started Oct. 2012)**
- New phase I/PK lab inspection checklists
- Top 20 Phase I Unit training in Tianjin
- PUMC inspection with QAs from industry
- Ready for Class A/B/C system
- Only Class A Unit can conduct FIM studies

Bianalytical Lab Certification?

- **Currently together with Phase I Unit (GCP)**
- **On CFDA agenda now**
- Indicated CNAS (ISO 17025) accreditation minimum requirement
- New checklist similar to CNAS
- Individual lab certification (OECD GLP, etc.)

Opportunities:

Phase I Study in China

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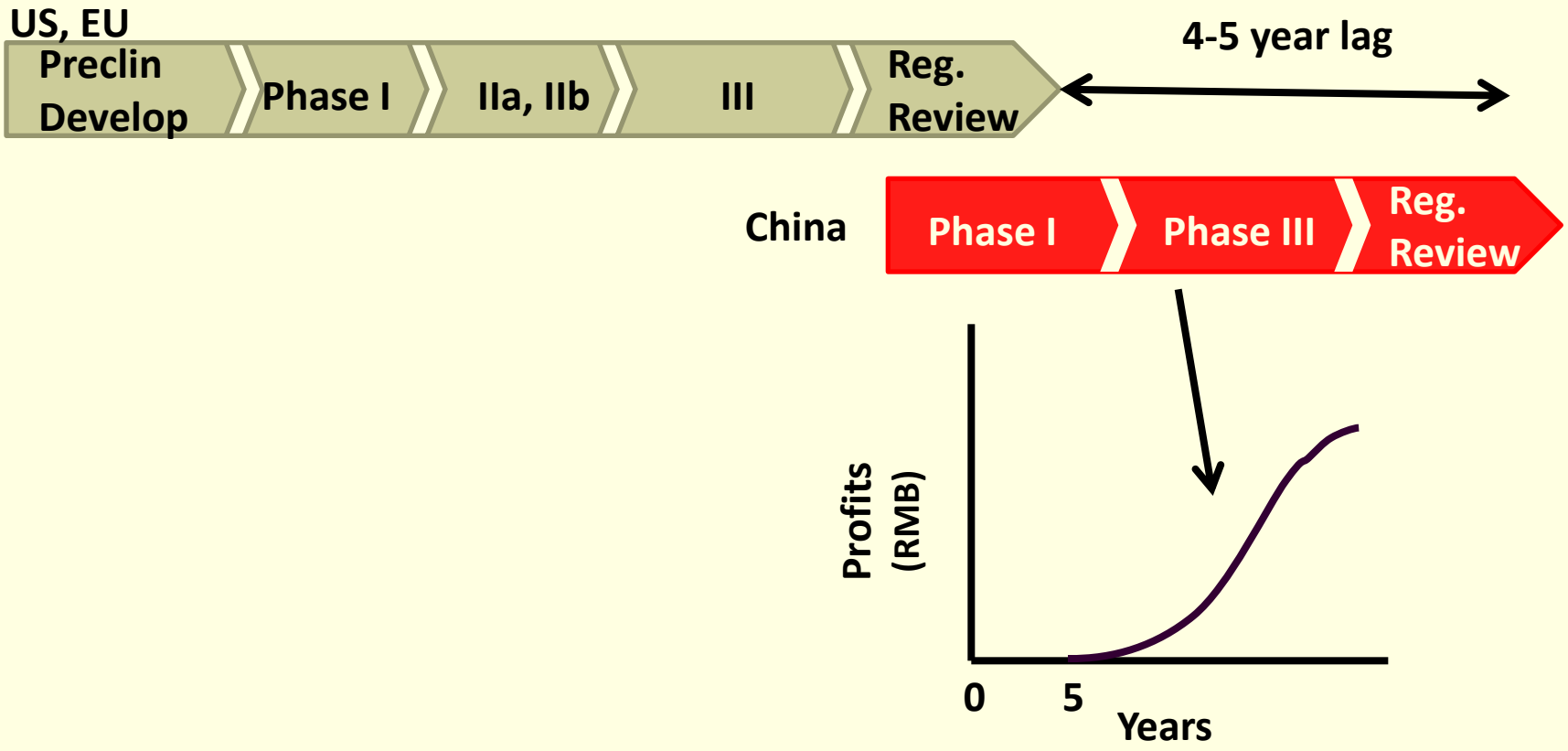
Drivers for Phase I Trial Growth

