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方恩医药发展有限公司

FOUNTAIN MEDICAL DEVELOPMENT LTD.

Managing Safety/Regulatory Issues in Clinical Development in China: The Role of CRO

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May, 2012

Presentation Topic

- Differences in Safety Handling between China vs. ICH
  - Safety handling in IND studies
    - Phase I
    - Phase II/III
  - Post-marketing Safety Surveillance
- Outsourcing of Safety Handling
  - Opportunities
  - Challenges
- Upcoming changes
  - SFDA
  - Sponsors

Safety Handling In China

- Definition of AE/SAE: drug vs. device trial
  - SAE definition are different (hospitalization)
- Safety reporting
  - Reporter: PI and sponsor/CRO
  - Reported cases: all SAEs immediately for IND studies.
  - Reporting timelines for post-marketing (July 1, 2011):
    - Drug:
      - 24 hours for Death Case and Group Events
      - 15 days for New SAEs
      - 30 days for AEs
    - Device医疗器械不良事件监测工作指南（试行）(Sept 29. 2011):
      - 24 hours for group/series of SAEs
      - 5 days for death case,
      - 15 days for other SAEs
  - New requirement for registering safety handling officer

Safety Handling in China

- Safety database
  - Coding
    - Normally use WhoArt or CoStar
    - MedDRA (Chinese version 12.1) has not been the generally accepted; Training just started recently
  - No guidelines for DM, thus no guidelines for safety database either
    - Only one or two GCP centers adopted Oracle Clinical or ClinTrace.
    - No dominant safety database system is available yet
- Requirement for the report of AE/SAE events outside of China
  - Reporter; importer for imported product
  - Timeline:
    - 1 month for initial reporting
    - 5 days for any follow-up requested by SFDA

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Safety Handling in Phase I trial

- Tolerability trial
  - Risk Minimization Plan
  - NCI-CTCAE (common terminology criteria for adverse events 4.0): acceptance and training
  - DLT handling
    - Tend to be conservative
    - Ethical argument
  - DSMB
    - Guidelines
    - Practice

Safety Handling in Phase II/III

- Safety Reporting issue
  - Dual reporting: from site and from sponsors/CROs
    - Reconciliation
  - Abnormal lab value
  - Under-reporting vs. over-reporting
  - Periodic safety surveillance meeting
- Signal detection practice
  - Just started
- Global vs. local trials
  - Qualification of personnel

Safety Handling for Device Trials

- Adverse Event Handling for Medical Device Operation and its Re-evaluation医疗器械不良事件监测和再评价管理办法（试行）
  - Issued on Dec 29, 2008
  - Record keeping:
    - validation date+2 more year;
    - Minimum 5 years
  - AE/SAE collection: manufacturing
  - Reporting: manufacturing, distributors and users

Safety Handling for Device Trials

- Adverse Event Handling for Medical Device Operation and its Re-evaluation医疗器械不良事件监测和再评价管理办法（试行)
  - Reporting timeline
    - Pandemic or group SAEs: 24 hours
    - Death: 5 days
    - Other SAEs: 15 days
    - Class II/III products: annual report (Jan, each yr)
    - Different from drug SAE reporting timeline
  - Report to
    - Provincial SFDA safety department
    - Can report directly to SFDA in Beijing

Safety Outsourcing in China

- Safety handling by CROs in China
  - AE/SAE event collection and monitoring
  - Coding
  - Reportability Assessment
  - Reporting
    - SFDA
    - Sponsor
    - FDA/EMEA (via sponsor or via offices outside of China): global CRO with China operation
  - DSMB
  - Signal Detection

Outsourcing of Safety Operation

- Opportunities
  - China has talents:
    - Academics
      - GCP trained clinicians: more than 200 GCP centers
      - More investment by MOST/MOPH
    - Industry
      - Pfizer global safety operation team in China
      - CRO to handle outsourced safety handling work

Outsourcing of Safety Operation

- CRO’ s safety handling services in China
  - General safety process handling
    - Safety event information collection
      - Paper-based or via EDC
    - Coding: MedDRA v12.1, with China user-supporting group
    - Reportability assessment and Regulatory filing
    - DSMB and Periodic Safety Surveillance Meeting
      - FIM consideration and global acceptance of safety data.
  - Organ system-focused safety handling
    - Cardiovascular
      - EKG central reading: QT measurement

Outsourcing of Safety Operation

- Challenges
  - Experience of Drug Safety Handling personnel
    - PI experience in safety handling
      - Reporting consideration
    - CRO experiences
      - Global vs. local trials
    - Handle the differences among different regulatory systems
  - Safety Database consideration
    - Would CRO can access to sponsor’ s database?

