celerion

Applied Translational Medicine

Welcome to Celerion's Dinner and Discussion Program

Tokyo, Japan

Apr 2, 2015

celerion

Applied Translational Medicine

Fast to Patient: The Push For Earlier Signals of Efficacy in Clinical Research

J. Fred Pritchard, Ph.D.

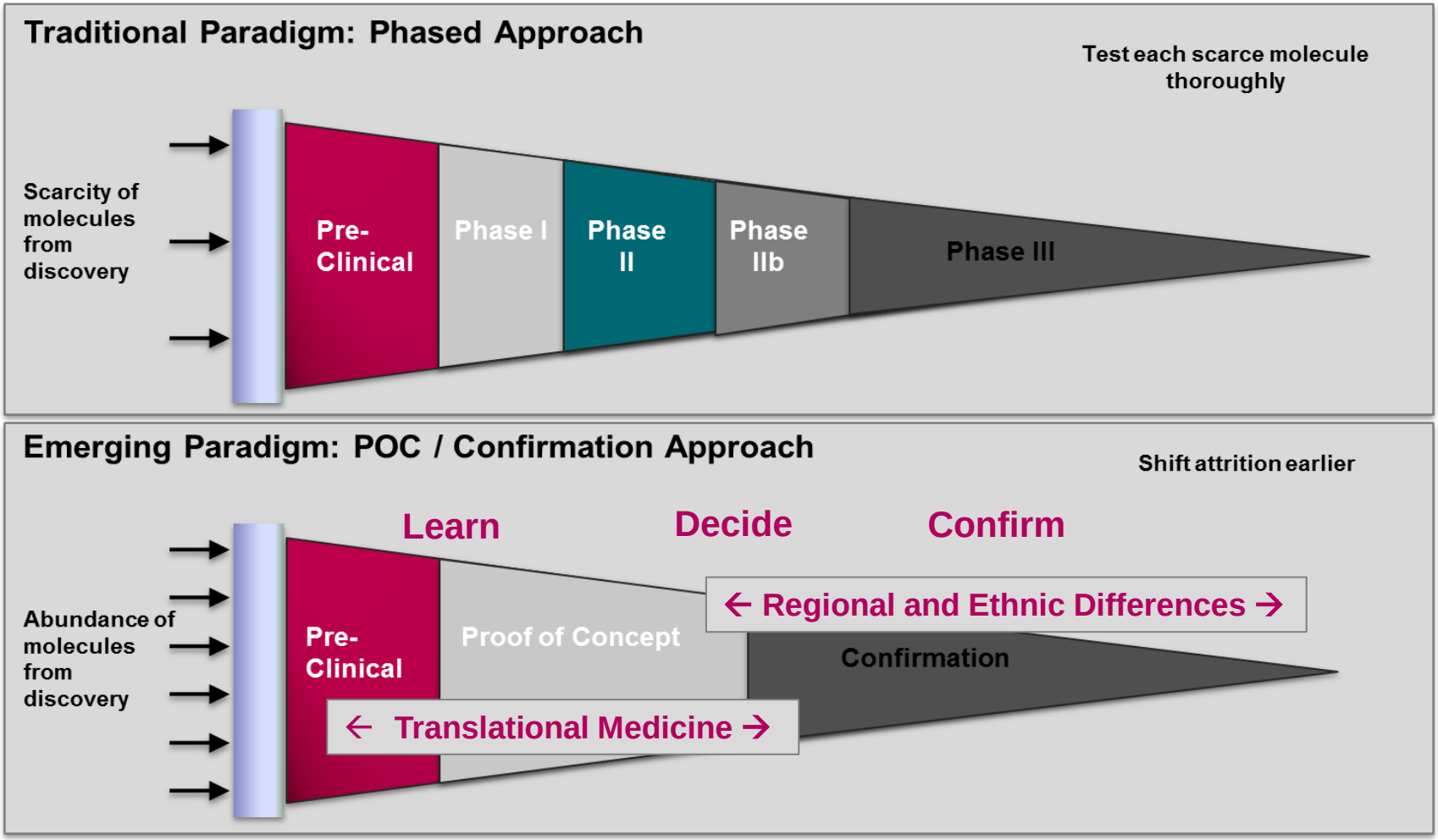
Vice President, Global Drug Development

Questions

- How is early clinical research changing?
- What are some challenges and strategies for engaging patients in early clinical studies?
- What are some challenges in conducting early clinical research studies in patients?
- Why is there increasing attention to Asia-Pacific region in early clinical research?
- What innovations are making early clinical research more efficient and effective?

