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Applied Translational Medicine

# Emerging Early Clinical Research Capabilities in Asia-Pacific

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# Questions

- What is driving the interest in performing early clinical research studies in the Asia-Pacific region?
- How have different countries approached developing early clinical research capabilities?
- Are there unique capabilities or patient access that make the region attractive to global drug developers?
- What are the challenges in conducting early clinical research studies in this part of the world?
- What are the growth areas to watch in the future?

# What's Driving Change in Early Clinical Studies

- Fail fast in Phase I
  - More information needed for early drug development decisions
- Clinical Pharmacology studies becoming more complex
  - Inclusion of patient cohorts
  - More biomarkers, more sampling
    - Sampling logistics challenges
  - Fusion and adaptive designs
  - More biologic drug candidates – immunogenicity
  - Earlier robust cardiac safety assessment

# Reasons for Performing Clinical Pharmacology Studies in Asia-Pacific Region

## Market Drivers

1. Access to patients for early clinical assessment of safety, PK and signals of efficacy and dose response
2. Bridging PK and PK/PD studies to support registrations of drug products in Asian markets
3. Support First-in-Human assessments of drugs discovered and developed in Korea, Singapore, China, Japan and other Asian nations

## Operational Factors

1. Modern, well equipped clinical trial centers at major medical centers with ready access to many patient populations
2. Some regulatory environments similar to North America and Europe
3. Well-trained scientific and medical staff that can communicate in English

## Needs

1. Pharma companies need studies to support products for Asian markets
2. Asian CTCs need access to global pharma study opportunities and best operating practices for running efficient operations

# How have different countries approached developing early clinical research capabilities?

- Singapore
  - Adapted ICH GCP and implemented SGGCP since 1998
  - Pharma-owned Phase I units
  - Academic clinical research centres with Phase I units
  - Regulatory
    - Rolling submission
    - 30 day approval
      - 15 days for low risk Phase I studies
      - e.g. BE studies
  - IRB/Ethics Committee
    - 2 main IRB
    - Monthly meetings
    - Cross recognition of each other's review – 1 IRB review for multisite studies
  - Parallel submission
    - Overall approval timeline about 6-8 weeks



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# How have different countries approached developing early clinical research capabilities?

- South Korea
  - Adapted ICH GCP and implemented KGCP since 2000
  - Phase I units in 15 hospital based Clinical Trial Centers
  - Regulatory
    - Approval timeline 30 to 60 days
  - IRB/Ethics Committee
    - IRB meeting once every 2 or 4 weeks
  - Parallel submission
    - Overall timeline is about 60 days



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# How have different countries approached developing early clinical research capabilities?

- China
  - GCP implemented in 1999
  - SFDA accredited Phase I units in hospitals
  - Regulatory
    - Approval timeline ~ 11 months
  - IRB/Ethics Committee
    - ~ 60 days
  - Sequential review
    - Overall timeline > 1 year



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# How have different countries approached developing early clinical research capabilities?

- Japan
  - Adapted ICH GCP for implementation since 1998; J-GCP is more comprehensive with additional requirements
  - Regulatory
    - Start if no queries from PMDA 30 days after CTN submission
  - IRB
    - Variable approval timeline



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# How have different countries approached developing early clinical research capabilities?

- Australia
  - Implemented ICH GCP with adaptations since 2000
  - 5 early phase clinical research units and a number of academic clinical pharmacology units
  - Regulatory
    - Clinical Trial Notification Scheme; acknowledgement received within a few days of notification
  - IRB/Ethics Committee
    - ~12-16 weeks for approval



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# Early Signals of Clinical Safety and Efficacy are the Key to Applied Translational Medicine

To get an early sense that a drug is working in humans as it was designed, you need:

Patients

- Small number
- Stable disease
- Minimal confounding treatments
- Appropriately motivated

Investigators / Clinical Trial Centers

- Small number of sites
- Scientifically / medically robust
- Controlled study setting
- Follow global GCP standards
- Ethical conduct

# Access to Patient/Special Populations and Specialists

## Special Populations

- Renal Impairment
- Hepatic Impairment
- Elderly
- Women

## Patient Populations

- Diabetes Mellitus
- Asthma
- COPD
- Rheumatoid Arthritis
- Systemic Lupus Erythematosus (SLE)
- Psoriasis
- Alzheimer’s Disease
- Schizophrenia
- Depression
- Cancer
- Hypertension
- Hyperlipidaemia
- Infectious Diseases