Manage CRO for safety outsourcing

- Selection of CRO
  - People/system/track record
- Management of CRO operation
  - Integrated approach for long-term relationship
    - SOP synchronization
    - Training plan
    - Implant a PM inside a CRO
    - Database consideration
  - Short-term relationship
    - Communication!
    - Plan B

Upcoming Changes: SFDA

- SFDA’s effort
  - SFDA’s management system: IND vs Post-Marketing Surveillance
  - Revise safety guidelines
    - AE/SAE forms
  - eAE reporting system
    - Nation-wide system
    - Access to the Safety Database
  - Data Management guidelines

Upcoming Changes: Sponsors

- More in line with ICH standard
  - Sponsor would have more qualified safety handling persons
  - Training will be in huge demand
  - Local trial vs global trial would be more converged on safety handling
  - EDC adoption would be increased
  - DSMB and Risk Management practice would be popular

Additional Changes

- SFDA
  - Personnel Changes
    - Leadership
    - CDE: complete change
- Management Structure Change
  - CDE: separation of NCE vs. Generic Review
- Technical guideline development
- Communication with SFDA
  - IND
  - End of Phase II

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IND in China

- Two pathways:
  - Standard Process:
    - 9~12 months (up to 15 months)
    - Requirement for CMC and Long Tox data
    - No pre-IND consultation
  - Special Handling Procedure
    - 6~12 months (min 4 moths)
    - For NCEs, un-med medical need, orphan indication
    - Rolling submission allowed
    - Pre-IND consultation available with binding meeting minutes
    - Risk/Benefit analysis required

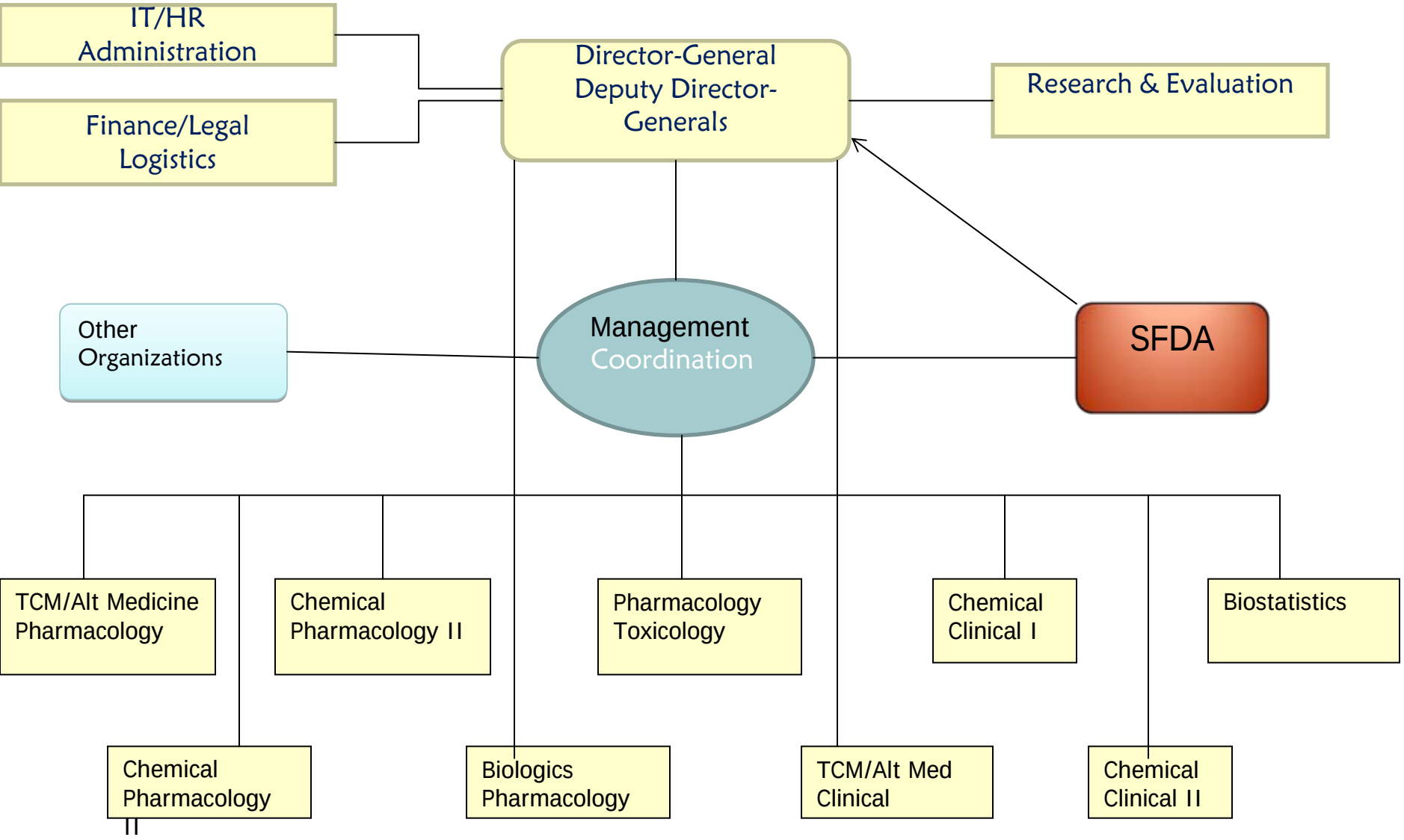
Special Handling Procedure (I)