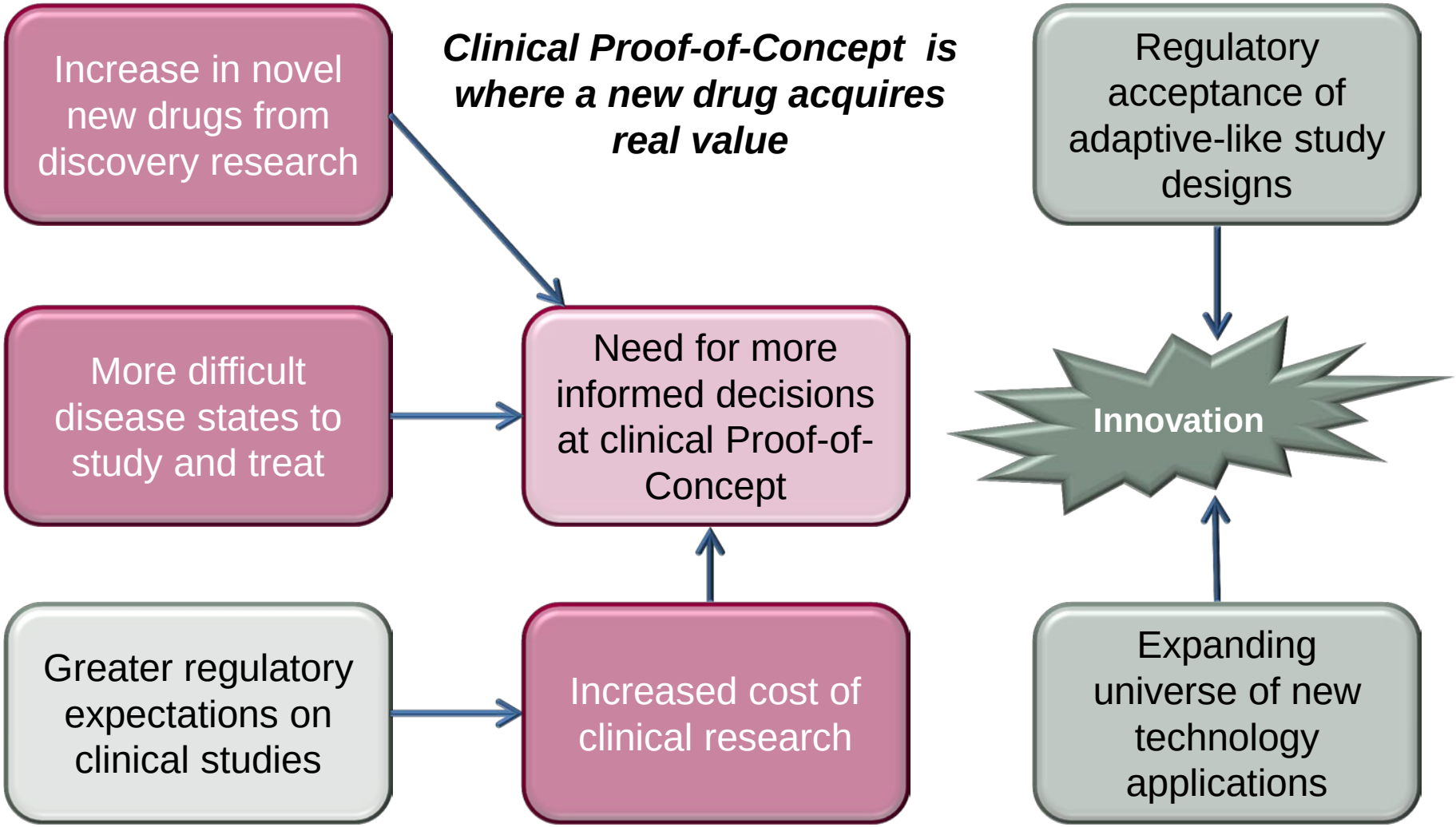
celerion

Changing Paradigm



Source: William Blair & Company, (Bain and Company) Covance Investors Overview June 16, 2010

What's Driving Evolution of New Paradigm?



Important “Proofs” in Early Clinical Research

- **Proof-of-Presence**
  - Does the drug get to its site of action?
  - Value Add: $

- **Proof-of-Mechanism**
  - Does the drug affect the biological target as it was designed?
  - Value Add: $$$

- **Proof-of-Concept**
  - Is there a sufficient signal that the drug favorably impacts the disease with acceptable risk of toxicity that would stimulate further investment in the drug?
  - Value Add: $$$$$

- Pharmacokinetics
- Tissue concentrations
- Healthy subjects (HS) or patients

- Biomarkers reflecting target engagement
- Biomarkers of toxicity (liver, kidney effects)
- Healthy subjects or patients

- Biomarkers reflecting impact on disease
- Biomarkers of toxicity (liver, kidney effects)
- Patients

celerion

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 (CTCs)

- Small number of sites
- Scientifically / medically robust
- Controlled study setting
- Follow global Good Clinical Practice (GCP) standards
- Ethical conduct

