Fountain Medical Development
Leading full service clinical CRO in Asia

Conducting Clinical Trials in China

Dan Zhang, MD, MPH
Chairman and CEO

Apr. 8, 2015
Dan Zhang, MD, MPH, MA: Founder & CEO of FMD

Education

• Medical Degree from Peking Union Medical College
• MPH Health Care Policy and Management, Harvard School of Public Health, Harvard University
• MA Health Care Administration, The Wharton School, University of Pennsylvania, 1995

• 20 years of experience in the Pharma industry
  ➢ Head of Global Safety Assessment and Clinical Drug Development of Sigma-Tau USA, (2002-2007)

• Long term advisor for the CFDA,
  • New drug review committee
  • Member of grant review committee for the National Key Drug Development
Discussion Topics

• Regulatory Differences Between US and China
• Conducting Trials in China
  – Process
    • IND/CTA
    • IRB/EC
  – Personnel
  – Sponsors
  – Technology
  – Speed vs. Quality
• Next Step
## Drug Approval Process: US vs. China

<table>
<thead>
<tr>
<th></th>
<th>US</th>
<th>China</th>
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<tbody>
<tr>
<td><strong>Meeting with FDA / CFDA</strong></td>
<td>– Type A Meeting;</td>
<td>– Weekly ad hoc consultation;</td>
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<td></td>
<td>– Type B Meeting;</td>
<td>– Pre-IND consultation;</td>
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<td>– Type C Meeting.</td>
<td>– End of Phase I, End of Phase II meeting</td>
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<tr>
<td><strong>IND Practice</strong></td>
<td>One-month waiting period</td>
<td>Review time is lengthy and IRB relies on the approval</td>
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<tr>
<td><strong>NDA Practice</strong></td>
<td>Two or more pivotal trial; Successful rate is low</td>
<td>One (1.5) pivotal trial; High percentage of approval</td>
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<tr>
<td><strong>Special Procedure</strong></td>
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Table 3: Waiting Timelines for Various Applications (months)

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<td>IDL renew</td>
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</table>

IDL: import drug license
IND: Investigational New Drug
NDA: New Drug Application
ANDA: Abbreviated New Drug Application
Conducting Clinical Trials in China: Process

• IND/CTA Application
  – IND for New Drug
    • Foreign firm is not allowed to conduct First-in-Man trial in Chinese Population
      – “Foreign” is defined as the manufacturing site
  – CTA for Global Trial
    • Definition of Global Trial: more than 2 countries
    • Study Drug produced outside of China
    • Study Drug has started phase II trial outside of China
  – CTA for registration trial (Importation Drug License)
    • After NDA approval outside of China
  – Importation IND (?)
Conducting Clinical Trials in China: Process

- Standard IND/CTA application
  - Required document looks like a NDA package
    - Extensive CMC documentation
    - Long-tox is a must
    - No pre-IND consultation
    - No Rolling Submission allowed
    - Take 18~24 months

- Special Review Process (特殊审评程序)
  - Equivalent to standard IND in US
  - Qualification:
    - 1). NCE, 2). Unmet Medical Need, 3). Rare Diseases
Conducting Clinical Trials in China: Process

• IRB/EC
  – No Central IRB,
  – All locally-based as a pre-requisite for GCP certification
  – IRB composition follows CFDA guideline
  – Only start to work after IND/CTA approval
  – Conservative:
    • NCE
    • Placebo-control
Conducting Clinical Trials in China: Process

• GCP Center
  – All IND studies must be conducted in GCP Centers
  – Pre-certified by CFDA and NHFPC
    • Re-certification every 3 years
      – Failure rate up to 30%
    • GCP center must have trained employees who passes GCP tests enacted by CFDA
    • Certification is based on the therapeutic expertise
  – Total number of GCP centers: ~420
    • One-time temporary certification is granted
  – Almost all are government-run tertiary med center
  – Hong Kong (5) and Taiwan Sites (4)
Distribution of GCP Centers in China

Coverage 34 Cities
248 people in CO Department
FMD has wide geographic coverage, not only in Asia-Pacific, but also in US.
400 employees and growing.
Conducting Clinical Trials in China: Personnel

• Personnel at the GCP centers
  – All GCP qualified
  – Have full-time employees
  – Experience level are quite different:
    • Peking Union Medical College Hospital
    • Lack of experience dealing with NCEs
    • Lack of experience of designing qualified protocols
  – Training varies:
    • 8 year, 7 year, 6 year, 5 year and 4 year MD program
    • Barefoot doctor becomes village doctor
    • No compulsory re-certification requirement for a MD
Conducting Clinical Trials in China: Personnel

• Personnel at the GCP centers
  – Emerged Academic CROs
    • Tian-tan Hospital for CNS
    • Fu-wai Hospital for Cardiovascular
    • Cancer Hospital of CAMS for oncology
  – Global Trial Experiences for the sites in Beijing, Shanghai and Guangzhou
    • Most PIs and members of CFDA advisory committee come from above three cities
    • Better equipped due to the GCP funding from the National Key Drug Development Fund of 11th and 12th five-year plan
Academy Player