- Local pharma/MNC R&D
- MNC early entry into market/global strategy
- CFDA-changing rules and opening doors slowly
- Large subject pool, growing interests
- Relatively low cost
- Rich PK/BE experience
- Sites- well established facility

MNC Sequential Approach
Local Bridging Studies



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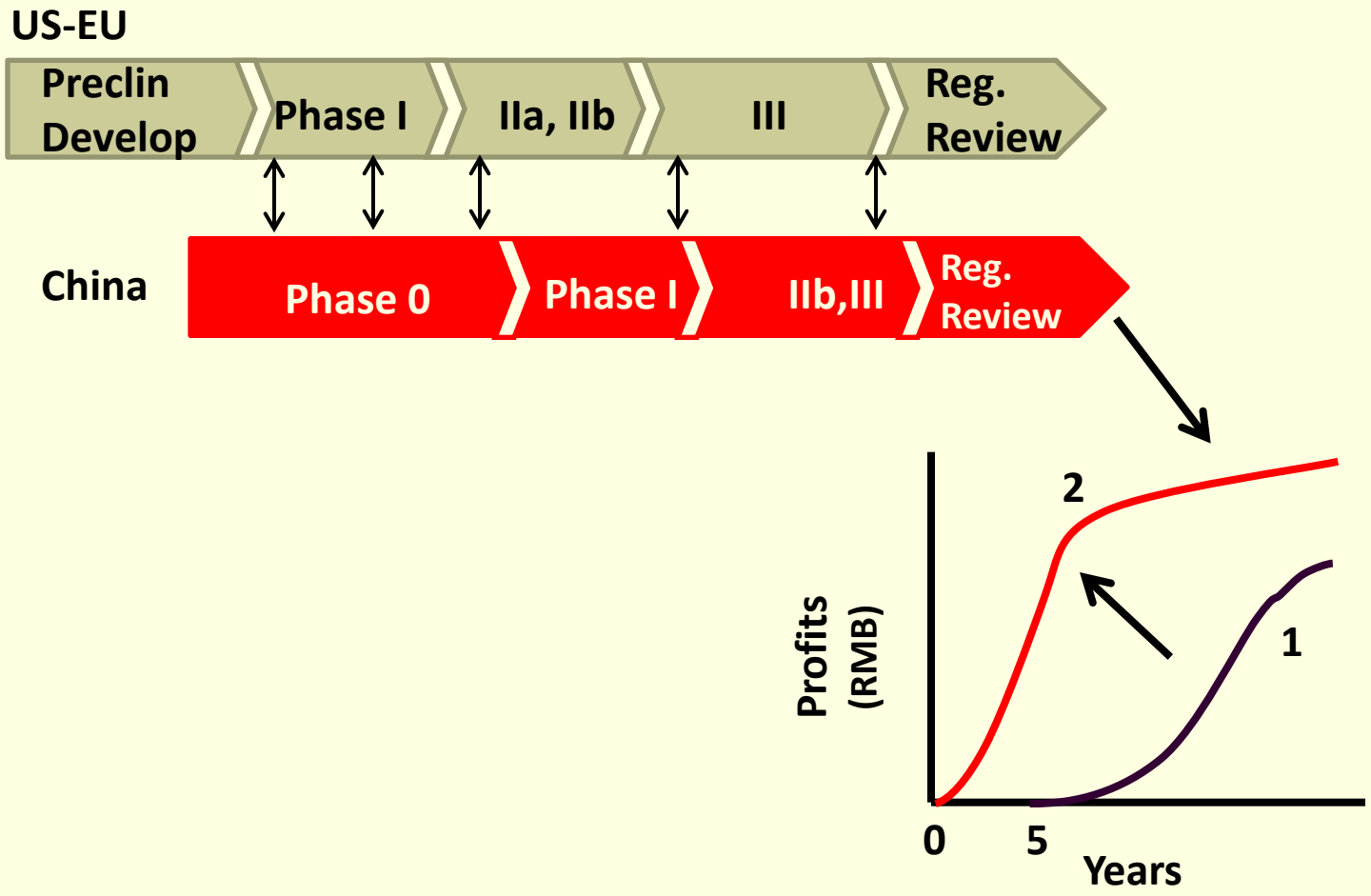
MNC Simultaneous Approach Integrated Plan