Access to Patient/Special Populations and Specialists

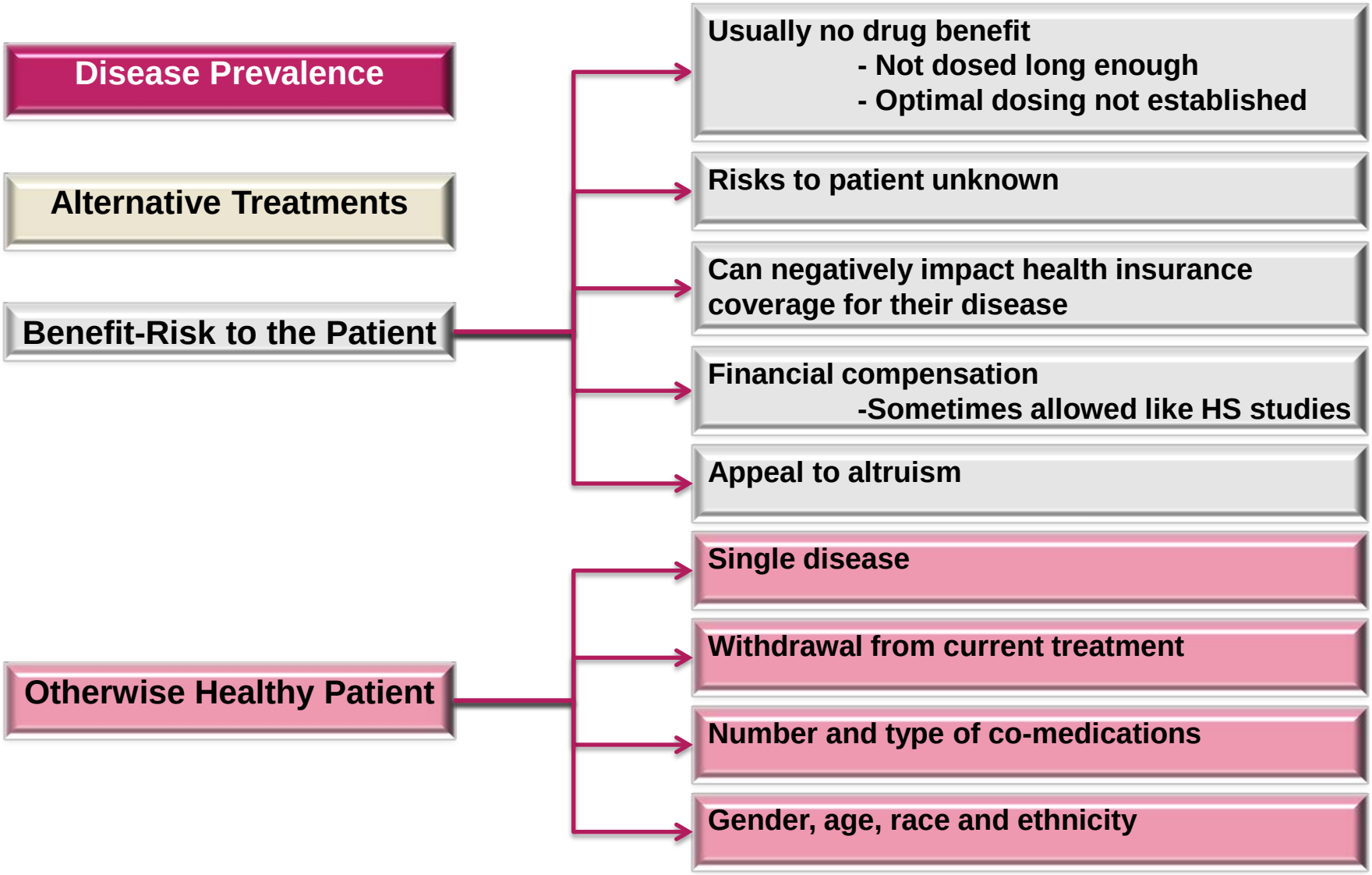
Special Populations

- Renal Impairment
- Hepatic Impairment
- Elderly
- Women
- Pediatric/Adolescent

Patient Populations

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

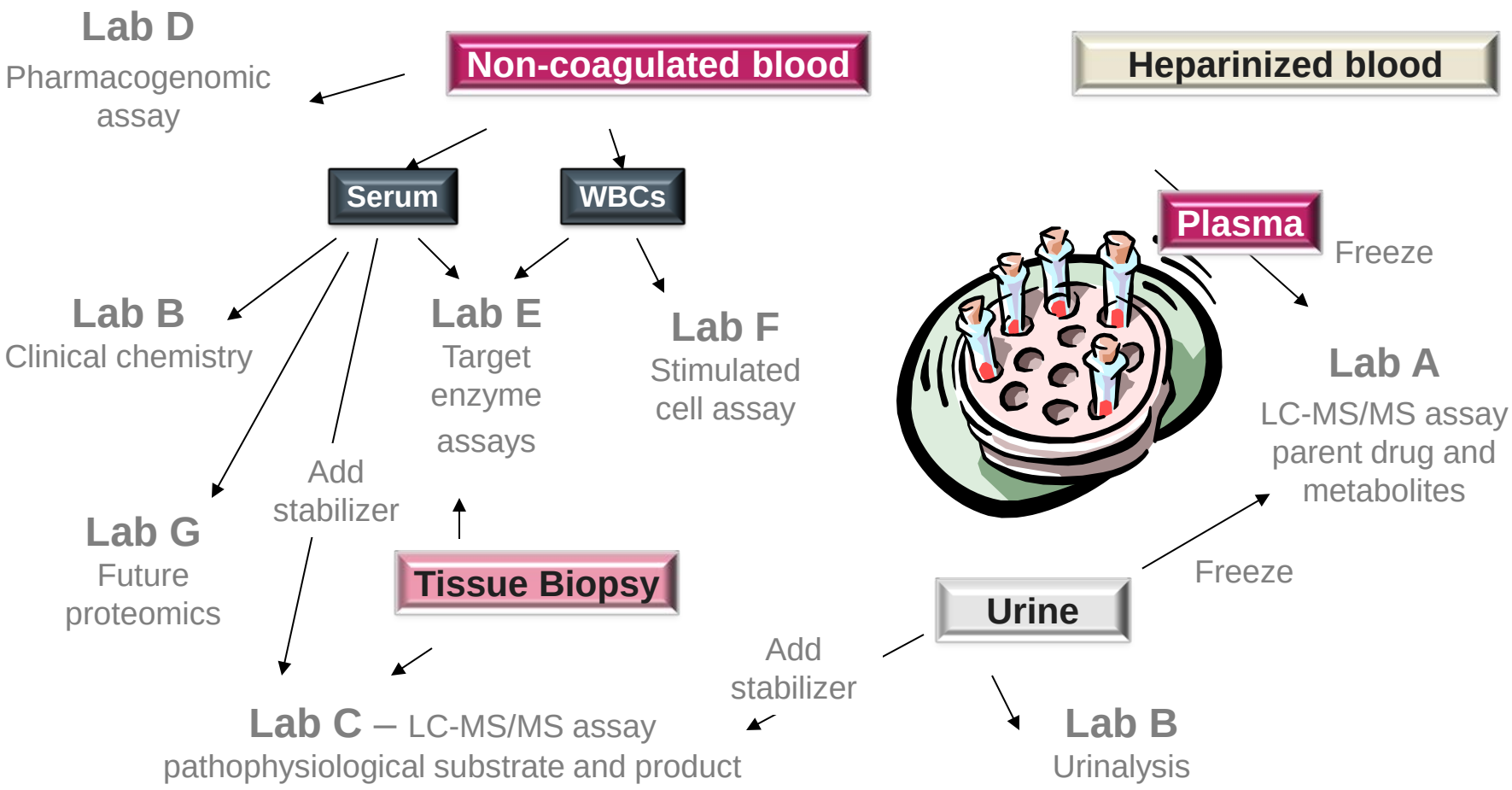