Fudan University Shanghai Cancer Center

Beijing Hospital

SUN YAT-SEN UNIVERSITY CANCER CENTER

Universitas Amoensis

Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School

West China School of Medicine/West China Hospital, Sichuan University

Tianjin Medical University Cancer Institute & Hospital
Conducting Clinical Trials in China: Personnel

- Sponsor/CRO
  - CRAs are all with medical or pharmacology degree
  - Have to pass GCP tests
  - Turnover is high
  - Average working experience is about 2-3 years
  - Have either local or global trial experiences
  - Global firm’s China operation becomes a training camp
  - Local firm’s medical team is unstable and less-experienced for NCE development
Global Players in China

- Novartis
- Roche
- GlaxoSmithKline
- Bayer
- GE
- Johnson & Johnson
- Ferring
- Astellas
- Dainippon Sumitomo Pharma
- Abbott
- Lundbeck
- Medtronic
- Sanofi
- Alcon
- Servier
- AstraZeneca
- Mundipharma
- Eisai
- Boston Scientific
- Arbor Research Collaborative for Health
- Siemens
Domestic Firm Conducting NCE Trials
Conducting Clinical Trials in China: Technology

• EDC/CTMS system
  – Draft DM guideline in preparation
  – Most of local trials and all global trials are EDC equipped
  – More mobile tools are in development

• Central Lab
  – CAP certified labs are available
    • Sample shipping has multiple options
  – Is not required for local registration trial

• Central Pathology and Image reading

• Central EKG reading
Conducting Clinical Trials in China: Speed

• Enrollment Speed
  –Normally 2-3 times faster
    • RU486 Trial: 10,000 study subjects enrolled within 1 yr
      –PI was Prof. Sang, Guo-Wei, former Deputy Speaker of House
      –Less than 1% dropout rate
    • COMMITT Trial: 45,000 AMI patients from 1,250 sites
      –PI was Prof. Jiang, Li-Xin of Fuwai Hospital of CAMS
      –Designed by Oxford University CTSU (China Trial Service Unit)
      –New indication approved by FDA for clopidogrel
    • COPD trial: 10,000 patients enrolled within 1 year
  • Phase I trials:
    –3~6 months for healthy volunteer
    –6~12 months for patient trial
Conducting Clinical Trials in China: Quality

• GCP guideline issued by SFDA: Sept 1, 1999
  – Enforcement by CFDA
    • During Mr. Zheng’s Era:
      – Very little enforcement for Clinical trials
      – Minimum 40% of applications were with questionable data
    • Post Mr. Zheng’s Era:
      – GCP Center Certification and re-certification every 3 years
      – IND/CTA: provincial/city CFDA would conduct document verification visit
      – NDA: CFDA would assemble inspection for GCP site inspection and manufacture site inspection
Conducting Clinical Trials in China: Quality Inspection by US FDA

- AZ’s COMMIT Trial
  - Inspections were conducted in
    » Fuwai Hospital: No. 1 enrollment site
    » Hospital in Anhui: perceived as less experienced site
  - No major findings
  - New Indication was approved with all clinical data from China

- BMS’ Global Phase III ARISTOTLE Trial
  - Blood Thinner product: Eliquis
  - Findings: data manipulations at one Shanghai site
  - Results: questionable data were deleted and there was nine month delay for the approval
Conducting Clinical Trials in China: Cost

• Direct cost in China is about 1/3 of US cost
  – Both CRO fees and pass-through fees are lower
    • However the cost increases rapidly
      – CRA annual salary increase 30~40%
      – Investigator grant is also increased rapidly especially at the experienced site
  – Biomarker testing kits may cost more in China

• China local investors would finance China portion of the trial
  – Obtain national grant and local government grant
Next Step

• Speedy IND/CTA approval
  – More headcounts for CDE (Center for Drug Evaluation)
  – More budget via user fees
  – Purchase review services from community
  – More experienced reviewers and managers

• More training program for clinical pharmacology and trial designs

• Becoming ICH country

• For domestic innovative firms: go global
  – Take advantage asymmetry of regulatory system to derive higher return
Dan Zhang· MD MPH
CEO
Phone(China): +86-13611142168
Email: dan.zhang@fountain-med.com

Emil Fu· PhD
VP, Integrated Project
Phone: +86-15905813125
Email: emil.fu@fountain-med.com
New Branch Offices – Geographical Coverage

New Jersey/New York (BD & PM)

Tianjin (CO, PM, Safety, RA, BD, PE)

Shanghai (CO, BD, PM, Medical Advisors)

Beijing (CO, PM, Safety, RA, BD, PE)

Taipei (CRA&PM)

Seoul (CRA&PM)

Pennsylvania (DM&BS)

FMD is in Asia-Pacific, US and East Europe
More than 400 employees and growing

San Diego (BD)

Chengdu (CO)

Nanjing (CO, PM, DM, Biostatistics)