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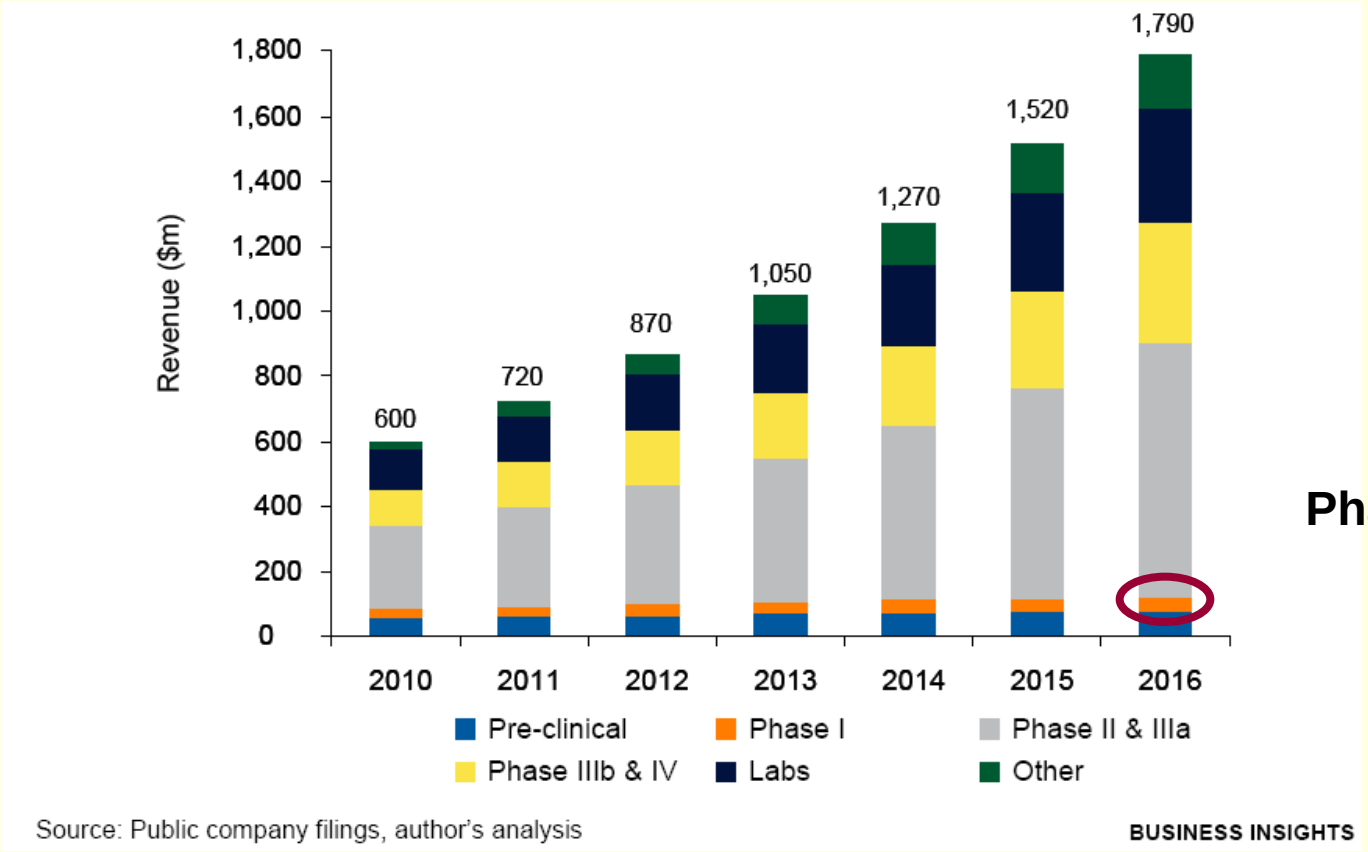
Shifting from Bridging Study to Global Strategy

