



How To Be a Global Player in Early Clinical Development?

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Topics

- Why early clinical development in Asia-Pacific?
- Access to patient populations
- Global expectations
- Efficient operations
- Access to specialists/resources e.g. imaging
- Others - regulatory/IRB, language challenges, costs

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 an efficient clinic operations

Access to Patient/Special Populations and Specialists

Special populations

- Renal impairment
- Hepatic impairment
- Elderly
- Women

Patient populations

- Diabetes Mellitus
- Asthma
- COPD
- Rheumatoid arthritis
- SLE
- Psoriasis
- Alzheimer's disease
- Schizophrenia
- Depression
- Cancer
- Hypertension
- Hyperlipidaemia
- Infectious diseases

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 Units

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

Impact on Clinical Trial Units/Centers

- Access to physicians
 - Time/Resource
 - Interest
 - Incentives
 - Hospital and community based
- Access to patients/special populations
 - Database
 - Referrals
 - Barriers
 - Collaborations/research networks

Global Expectations of Clinical Trial Centers

- PI oversight
- Quality control:
 - Documentation regarding the QC processes during conduct of clinical trials and for the data collected.
 - Sponsor monitoring versus internal QC processes.
- Quality system:
 - SOPs in an organized system and have an Index or Table of Contents available for review.
 - Quality Reviews at a higher level.
- Phase I Unit (facilities):
 - Units which are clean, well organized and maintained in an acceptable manner.
 - Staffing and required equipment to conduct early phase clinical research.

Global Expectations of Clinical Trial Centers

- Clinical Processing Laboratory/Sample Management
 - Documented procedures for sample management.
 - Laboratory facilities which are in good order.
 - Well defined equipment management.
 - Good tracking of samples from collection through processing and results.
- Study Set-up, Execution, Logistics
 - Good standard forms for documenting study processes: screening, enrolment, study conduct, follow-up, etc. This ensures study events and data collected can be verified easily.
- IRB/EC
 - Clear and well documented IRB submission process for review
 - Timely submissions/approvals.
- Data Management
 - Data QC, handling and management standard processes are documented.

Global Expectations of Clinical Trial Centers

- Pharmacy
 - Log book for visitors to sign in and out of the pharmacy.
 - Humidity monitoring and control in addition to temperature monitoring and control.
 - Segregated/clean area for the preparation and packaging of drugs.
 - Chain of custody of IP should be clear.
- Equipment (calibration, maintenance)
 - Equipment List with complete information on the list.
 - Inconsistencies in record keeping: late filing of certifications, discrepancies in equipment labels, logs and maintenance records.
 - Records not kept for required retention period for study records.
- Facility Security
 - Documentation of visitors' entry and departure need to be recorded.
 - Access must be controlled.
- BCP/DRP & Testing
 - Relevant policies and/or procedures, testing and documentation of different scenarios needed.

Global Expectations of Clinical Trial Centers

- Quality Assurance
 - QA function, oversight, and documentation – available?
 - QA audits of the clinical trials - consistently carried out?
 - Audits - study specific or systems type?
 - SOPs - appropriate version control and/or approval?
- Regulatory Inspection
 - A formal process for facilitation of Regulatory Inspections (and/or sponsor audits) needed.
 - A listing of past regulatory inspections needed.
- Accreditations
 - Accreditations made available for review?
- Unit Organization Chart
 - Org charts - available/not complete/inaccurate?

Global Expectations of Clinical Trial Centers

- Corrective and Preventive Actions (CAPA)
 - Formal CAPA process needed (documentation of process, tracking, effectiveness evaluation, closure – even for sponsor audits/regulatory inspections).
- Archives/Document Storage
 - Controlled access should be verifiable - documentation of visitors/unauthorized staff entry and departure.
 - Fire protection.
 - A formal process for contacting sponsor and documentation of the contact prior to destruction of documents available?
 - Documents beyond expiration dates are required to be retained to support the clinical trials being conducted within that timeframe.

Global Expectations of Clinical Trial Centers

- Computer System Validation
 - Knowledge of Computer Systems Validation (CSV) process and requirements so that validation and its documentation may be completed.
- Information Technology
 - Familiarity of basic IT requirements for data security, backup and restore is required so that staff can ensure documentation is available for review.
- Staff Qualification Records (CVs, JDs)
 - There is a challenge in ensuring JDs for non- staff members of the Phase I unit are available and up to date. Similar challenge with CVs.
 - Previous versions of JDs and CVs need to be retained to support clinical trials conducted at that time.
- Staff Training Records
 - Same challenge as for CVs and JDs.
 - Centralized staff training records which are easily retrieved.
 - Complete SOP training records.
 - Industry standard: GCP training at least every 2 years.
- Vendor Management
 - Vendor qualification needs to go through a documented formal process