# Access to Patient/Special Populations and Specialists

- South Korea
  - Patient pool concentrated in large hospitals located mainly in Seoul and Busan, fast recruitment
  - High incidence/prevalence of gastric cancer, hepatic cancer, and Hep B
  - Common Hep C genotype is Type 1b, followed by 2a. (versus Type 1a in North Europe and North America)
  - Many well trained pharmacologists and specialists, mainly trained in North America
  - Becoming global leaders in imaging and pharmacogenomics

# Access to Patient/Special Population and Specialist

- Singapore
  - Small city state with multiple ethnic groups including Chinese and Indians
  - Ideal for studying ethnic differences in pharmacology as well as disease pathogenesis
  - High incidence/prevalence of nasopharyngeal cancer, hepatic cancer, Hep B, Brugada syndrome and dengue fever
  - Specialists trained in both North America and UK

# Access to Patient/Special Population and Specialist

- China
  - Huge population of treatment naïve patients
  - Fast recruitment
  - Dual disease burden of developing countries with both communicable and non-communicable diseases

- Australia
  - Good for seasonal diseases when incidence is low in Northern hemisphere countries
  - Very high melanoma rate

# Study Populations in Asia

| Disease/Study Type | Comments |
|---|---|
| Oncology | • Early clinical trial units available as part of Cancer Hospitals in South Korea, Singapore<br>• South Korea and Singapore have excellent tumor imaging capabilities |
| Rheumatoid Diseases | • Specialty units in South Korea have the biomarkers and patients<br>• Good patient access in South Korea and Singapore (smaller scale) |
| HCV, HBV, Hepatic Insufficiency | • HCV and HBV are prevalent in Korea; HBV prevalent in Singapore<br>• Higher percentage of HCV Genotype 2 patients in Korea than NA or Europe |
| CNS with PET Imaging | • South Korean and Singapore sites have PET scanners for research use, cyclotrons and a good collection of PET imaging agents |
| Ethnic Bridging | • Sites in South Korea are building databases of Japanese, Korean and Caucasians for ethnic bridging studies.<br>• Singapore has good access to Chinese, Indians and Caucasians |
| Cardiovascular | • Modern diagnostics including imaging and catheterization are available at key centers in South Korea and Singapore |
| Renal Insufficiency | • Experience at centers in South Korea |
| GI Diseases | • Experience with gastric intubations with pH monitoring in South Korea and Singapore where high incidence of GI disease occurs |
| FIH - Korean Pharma | • Leading sites manage collectively 15-25 FIH studies a year |
| Pediatrics | • Seoul National has pediatric study center as part of Children's Hospital |

# Challenges to Conducting Clinical Trials in Asia Pacific

- Access to Physicians
  - Time/Resources
  - Interest
  - Incentives
  - Hospital and Community-based
- Access to Patients/Special Populations
  - Database
  - Referrals
  - Collaborations/Research Networks
  - Barriers