- MNC
  - Setting up early development team in China
  - Bayer
- U.S. Biotech
  - U.S./Singapore Phase I studies
  - China PK/Phase II studies
- Chinese Pharma
  - Simultaneous US FIM/China IND

China CRO Outlook 2016

- Annual Growth of ~10%



Phase I

Challenges

Phase I Study in China

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Regulatory Issues

- Lengthy approval process (4-12 months)
- CFDA reviewers with limited experience
- Adaptive design almost impossible
- No radio-labeling studies
- Restrictions on clinical sample shipping

Limited Resources/Experience

- Limited FIM experience
- No independent Phase I CRO
- Few qualified clinical pharmacologists
- Few qualified bioanalytical lab/central lab

Compliance Issues

- GCP certification system
  - Inspections are performed by peers
  - Lack of proper/on time documentation
- Lack of compliance mindset
- Lack of QA auditors
- Limited ICH GCP exposure

Finding Solutions

Phase I Study in China

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MNC Solutions

- Translational Research collaborations with academics/hospitals
- Clinical Pharmacology Program
  - AZ-Beijing Univ. No. 3 hospital
- Clinical Sciences development program
  - Bayer-Beijing Univ.(School of Pharmacy)
- Fellowship/Grant/Training program

MicroConstants Solutions

Building Phase I Capability in China through CRO/SMO Integration

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MicroConstants Overview

- **MicroConstants Inc., San Diego, California, USA (1998)**
  - DMPK/Bioanalysis specialty CRO
  - Audited three times by FDA
  - No 483 during latest inspection (Oct. 2012)

- **MicroConstants China Inc., Beijing, China (2007)**
  - First OECD GLP endorsed bioanalytical lab in China
  - Co-manage a Phase I Unit in Beijing
  - SMO agreements with a number of clinical sites

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SMO Partner:
CPU of No. 307 Hospital

- 1,100+ bed oncology specialty hospital
- Over 15,000 breast cancer patients/year
- CFDA GCP certified clinical trial center
  - Oncology
  - Hematology
  - Drug dependency

- 40 bed Phase I Unit
- Clinical Pharmacology postgraduate program

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CPU of No. 307 Hospital: in Year 2008

- BE/PK studies for domestic companies
- Competitive advantage-Price
- Few exposure to ICH GCP
- Few international sponsors
- Limited support from hospital

Early Phase of Collaboration

- Co-application for National Key Projects (2008)
- SOP development/GCP training (2009)
- Fixing Major Deficiencies (2009)
  - Independent QA
  - Restricted access to archive room
  - Double locked, badge-access door to Clinical Ward
  - Subject identification system
  - Refrigerated centrifuge for sample processing
  - Temperature monitoring system (24/7)

In-Depth Collaboration

- CTMS development (CTIMS, 2009-2011)
- Joint top 30 MNC project (2010)
- SOP development for Phase II/III studies (2011)
- Joint major MNC project (2012)
- SIDCER/FERCAP EC recognition (2012)
- Project management, marketing, QA integration
- SMO agreement (2013)