The Challenge of Recruiting Patients to Early Clinical Studies



Early Clinical Research Requires Resources Dedicated to Research

Complex sample collection schedules and processing procedures

Example: First-in-Patient study – 14 tests, 7 labs



WBCs: Whole Blood Cells

A Perfect Scenario for Fast-to-Patient Strategy

- Single Ascending Dose (SAD) Study
- Novel Dipeptidyl Peptidase-4 (DPP4) Inhibitor in Mild Diabetic Patients
- No other drugs

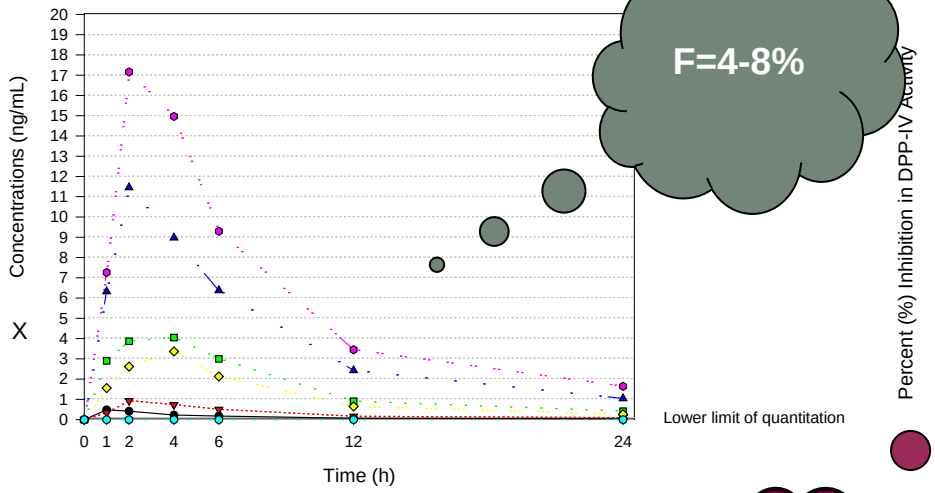
Sequence	Patients	Treatment Periods		
		P1	P2	P3
1 2 3	N = 5 N = 5 N = 5	PLA 25 mg 25 mg	75 mg PLA 75 mg	200 mg 200 mg PLA