- Equivalent to US IND
  - Applicable:
    - Class I product
    - Un-med Medical need: oncology, AIDS, TB
    - Orphan Indication
    - New combination of herbal products
  - Started on Jan. 7, 2009
  - About 30 Applications in 2009
    - Oct 2011:
      - IND: 3/37 NCE 1/47 Generics ;
      - NDA: 1/43 for new drug; 0/234 for ANDA.
  - Shortest time for IND: 4 months

Special Handling Procedure (II)

- NDA
  - Fastest: 6 months (for both market clearance and manufacturing certificates)
- Government Sponsored Projects
  - 12th-5 Year National Key Drug Development Program
    - *International Collaborative Program*
- Could speed up further
  - New CDE management system and policies
  - More reviewers on NCEs
  - More training for reviewers

Organization Chart： CDE



NDA in China

- Timeline: 6 months ~24 months
  - CTD (July 1, 2011) application faster, efiling has started
- Total Number of Patients needed
  - Diabetes: 500 patient-years
  - Drug-Eluting Stent: 1200 patients
- Pivotal Study
  - No requirement for two pivotal studies
  - End of phase II meeting is possible for certain products
- No User-fee system; No 505 b(2)
- Accelerated approvals possible for certain products/indications

NCE vs. Generic Approval

- IND/NDA approval process
  - NCE:
    - Parallel process
    - Rolling submission
    - Pre-IND & End of phase II meeting
    - Open NDA review meeting
  - Generics:
    - Sequential process
    - One-step submission
    - No Pre-IND & End of phase II meeting