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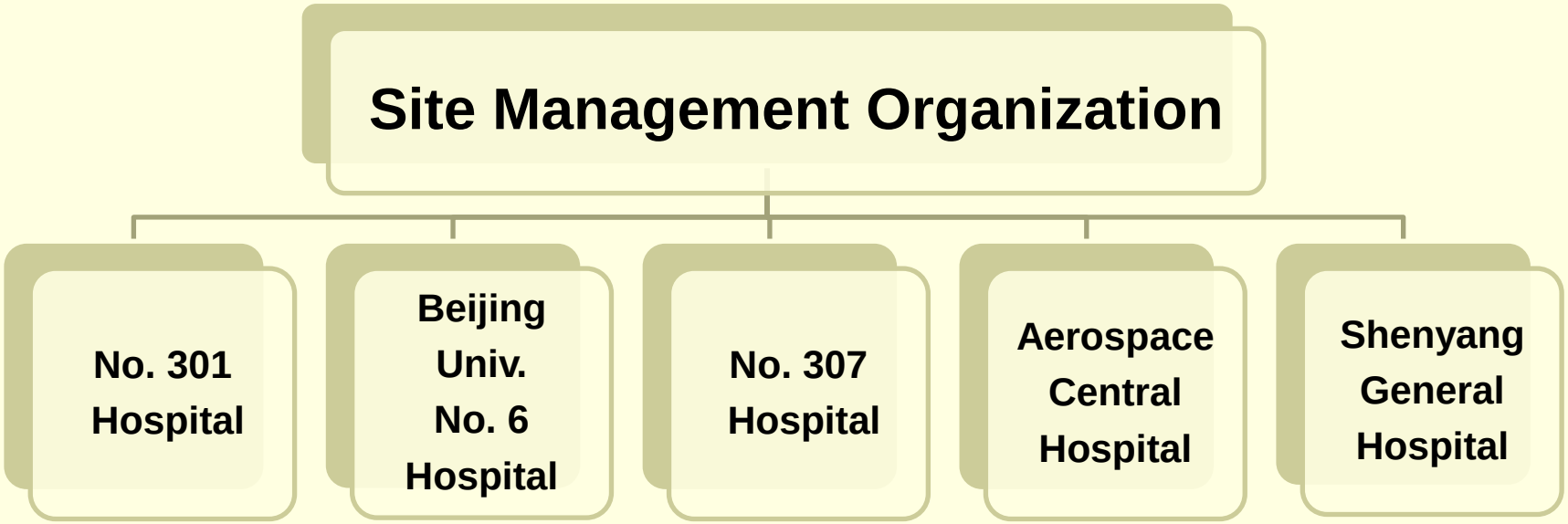
CPU of No. 307 Hospital in Year 2012

- Qualified by three major MNC
- Two NCE Phase I studies
- 3X 2008 revenue (with ½ projects of 2008)
- Building cardiac safety study capability
- Rated best clinical trial center by Beijing government

MicroConstants China Expanding SMO Network



Providing project management/quality assurance/CRC functions

Phase I, Oncology, Cardiovascular, CNS, Respiratory, Urology, Endocrinology, GI tract, Immunology, Ophthalmology, etc.

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Compliance Mindset Training

- Comparison of U.S. and China
  - Traffic situation
  - Smoking restriction in restaurants
  - Law enforcement
- No need to hide non-compliance/deviation
- Identify deviation by our own QA is much better than being caught by sponsor

Compliance Mindset Training (II)

- SOPs are written by those who use them
  - Can be updated
  - Can be obsolete
- Internship in MicroConstants lab
- Identify right QA candidates

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Details, Details, and Details

- Use detailed record/forms
- Hand-on training during project execution
- Periodical audit/discussion on findings
- CAPA
- Promote problem solving capability

Identify the Right Partner

- Motivation/Commitment
- Resources available
- Common goals/Mutual benefit
- Chemistry
  - Working style
  - Personality

Future SMO Directions

- Expand SMO network
- Cardiac safety study
- EDC system implementation
- Expansion into Phase II/III studies

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Thank You!

Q. David Yang, Ph.D.
dyang@microconstants.com
+86 (139) 1029 4684

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