Hong Kong (CRA&PM)

Guangzhou (CO, PM)

Tianjin (CO, BD, PM, Medical Advisors)

Armenia (CO, DM)

Shanghai (CO, PM, Training, BD, Medical Advisors)

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Beijing (CO, PM, Safety, RA, BD, PE)
The Company – Service Scope

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

- **Regulatory**
  - For product filing in China, Hong Kong, Taiwan, South Korea & USA
  - Regulatory strategy consulting
  - Document preparation
  - Submission for IND and NDA

- **Clinical Trial Management Services**
  - Phase I-IV drug and device trials
  - Cover sites in mainland China, Hong Kong, Taiwan & South Korea
  - Project management services offered in China, HK, TW & South Korea
  - Clinical operation management
  - Clinical study or site feasibility
The Company – Service Scope (Cont’d)

• **Data Management and Biostatistics**
  - Data entry, Database building & Query management
  - Statistical planning, SAS Programming & Reporting
  - EDC
  - We are an accredited service provider of the industry’s leading MediData Rave system
  - Also certified to do study build in Oracle Inform and Oracle Clinical
  - Familiar with other smaller EDC vendors

• **Medical Affairs**
  - Clinical trial design and protocol development
  - Post-market drug safety
  - Medical monitoring
  - Pharmacoeconomics: reimbursement support, pricing support
  - Medical monitoring
  - KOL planning/meeting
  - Medical writing: Protocols, IB, CSR, annual safety reports, etc.
Our Therapeutic Experience

- Outcomes
- Others
- Medical Devices
- Inflammatory
- Peripherial vascular
- Osteoporosis
- Oncology
- Infectious
- Dermatology
- Adiposis
- Gastroenterology
- Gout
- Hepatosis
- Nephrology
- Respiratory
- Cardiovascular
- Neurology
- Neurology
- Ophtalmology

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Active Projects by Phase & Sponsor

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</tbody>
</table>
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2. New approach by CFDA
3. Alternative strategies
4. Case studies

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Figure 1: From 2010 to 2013, Technical Reviewing Conducted by CDE
Table 1: NDA Approvals in 2013

<table>
<thead>
<tr>
<th>Category</th>
<th>New Drug</th>
<th>New Formulation</th>
<th>Generic Drug</th>
<th>Import Drug</th>
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<tbody>
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<td>Traditional Chinese Medicine</td>
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<td>Biological Products</td>
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<td>9</td>
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Table 2: CDE Approved Clinical Trials in 2013

<table>
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<th>Category</th>
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<tr>
<td>Traditional Chinese Drug</td>
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<tr>
<td>Biological Products</td>
<td>49</td>
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</tr>
</tbody>
</table>
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Botanical Medicine Development

• **US FDA**
  – Botanical Medicine Guideline (10 years)
  – 550 applications
  – 2 approved

• **China:**
  – TCM Pathway

• **Enter into US Market**
  – 丹参滴丸
  – 康莱特
Clinical Data from Taiwan

• ECFA6
  – Not fully explored yet
    • Phase I data has not been widely accepted yet
      – No CFDA certified phase I center
      – No Inspection has happened
    • Phase II/III data has been accepted by CFDA for both efficacy and safety
  – Mainland China’s Taiwan Office
    • Could be a powerful intermediary to influence CFDA
    • Only a very small percentage of Taiwan Company has tried this pathway.
• Phase I trial
  – CTN (95%) vs. CTX (GMO, 5%)
  – IRB: commercial (2 weeks); academics (4-6 weeks)
• Pre-clinical Data
  • GLP vs. Non-GLP
• CMC:
  • GMP vs. Non-GMP
• R&D rebate
  – Australia
  – Outside of Australia
Australia’s Impact on China IND

• Special Review Procedure
  – Apply for phase I, II, III combined
  – Timing management
  – Supplemental information

• Standard Procedure

• Partnership with global firms
  – Global quality
  – Asian population
General Procedure of R&D for Drug Regulatory Approval in China

1. Applicant submits dossier with samples
2. Acceptance by SFDA
3. Technical review by CDE
4. Administrative examination and approval by SFDA
5. Approval for clinical trials
6. Submit dossier upon the completion of clinical trials
7. Technical review by CDE
8. Administrative examination and approval by SFDA
9. Approval for importation and Release of Import Drug License

Precondition: The drug have been approved for marketing in the original country/region prior to SFDA submission.
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
IND in China

• Two pathways:
  – Standard Process:
    • 9~12 months (up to 15 months for global firms)
    • Requirement for CMC and long tox data
    • No pre-IND consultation and no rolling submission
  – Special Handling Procedure
    • 6~12 months (min 4 moths)
    • For NCEs, un-met medical need, orphan indication
    • Rolling submission allowed
    • Pre-IND consultation available with binding meeting minutes
    • Risk/Benefit analysis required
IND/CTA Package Requirement