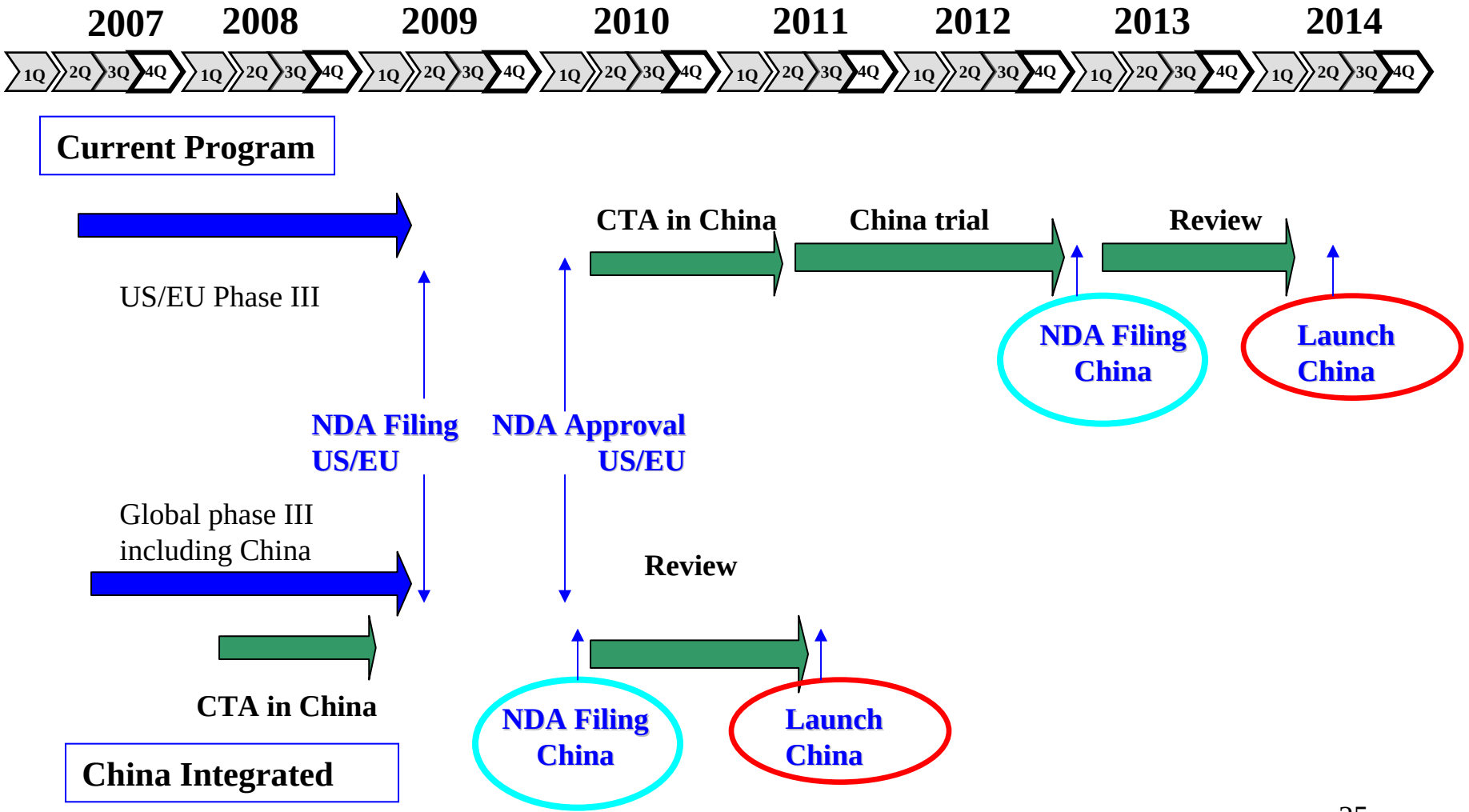
Current model of global trials —--

China integrated into global development-Simultaneous filing

Advantages of China integrated into global development-Simultaneous filing

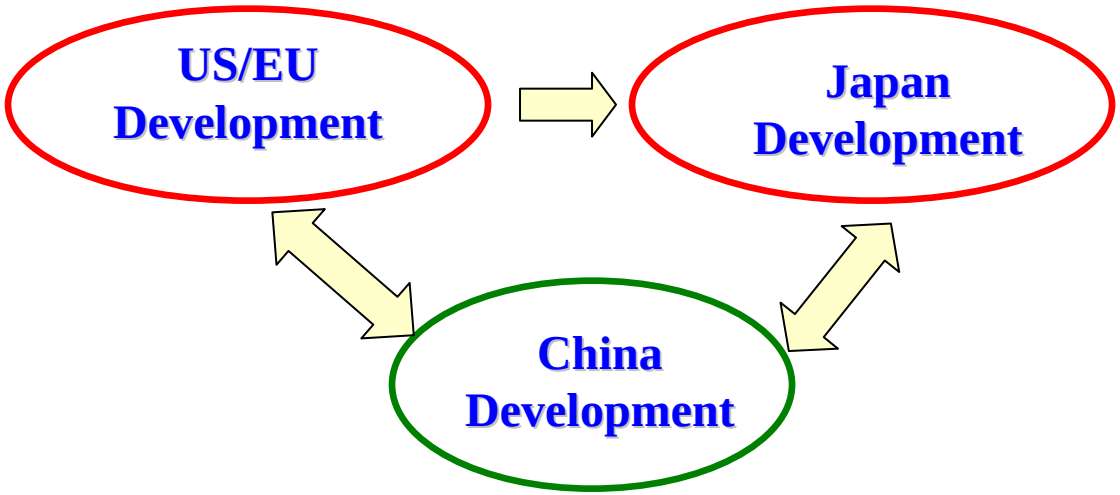
- Significantly shortens time to launch in US/EU market
  - Faster enrollment in China speeds up global trial timeline
- Significantly shortens time to launch in China
  - Three year earlier access for world's #5 market
  - Potential to qualify for "green channel" in obtaining CTA from SFDA