Sequence	Patients	Treatment Periods		
		P'1	P'2	P'3
4 5 6	N = 5 N = 5 N = 5	PLA 50 mg 50 mg	100 mg PLA 100 mg	300 mg 300 mg PLA

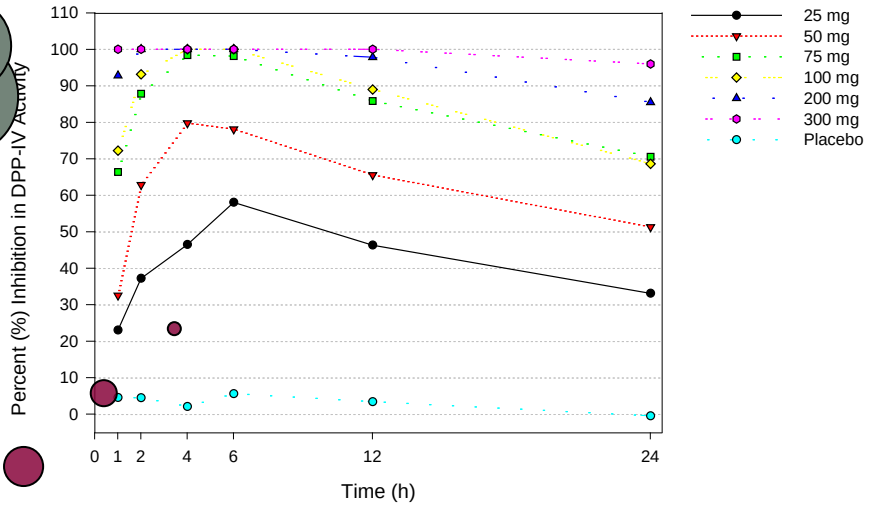
PLA: Placebo

Results of SAD Study in Mild Diabetic Patients: *Early Evidence of Efficacy*

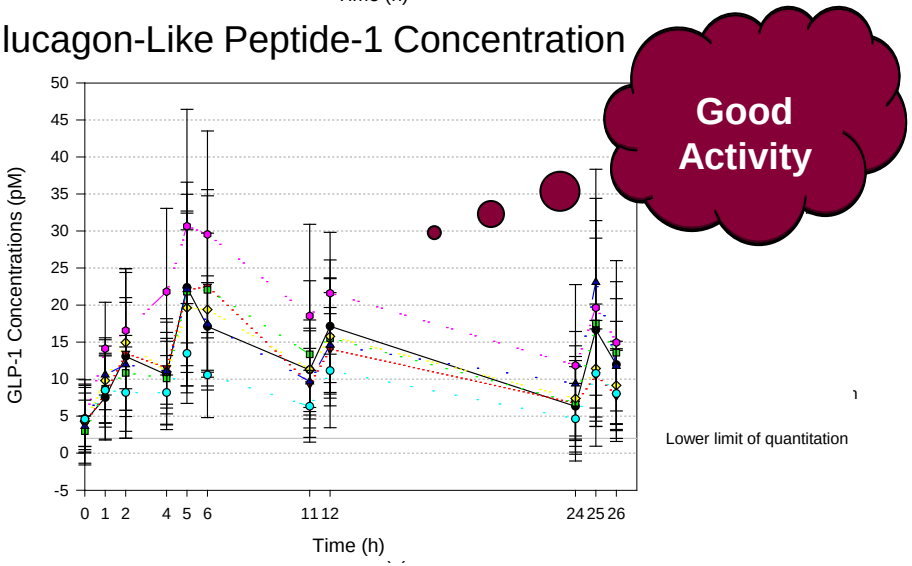
Drug Plasma Concentration



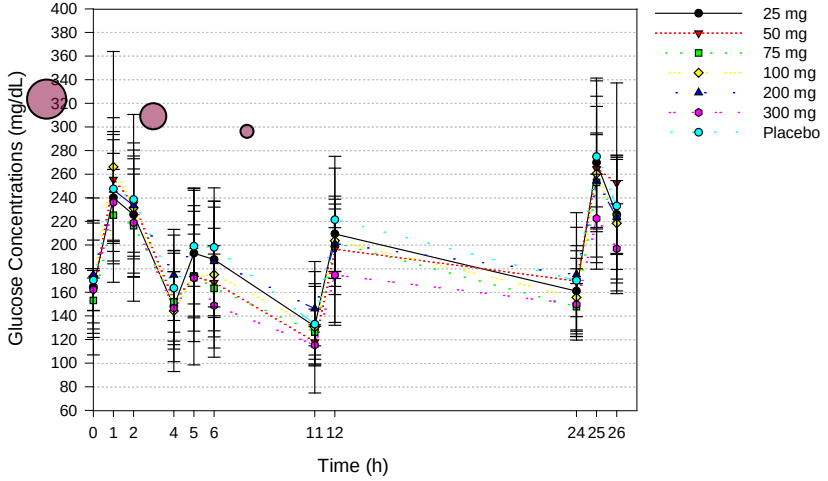
Percent DPP4 Inhibition



Glucagon-Like Peptide-1 Concentration



Glucose Concentration



Global Clinical Pharmacology Unit Networks

- Most patient needs in early clinical research cannot be met by a single center
- Increasing the number of sites has its own challenges
- Need to evolve similar partnering and alliance models among groups of clinical pharmacology units
  - Work to same quality standards (undergo common systems Quality Assurance audits)
  - Coordinate through a group which also brings in other study services as protocol preparation, bioanalysis, pharmacokinetics, data management and statistics, clinical study report preparation

celerion

Celerion Locations and Partner Sites

A Global Network of Specialty Clinics and Labs

celerion

Examples of networks and therapeutic clusters

Patient Population	Celerion Site	External Site Network
Diabetes / Obesity	**Phoenix Lincoln**	**Supporting networks in North America, Europe, South Korea and Singapore**
Respiratory and Inflammatory (asthma, COPD, cystic fibrosis)	**Belfast**	**Strong network in UK and Germany (therapeutic cluster)**
Ophthalmology	**Belfast Phoenix**	**Strong network in UK and Germany (therapeutic cluster)**
Cardiovascular (hypertension, hypercholesterolemia, hyperlipidemia, thrombosis)	**Belfast Phoenix**	**Strong networks in Europe and Korea (therapeutic cluster)**
Oncology (blood, breast, colon, prostate, lung, pancreatic, ovarian, skin)		**Strong networks in Korea (therapeutic cluster) Good access in Europe Major academic cancer centers dominate North America**
Renal or Hepatic Insufficiency		**Strong network in US and Europe**