1. GMP certificate
2. Declaration of patent validity in China
3. CMC Data
4. Pharmacological and toxicological data
5. Clinical trial summary for completed studies
6. Investigator brochure
7. Planned Clinical trial protocol and Informed Consent
8. Risk/Benefit Analysis: for special handling procedure
NDA in China

- **Timeline:** 6 months ~24 months
  - CTD (July 1, 2011) application faster, e-filing under development

- **Total Number of Patients needed**
  - 100 pairs
  - 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**
Special Handling Procedure for Small Molecules

- Equivalent to standard US IND
- Enacted Jan 2009

Good for:

- NCE
- Unmet Medical Need: pandemic diseases; oncology; drug-resistant TB
- Rare Diseases: no official definition for “rare” in Chinese population

Need to apply for this designation

Many global firms have taken this route, while domestic firms need to play catch up games

- Simultaneous early phase clinical development scheme
- Shorten 1~2 quarters in overall review time
Drug Registration Update (II)

• Special Handling Procedure for Biologics
  – Published by CDE on Mar 11, 2013
    • National New Drug Innovation Program for 11\textsuperscript{th} and 12\textsuperscript{th} five-year plan.
    • Never approved anywhere else.
    • Not in China yet, CDE/KOLs favorable review for clinical value
    • Not the first application in China, but deal with urgent clinical need, determined by CDE/KOLs
    • Global trials dealing with AIDS and drug-resistant TB
    • Timeline is similar to other special handling procedure
Drug Registration Update (III)

• Biosimilar Guideline
  – Oct 29, 2014 after many rounds of internal discussion
  – Key elements
    • Reference products: must be approved in China
    • Non-clinical: step-wised approach
      – PK, PD, Immunogeneity
      – Toxicology
      – “Original approach”
    • Clinical: step-wised approach
      – PD, PK, Immunogeneity (pre-clinical results)
      – PD, PK, Immunogeneity, Safety Trial
      – Clinical “Equivalent” or Non-inferior design
      – “Original approach”

– When?

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Drug Registration Update (IV)

• Fast-track review and approval for generic drugs:
  – Urgent need for public access consideration
  – Dealing with high price of brand-name drug
  – Special population: pediatric and orphan indication
  – Global quality manufacturing
  – Prioritized by CFDA
    • Efficacy
    • Pharmaco-economics
Drug Registration Update (V)

• Revision of Drug Registration Law
  – IND: US style? One-month waiting period?
  – NDA: US style?
  – Revision of Drug Registration Guideline

• Center for Drug Evaluation (CDE)
  – Capped at 120 headcounts
  – New Acting Director-General

• Purchase of Qualified Review Services
  – Started in pre-clinical stage
Drug Registration Update (VI)

• MRCT Issue
  – Paper by Dr. Yin, Hong-Zhang and Dr. Luo, Jian-Hui
    • Different consideration for MRCT trial vs. local registration trial by CDE reviewers
    • Re-apply for registration trial
  – Impact on the IDL
    • Added time (2~5 years more)
    • Added cost if additional trial is needed

• Suggestion:
  – Special Handling Process
    • Face-to-face meeting with CDE
Device Registration Update (I)

• Innovative Device Registration Pathway
  – Already started on June 1, 2014, and Oct 1, 2014
    • An independent review panel would determine if the device is innovative enough
    • First batch: 12 devices
  – Speed up review process for the innovative products
    • Up to 18 months shorter for the product market clearance
    • How to define “Innovative”? 

• 510(K) approach
  – Clinical data is required for all product,
  – However, more than 300 types of products are in the trial-waiver list
Device Registration Update (II)

• More third party device testing institutions
  – More than 50
  – All academic/government institutions, no private operations

• CFDA device management system revised:
  – From one department into two:
    • Device Registration Department: for unapproved products
    • Device Management Department: for approved products
Device Registration Update (III)

• Clinical trial approval is needed:
  – For the class III device with significant human risk

• Center for Device Evaluation
  – Increased headcounts: from 30 to 70
  – More Junior reviewers added recently
  – Close to 9,000 applications yearly, with more than 11,000 requests for more information every year
  – Need additional technical supports
    • Purchase qualified review services from third party organizations
General Trend (I)

• Special Handling Procedure becoming a trend
  – Not all the qualified clients have taken advantage of this trend yet
    • Not being up-to-date about the regulatory changes
    • Not familiar with the key elements in order to apply for this designation
    • Some sponsors tried to do it by themselves for the first time without fully prepared or advised by an experienced team
General Trend (II)

• Purchase of Qualified Review Services
  – A mandate from the State Council
  – The goal is to control the total headcounts in the government agencies
  – It may speed up review process
  – How to avoid potential conflict of interest?
General Trend (III)

• Hiring More Reviewers
  – Advertisement

• Reforming CDE/CFDA
  – Recent comments by CFDA senior officials
  – Started before the end of 2014

• Dealing with stock-piles of the applications
  – Previous experiences
  – Prediction by FMD
Impact on Drug Development Planning (I)

• Include China in company’s global drug development planning from the beginning
  – Try to simultaneously apply for IND in China
  – Or, try to get a blank approval for phase I, II, III