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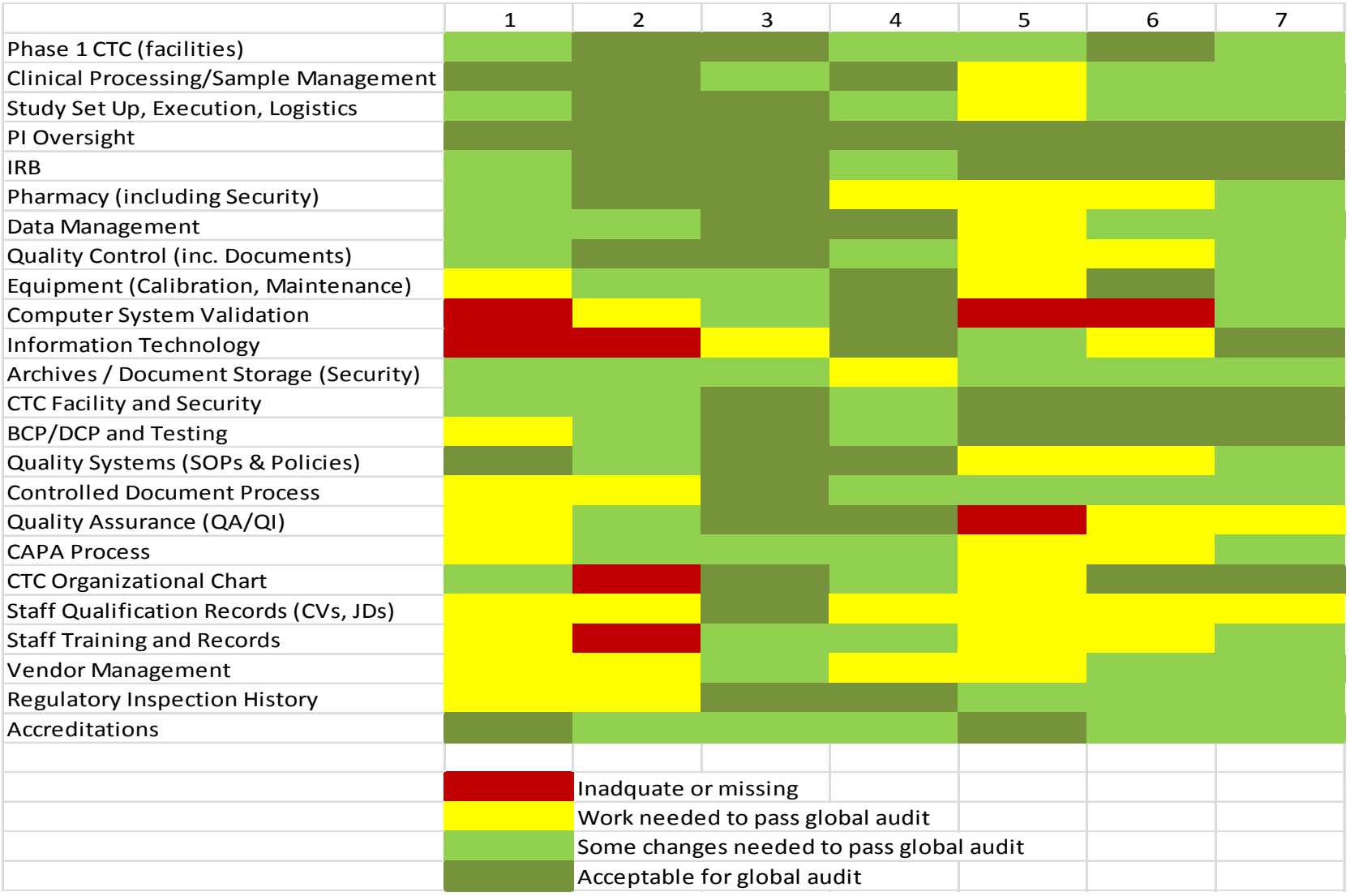
# Challenges to Conducting Clinical Trials in Asia Pacific

- Operational Expertise
  - Complex sample processing
  - Extemporaneous Compounding
- Local environment
  - Additional local regulatory requirements
- Language
  - Business language – English
  - Translations
  - Communication
  - Cultural differences

# Audit Results of 7 Asian CTCs 2013-2014



# Quality

- Most sites never had a full systems audit against global standards/ expectations
- Variability across sites in areas of strength and weakness
- Strengths: Across all sites were Phase I CTC facility and Security, PI Oversight and IRB
- Weaknesses:  Staff Qualification records (6 of 7 sites), IT and Computer System Validation (4 of 7 sites),  QA (4 of 7 sites),  Vendor Management (4 of 7 sites), Staff Training Records (4 of 7 sites), Pharmacy (3 of 7 sites) and CAPA process (3 of 7 sites)

# Future Growth Areas

- Hong Kong
- Taiwan
- South East Asia


# Summary

- Growth in early clinical research in Asia-Pacific region driven by:
  - Access to patients and Asian ethnicities
  - Modern hospital-based clinical Phase I units with well-trained medical staff
  - Novel drug discovery emerging from non-Japanese countries
- Variations across countries in regulatory timelines, patient types, communications, import/export
- Variations across sites in experience, patient types, implementing global quality expectations
- Challenges include distance, language, and building more awareness of region's capabilities to conduct early clinical research



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