Development Program-China Prior to NDA vs China after



Regional Harmonization

- China-Japan-South Korea discussion
  - Data from China support US/EU filing and Japan filing
- China-Taiwan: ECFA 6



Regulatory Application Process & Timeline

China		8-10 months ≈	EC Approval 4-6 weeks
Hong Kong		14-16 weeks	2 days after CTC granted
Korea		10-16 weeks	
Taiwan		10-16 weeks	

Partnership with Locals

- Format: various
  - Academic Centers vs. Commercial Entity
- Funding
  - National and local grant
- Regulatory Affairs
  - First-In-Man study
  - NDA application
  - Speed for approval
  - Speed for enrollment
  - Liability consideration

"Thousand Talent Program"

- Program to attract top talent globally
  - One quarter for Life Science/Biotech Talents
  - Influence on SFDA
  - Influence on MOST/MOPH funding allocation
  - Priority Funding for the talents admitted
    - Grant
    - VC/PE
- Expanding
  - Young Talents
  - More sub-specialties

SFDA: Next Step

- More Personnel Changes in next 6~9 months
  - More professional managers in power
  - More technical reviewers
  - Short-term pile-up of applications
- More Emphasis on Safety Handling
  - Pharmcovigilence for marketed drugs
  - Pharmacovigilence for medical devices
- More Improvement on Technical Review Process
  - More technical guidelines issued toward ICH
    - More clinical development guidelines
      - Phase I and PK guidelines
    - Statistical guidelines
    - EDC guidelines

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SFDA: Next Step

- Accepting Non-Clinical Data outside China
  - Revision for the tox data required
- eFiling
  - Electronic Safety Handling System
- Impact to the Industry
  - More communication between SFDA and Industry Representatives
    - RDPAC
    - Bayhelix
  - Regulatory Professionals
    - Need more clinical personnel
    - Need more safety personnel
- More Transparent

New Update on SFDA

- Personnel Changes
  - A new commissioner
    - From MOPH, Mr. Li Yin, former Chief of Department of International Collaboration
    - Young
  - A new acting head of CDE
    - Dr. Zhang, Kang Kang-technical person
  - A complete line-up of CDE departmental head

New Update on SFDA

- New ideas in year 2012
  - Phase I
    - FIH
    - Classification of phase I centers
  - DSMB/DMC
  - Speedy IND review
  - DM/Biostat requirment
  - Pivotal Studies
    - end point consideration
    - Design of the trial (placebo vs active control)
  - Safety consideration (minimum sample size)

SFDA: Help Wanted

- Role of Industry
  - Educate general public for the risk/reward of pharmaceutical R&D in China
    - Media & General public’ s opinion on clinical trials
  - Training for KOLs
    - KOL and their advisory role to SFDA
  - Training for SFDA technical reviewers
  - Educate decision makers: prime minister/ministers
- Appeal for more headcounts
- Appeal for more changes
  - Drug Registration Law: access to lawmakers

FMD- Service scope

FMD provides **full line of services** for drug development process:

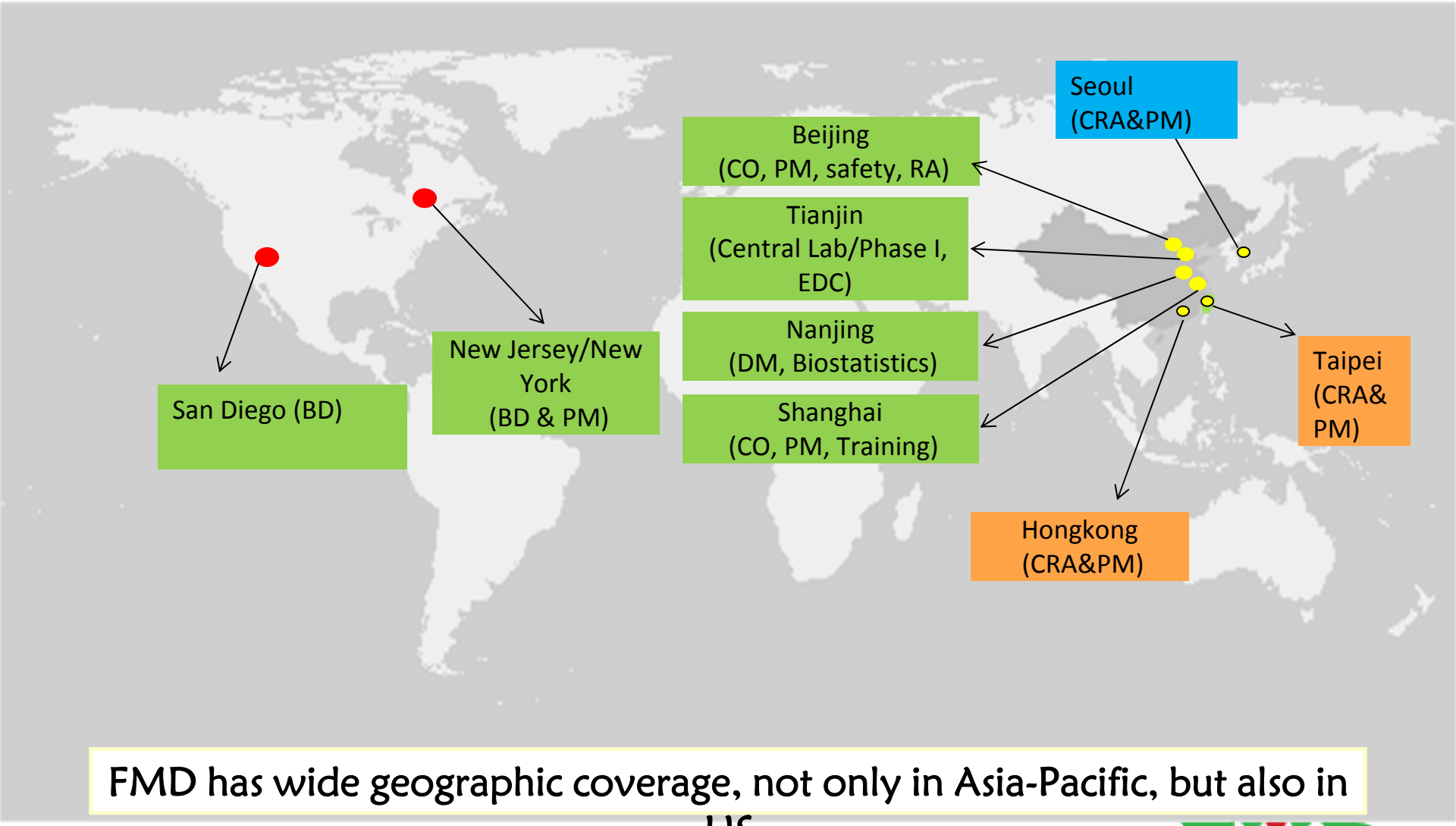
- Central Lab
  - for safety tests, biomarkers, pharmacogenomics and PK tests
- Phase I unit
  - for tolerability, bioequivalence, drug-drug interaction & special population trials
- Phase II/III/IV Drug and Device Trials
  - Cover sites in mainland China, Hong Kong, Taiwan & South Korea
- *Regulatory Affairs*
  - for product filing in China, Hong Kong, Taiwan, South Korea & USA
- Safety Handling
  - Safety event collection and processing, DSMB, signal detection and risk management planning

FMD – Service scope

FMD provides **full line of services** for drug development process:

- Data Management and Biostatistics
  - Data Entry, Database building & Query Management
  - Statistical planning, SAS Programming & Reporting
- EDC (Electronic Data Capture)
  - Both in Chinese and English
  - SFDA commissioned and US FDA 21 CFR Part 11 compliance
- Project Management
  - Offer PM services both in China, East Asia and USA
- Pharmacoeconomics
  - Re-imbursement Support
  - Pricing Support

The Company – Geographical coverage



FMD has wide geographic coverage, not only in Asia-Pacific, but also in US

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