• When licensing in a product in development outside of China
  – Get the clinical data package inspected for
    • Asian population data
    • AE/SAE profile
  – Try to get certain waivers in China
## Impact on Drug Development Planning (I)

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- **Phase 2/3 study run in the US** (2016)
- **DM/CSR** (2017)
- **CSR indication for PE approved by U.S.** (2017)
- **In US**
- **Dossier review and translations**
- **IND submission** (2018)
- **CDE review and approved** (2018)
- **Conduct clinical trial**
- **IDL submission**
- **CDE review and approved** (2019)
- **In China**
Impact on Drug Development Planning (II)

• Continue to play the global trial card:
  – Use CMC info for the global trial to support other global study involving Chinese population
  – Meanwhile, consider building up manufacturing capability in China
  – Make up rest of the required trials, plus BE study, to plan for the strategy of China NDA first
## Impact on Drug Development Planning (II)

<table>
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<td><strong>DM/CSR</strong></td>
<td><strong>CSR indication for PE approved by U.S.</strong></td>
<td><strong>In US</strong></td>
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<td><strong>CTA submission</strong></td>
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<tr>
<td><strong>China QV</strong></td>
<td><strong>CDE review and approved</strong></td>
<td><strong>In China</strong></td>
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<tr>
<td><strong>Conduct clinical trial</strong></td>
<td><strong>IDL submission</strong></td>
<td><strong>CDE review and approved</strong></td>
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</table>
Impact on Medical Device Development

• Pay attention to the requirement of clinical trials: is your product on the trial-waiver list?
  – Consider to register a class I/II product first in China and then try to get clinical waiver for other products

• Product testing can be done at third parties

• Rigorous “risk management plan” to avoid or minimize delays caused by “CFDA request for more information”

• Follow the most current guideline for the special handling procedure for innovative products.
Contents

1. 2013 CDE Annual Report
2. New approach by CFDA
3. Alternative strategies
4. Case studies
Alternative Strategies-Licensing Out

- Product development outside of China: out of top three position
- Indication is suitable for China market
- Partner with China local licensee who has the right qualification for speeding up the clinical development process
  - Expert from “Thousand Talent Program”
  - Legally regarded as “local firm”
  - Holder of central government R&D grant
    - Such as National Key Drug Development Fund
- China requires only one pivotal trial for NDA
Best Practice: Global Development Planning

- Add enough sites in China during global phase II/III development phase
  - 100 pairs minimum
  - Clinical data from Hong Kong and Taiwan count
  - Would obtain importation license after NDA approval outside China

- Case study: please see next slides
Contents

1. 2012 CDE Annual Report
2. New approach by CFDA
3. Alternative strategies
4. Case studies

www.fountain-med.com
<table>
<thead>
<tr>
<th>Drug name</th>
<th>Sponsor</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dasatanib (SPRYCEL)</td>
<td>Bristol-Myers Squibb Pharma EEIG</td>
<td>CML</td>
</tr>
<tr>
<td>Saxagliptin (Onglyza)</td>
<td>Bristol-Myers Squibb Company</td>
<td>Diabetes</td>
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<tr>
<td>Prucalopride succinate tablet</td>
<td>Shire-Movetis N.V.</td>
<td>chronic constipation, CC</td>
</tr>
<tr>
<td>Ilenalidomide capsule</td>
<td>Celgene</td>
<td>multiple myeloma, MM</td>
</tr>
<tr>
<td>Lenalidomide capsule</td>
<td>Celgene</td>
<td>multiple myeloma, MM</td>
</tr>
<tr>
<td>Everolimus tablet</td>
<td>Novartis Sverige AB</td>
<td>RCC</td>
</tr>
<tr>
<td>Crizotinib capsule</td>
<td>Pfizer Inc.</td>
<td>NSCLC</td>
</tr>
<tr>
<td>Linagliptin tablet</td>
<td>Boehringer Ingelheim</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Dabigatran Etexilate</td>
<td>Boehringer Ingelheim</td>
<td>Atrial fibrillation</td>
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<tr>
<td>Alogliptin</td>
<td>Takeda Pharmaceutical</td>
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## Trial-waiver due to Rare Disease

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<th>Indication</th>
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<td>Pfizer Inc.</td>
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<td>Caffeine citrate injection</td>
<td>Chiesi Farmaceutici</td>
<td>Apnea of prematurity</td>
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<tr>
<td>Trepros injection</td>
<td>United Therapeutics</td>
<td>pulmonary hypertension, PH</td>
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<td>Miglustat (ZAVESCA)</td>
<td>Actelion Pharmaceuticals</td>
<td>Niemann-Pick disease type C, NPC</td>
</tr>
</tbody>
</table>
Regulation of combination treatment

Product: Bone cement (containing drug)
Manufacturer: DePuy International Ltd. Trading as Deput CWW, UK

Product: Sterilized dressing (containing drug)
Manufacturer: Yangling Company, China

Product: Bone cement (containing drug)
Manufacturer: Tecres S.p.A, Italy

Product: Stent (containing drug)
Manufacturer: Boston Scientific Corporation, USA
Best Practice - Partnership with Chinese Firm

• Novartis Vaccine Deal
  – Partnership with the local firm
  – Jointly applied for a national grant
  – Enjoy speedy approval

• Roche deal with Ascletis
  – Phase II asset for HCV - an important indication in China
  – Program leader is one of the experts from the Thousand Talent Program
Regional Trials

• Approval for regional trials by CFDA
  – Why regional trial: what is the scientific rational?
    • Genetic variation?
    • Epidemiology?
    • Homogeneous treatment pattern?