Celerion Audit Results of 7 Asian CTCs 2013-2014

	1	2	3	4	5	6	7
Phase 1 CTC (facilities)	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit
Clinical Processing/Sample Management	Acceptable for global audit	Acceptable for global audit	Some changes needed to pass global audit	Acceptable for global audit	Work needed to pass global audit	Acceptable for global audit	Acceptable for global audit
Study Set Up, Execution, Logistics	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit	Work needed to pass global audit	Acceptable for global audit	Acceptable for global audit
PI Oversight	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit
IRB	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit
Pharmacy (including Security)	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit	Work needed to pass global audit	Work needed to pass global audit	Work needed to pass global audit	Acceptable for global audit
Data Management	Acceptable for global audit	Some changes needed to pass global audit	Acceptable for global audit	Acceptable for global audit	Work needed to pass global audit	Acceptable for global audit	Acceptable for global audit
Quality Control (inc. Documents)	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit	Work needed to pass global audit	Work needed to pass global audit	Acceptable for global audit
Equipment (Calibration, Maintenance)	Work needed to pass global audit	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit	Work needed to pass global audit	Acceptable for global audit	Acceptable for global audit
Computer System Validation	Inadquate or missing	Work needed to pass global audit	Acceptable for global audit	Acceptable for global audit	Inadquate or missing	Inadquate or missing	Acceptable for global audit
Information Technology	Inadquate or missing	Inadquate or missing	Work needed to pass global audit	Acceptable for global audit	Acceptable for global audit	Work needed to pass global audit	Acceptable for global audit
Archives / Document Storage (Security)	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit	Work needed to pass global audit	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit
CTC Facility and Security	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit
BCP/DCP and Testing	Work needed to pass global audit	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit
Quality Systems (SOPs & Policies)	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit	Work needed to pass global audit	Work needed to pass global audit	Acceptable for global audit
Controlled Document Process	Work needed to pass global audit	Work needed to pass global audit	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit
Quality Assurance (QA/QI)	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit	Inadquate or missing	Work needed to pass global audit	Work needed to pass global audit
CAPA Process	Work needed to pass global audit	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit	Work needed to pass global audit	Work needed to pass global audit	Acceptable for global audit
CTC Organizational Chart	Acceptable for global audit	Inadquate or missing	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit
Staff Qualification Records (CVs, JDs)	Work needed to pass global audit	Work needed to pass global audit	Acceptable for global audit	Work needed to pass global audit	Work needed to pass global audit	Work needed to pass global audit	Work needed to pass global audit
Staff Training and Records	Acceptable for global audit	Inadquate or missing	Acceptable for global audit	Acceptable for global audit	Work needed to pass global audit	Work needed to pass global audit	Acceptable for global audit
Vendor Management	Work needed to pass global audit	Work needed to pass global audit	Acceptable for global audit	Work needed to pass global audit	Work needed to pass global audit	Acceptable for global audit	Acceptable for global audit
Regulatory Inspection History	Work needed to pass global audit	Work needed to pass global audit	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit
Accreditations	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit	Acceptable for global audit
	Inadquate or missing						
	Work needed to pass global audit						
	Some changes needed to pass global audit						
	Acceptable for global audit						

Conclusions from Audit

- Most sites never had a full systems audit vs. global expectations.
- Variability across sites in areas of strength and weakness
- Strengths across all sites were facilities, PI oversight, IRB and accreditations.
- Weaknesses: staff qualification records (6 of 7 sites), IT and computer system validation (4 of 7 sites), QA and vendor management (4 of 7 sites), pharmacy (3 of 7 sites) and CAPA process (3 of 7 sites).
- Sites eager for feedback and good progress has been made to rectify observations.

Efficient Operation of Facilities and Equipment

- Efficiency
 - Dense, cosmopolitan Asian cities with high real estate cost
 - Need to maintain high occupancy
 - Active management to maximise usage and minimise errors
 - Manage stress level
 - Streamlined, standardized processes
 - Tetris game to maximise space usage

Access to Resources

- Imaging resources
 - Dedicated for research
 - Performance standards for clinical trials
- Compounding pharmacy
 - Sterile
 - Solid dosage forms
 - Suspensions
 - Solutions
- Complex sample processing/handling capabilities
- Deep operational expertise
 - Method development
 - Special capabilities e.g. CSF sampling, glucose clamping, evoked potential testing

Language Challenges

- Business language - English
- Communications
- Cultural nuances
- Translation

Costing

- Cost plus versus premium
- Industry benchmark
- Services included

COMPETITIVE



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