• Acceptance of Clinical Data by CFDA
  – Depend on the stage of trial
  – Depend on the source of data
  – Depend on the utility of data
Clinical Data from Hong Kong

• All Hong Kong data is accepted by CFDA
  – Phase I data: must be generated from CFDA certified GCP centers
    • Phase I center of Hong Kong University School of Medicine
    • Phase I center of Hong Kong Chinese University School of Medicine
  – Could conduct first-in-human study
  – Phase II/III data: accepted for both efficacy and safety purpose
  – Hong Kong accepts US IND, as well as CTA from mainland China

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Partnership with local companies

• Joint Application for the special drug development funding
  – from National Drug Development Fund
  – From matching fund at local-level

• Quicker Approval for IND/NDA
  – Location of manufacture
  – Combined with clinical data from Taiwan and other locations.
Fountain Medical Development

Leading full service clinical CRO in Asia

Introduction
The Company – Service Quality

• **Accreditations**
  – MediData Rave/ Oracle Inform
  – CDISC Gold Member

• **SOP System**
  – FMD has completed the SOP system which is compatible with ICH-GCP

• **Audits by major global clients- All successfully passed**
  – Pfizer, BMS, Ferring, J&J, Novartis, Ariad, Servier, Duke DCRI, Lundbeck, Fibrogen, RB, Arena

• **Independent Quality Assurance system in place**
Clinical Operation Geographical Coverage
The Company – Competitive Advantages

1. **FMD has strong scientific relationship with CFDA**: effective managing and negotiating with agency on behalf of clients, significantly faster /NDA timeline than benchmark

2. **Global standard quality with affordable price**
   Conducted pivotal multi-country studies for filing at FDA/EMEA
   The only CRO receiving government support:
   • FMD project was the first one that received support from MOST (Ministry of Science Technology), Ministry of Public Health, Ministry of Commerce and SFDA

3. **One stop shop**: phase I-IV study conduct, sample analysis, DM/Biostat, report writing, PharmacoEconomic, Safety Handling, all performed with local rate.
The Company – Management Team

- **Dan Zhang, CEO**  MD, MPH, MBA
  Dan has 20 years of experience in the Pharma industry. Was on the expert committee of the MOST, and a senior consultant to CAMS (Chinese Academy of Medical Sciences); Chairing Bayhelix’ SFDA working committee

  As a long term advisor for the SFDA, Dr. Zhang is on the new drug review committee of the SFDA and a member of grant review committee for the National Key Drug Development.

  2002 – 2007, Head of Global Safety Assessment and Clinical Drug Development of Sigma-Tau USA.

  1995 – 2000, VP of Quintiles Transnational Corp., and the Chairman of Board for Quintiles Greater China Operation

- **Lijun Xiao, Director of Regulatory Affairs**
  Over 13 years of RA experience and has successfully registered a number of local drugs, drugs for global studies and imported drugs.

- **Joanne Jiang, CBO BD and PM**  PhD, MBA
  Director of global project management, Daiichi-Sankyo Development

  Senior global project manager, Sanofi-Aventis

  15 years of pharmaceutical development experience

- **Henry Wu, Head, DM/SA, PhD**
  Ph.D. in Biostatistics from UMDNJ, M.S. from UCONN, and dual B.S. degrees from Tsinghua University.

  14 years industry experiences, including Pfizer, Hoffman La Roche. Served as lead statistician for many submission projects and different phases of clinical trials, in different therapeutic areas.

- **Sophie Su, Portfolio Management Director, Clinical Operation.**
  10 years experiences in clinical trial, work for CRO and Biotech company within clinical trial management, clinical operations and outsourcing.

  4 years experience in supervise activities of CRA&PM. A certificated Project Management Professional, PMP

- **Sam Hsia, Director of Clinical Operation**  MD.
  Senior Medical Affairs Manager, Zambon, Siemens, Sanofi-Aventis

  13 years of pharmaceutical development experience
<table>
<thead>
<tr>
<th>Department</th>
<th>Experience</th>
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<tr>
<td>Phase I</td>
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<td>Phase II</td>
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<td>Regulatory Affair</td>
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<td>Safety</td>
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<td>Central Lab</td>
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<tr>
<td>Central Lab</td>
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The Company – Experience (by area)
Quality Management

Monitor

Quality Control

Quality Assurance Audit

Clinical trial

Fundamental Training
(GCP, ICH-GCP, related regulations, project training, Fountain SOPs, refresh training, extension training)

SOPs
REGULATIONS
Compliance

Project management
Risk management
Communication skills

DATA
RECORDs
REPORTs
## Clinical Experiences in Oncology Area

<table>
<thead>
<tr>
<th>Therapeutic Area</th>
<th>Indication</th>
<th>Phase</th>
<th>No. of Sites</th>
<th>No. of Patients</th>
<th>Recruitment Duration</th>
<th>Total Study Duration</th>
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<tr>
<td>Oncology</td>
<td>Lung cancer</td>
<td>Ia</td>
<td>1</td>
<td>24</td>
<td>6 months</td>
<td>3 years</td>
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<tr>
<td>Oncology</td>
<td>Lung cancer</td>
<td>RA</td>
<td>-</td>
<td>-</td>
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<td>Lung cancer</td>
<td>RA</td>
<td>-</td>
<td>-</td>
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<td>11 months</td>
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<td>Lung cancer</td>
<td>RA</td>
<td>-</td>
<td>-</td>
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<td>12 months</td>
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<tr>
<td>Oncology</td>
<td>Solid tumor</td>
<td>I</td>
<td>1</td>
<td>20</td>
<td>12 months</td>
<td>12 months</td>
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<tr>
<td>Oncology</td>
<td>Solid tumor</td>
<td>Ib</td>
<td>1</td>
<td>48</td>
<td>12 months</td>
<td>1 year</td>
</tr>
<tr>
<td>Oncology</td>
<td>Solid tumor</td>
<td>I</td>
<td>2</td>
<td>24</td>
<td>24 months</td>
<td>3 years</td>
</tr>
<tr>
<td>Oncology</td>
<td>Solid tumor</td>
<td>I</td>
<td>1</td>
<td>30</td>
<td>24 months</td>
<td>3 years</td>
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<tr>
<td>Oncology</td>
<td>Glioblastoma</td>
<td>I/Ila</td>
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<td>8 months</td>
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<td>Tumor</td>
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<td>0.75 month</td>
<td>18 months</td>
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<td>Oncology</td>
<td>Lower WBC count caused by chemotherapy</td>
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<td>1</td>
<td>46</td>
<td>NA</td>
<td>10.5 months</td>
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## Clinical Experiences in Oncology Area

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<th>Therapeutic Area</th>
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<th>No. of Sites</th>
<th>No. of Patients</th>
<th>Recruitment Duration</th>
<th>Total Study Duration</th>
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<td>Lower WBC count caused by chemotherapy</td>
<td>I</td>
<td>1</td>
<td>30</td>
<td>4 months</td>
<td>8 months</td>
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<td>Oncology</td>
<td>Advanced solid tumor and lymphoma</td>
<td>I</td>
<td>2</td>
<td>60</td>
<td>-</td>
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<td>Oncology</td>
<td>Antibody</td>
<td>I</td>
<td>1</td>
<td>36</td>
<td>1 month</td>
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<td>Oncology</td>
<td>Pancreatic cancer</td>
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<td>Brain tumor</td>
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<td>120</td>
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<td>Oncology</td>
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<td>200</td>
<td>2 months</td>
<td>3 years</td>
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<td>Oncology</td>
<td>Radiation induced fatigue</td>
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<td>3 years</td>
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<td>Oncology</td>
<td>Melanoma</td>
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<td>15</td>
<td>200</td>
<td>24 months</td>
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## Clinical Experiences in Oncology Area

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<td>Oncology</td>
<td>Breast cancer</td>
<td>II</td>
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<td>400</td>
<td>7 months</td>
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<td>HER2 positive stage II-III Early Breast Cancer</td>
<td>II</td>
<td>13</td>
<td>100</td>
<td>18 months</td>
<td>3 years</td>
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<tr>
<td>Oncology</td>
<td>non-small cell lung cancer (NSCLC)</td>
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<td>10</td>
<td>100</td>
<td>36 months</td>
<td>64 months</td>
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<td>300</td>
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<td>Breast Cancer</td>
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<td>6</td>
<td>750</td>
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<td>4 years</td>
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# Clinical Experiences in Oncology Area

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<th>Total Study Duration</th>
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<td>IV</td>
<td>13</td>
<td>100</td>
<td>18 months</td>
<td>36 months</td>
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<td>12.5 months</td>
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<td>Therapeutic Area</td>
<td>Indication</td>
<td>Phase</td>
<td>No. of Sites</td>
<td>No. of Patients</td>
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<td>Total Study Duration</td>
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<tr>
<td>Oncology</td>
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<tr>
<td>Oncology</td>
<td>Prostate cancer</td>
<td>DM/SA</td>
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<td>Oncology</td>
<td>Ovarian cancer</td>
<td>DM/SA</td>
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<tr>
<td>Oncology</td>
<td>T/NK cell lymphoma</td>
<td>DM/SA</td>
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<td>DLBCL</td>
<td>DM/SA</td>
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<td>No. of Patients</td>
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<td>Oncology</td>
<td>Hepatic cancer</td>
<td>RA</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6 months</td>
</tr>
<tr>
<td>Oncology</td>
<td>Solid tumor</td>
<td>RA</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>11 months</td>
</tr>
<tr>
<td>Oncology</td>
<td>Cancer</td>
<td>RA</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>11 months</td>
</tr>
<tr>
<td>Oncology</td>
<td>Pancreatic cancer</td>
<td>RA</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>10 months</td>
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<tr>
<td>Oncology</td>
<td>Liver Cancer</td>
<td>RA</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>12 months</td>
</tr>
<tr>
<td>Oncology</td>
<td>Intestinal cancer</td>
<td>RA</td>
<td>-</td>
<td>-</td>
<td>Biological product</td>
<td>23 months</td>
</tr>
<tr>
<td>Oncology</td>
<td>Rectal cancer</td>
<td>RA</td>
<td>-</td>
<td>-</td>
<td>Biological product</td>
<td>24 months</td>
</tr>
</tbody>
</table>
FMD Regulatory Affairs Service
FMD RA Department Scope of Work

- **Domestic Registration**
  - Drug, Medical Device, Health Food/Nutritional Supplement, Cosmetic
  - Clinical Trial Approval (CTA/IND), Marketing Approval (IDL/NDA), Supplemental Applications

- **Foreign Registration**
  - USA(IND only), Singapore, South Korea, Taiwan, Hong Kong

- **Consultation of medical product registration**
  - Strategic Planning
  - Technical Consultation
  - Feasibility Analysis
  - Provide Recommendations
Under the direction of CFDA FMD has drafted...

- Technical Guide of Phase I Clinical trials (First edition)
- Technical Guide of Pharmacokinetics(First edition)
- Technical Guide of Data Management (Third edition)
- Provided translation and edited the Technical Guide of FDA and EMA (more than 200)
In 2009, Dr. Dan Zhang, represented FMD and accepted the **Award of Special Services** which was awarded by Center for Drug Evaluation, CFDA.
IND Preparation Assurance

Fast and smooth IND approval process

- Good pre-submission communication
- Thorough compilation and preparation of regulatory dossiers
- Close follow-up of the review process and prompt response to CDE’s questions

Project management

External Advisors

In house expertise
Competitive advantages of FMD regulatory team

1. FMD’s CEO Dr. Dan Zhang is the only CDE advisor coming from China’s CRO industry. Thus FMD has the most up-to-date regulatory information in hand. FMD has the most experienced regulatory team handing fast-track/accelerated approvals in China.

2. FMD has a dedicated regulatory affairs team of 12 people in Beijing, handling more than 50 IND/CTA/NDA and regulatory consulting projects at the same time. In addition, FMD also has a team of regulatory consultants, including former CFDA employees.

3. FMD has a solid track record for handling difficult regulatory projects, and also the experience of completing test cases in China, such as early phase development.

4. FMD has a track record of handling IND/NDAs in South Korea, Hong Kong, Taiwan, Vietnam, Singapore, Thailand and USA (IND only).
Case of Success: acceleration strategy

- A global top 5 pharma phase I complete oncology compound
- FMD obtained CTA: earliest stage by far
- Asia clinical development, China Korea
- Possible acceleration strategy: phase 2/3 combined approach
- Requirement by CFDA:
  Repeat of phase I in Chinese Patients may be required
  Could utilize this opportunity to verify no ethnic difference in PK/PD
- DSMB
- Biomarker: not required, but desirable by KOLs
Fountain Medical Development

Leading full service clinical CRO in Asia

Safety Handling for Oncology Study in China

2014.2.14
Safety Handling in US vs. in China

• SAE handling during IND study
  – Definition is the same
  – What to report
    • US: unexpected, serious and drug-related
    • China: all
  – Timeline
    • US: 7 day and 15 days; annual report
    • China: ASAP (24 hours), annual report
  – Reporter
    • China: mandatory dual reporting from PI and sponsor
  – SAE occurred outside of China
    • Report back to China
Safety Handling in US vs. in China

• All AEs/SAEs are reported in Chinese
  – CFDA has published reporting template
• No mandatory dictionary
  – MedDRA has Chinese Language Capability
• DSMB/DMC: no guideline in China, but nice to have
• CTCAE not officially endorsed but applied widely
• Death case handling: very conservative
  – IRB pays special attention, can be clinically on-hold
Summary

• **China’s pharmaceutical market growing rapidly while the regulatory regime is changing fast and improving**
  – Fast-track CTA, outsourcing of review tasks, CT waiver

• **Select the product needed most in China**
  – Innovative drugs, unmet medical needs, oncology, pandemic diseases, drug-resistant TB, rare diseases

• **Create the most effective development strategy**
  – Parallel rather than sequential development, waiver application, local partner supported by government (e.g. grant or talent)

• **Work with the most insightful partner**
  – Leverage the experience and insights of local partner to keep pace with and take advantage of the fast changing regulatory landscape