COPD: Chronic Obstructive Pulmonary Disease

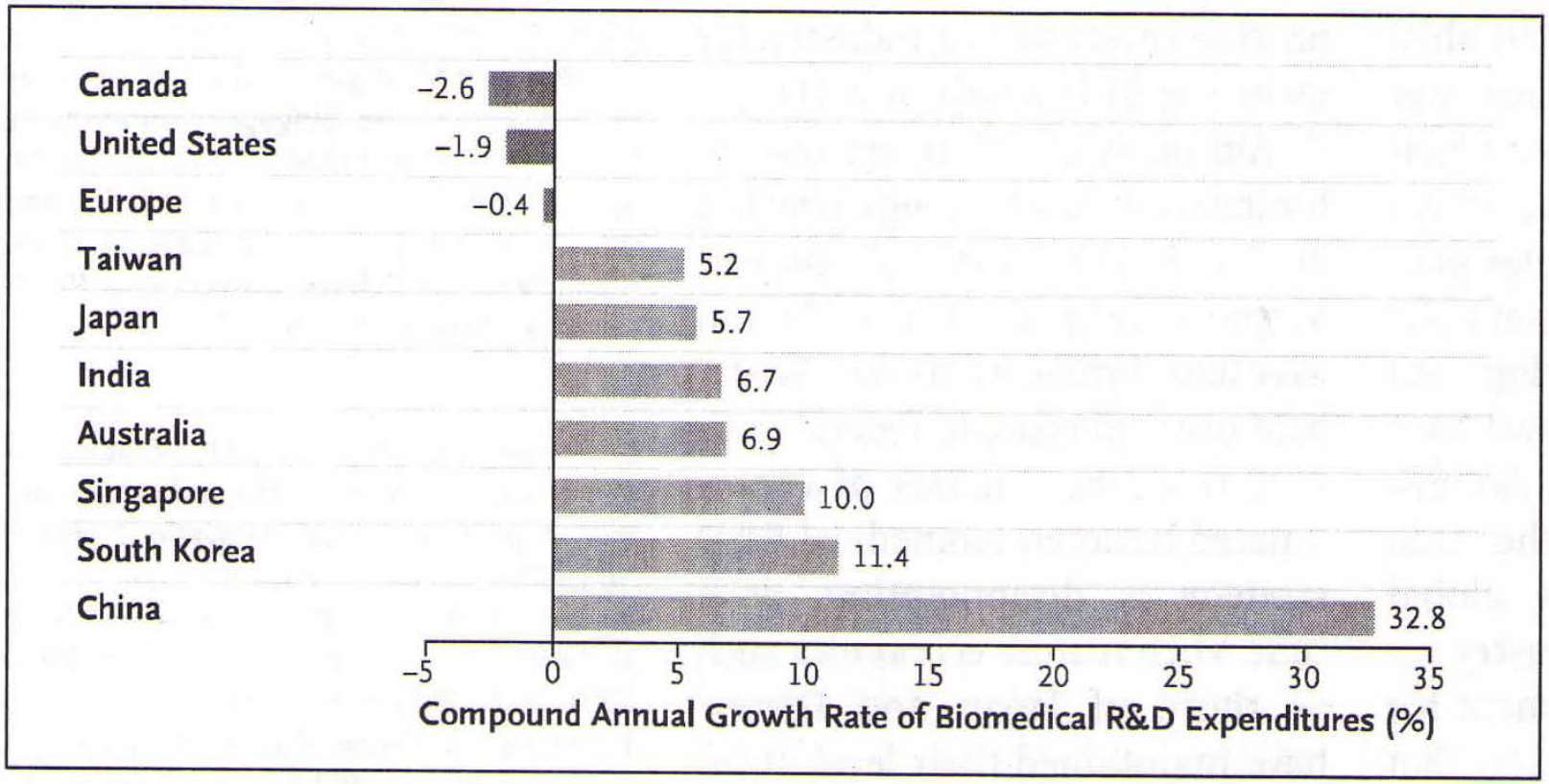
Examples of networks and therapeutic clusters

Patient Population	Celerion Site	External Site Network
Rheumatoid Diseases (RA, OA, SLE)	**Belfast**	**Strong networks in Korea and in Europe (therapeutic cluster)**
CNS /Neurology (Alzheimer's, schizophrenia, anxiety, depression, pain, Parkinson's, convulsion)		**Collaborative neuroscience network in US Good access in Europe and Korea**
Infectious Disease (HIV, HCV, HSV, influenza, bacterial)		**HCV – Europe and Korean sites (Asian phenotypes), Influenza/bacterial: access in Europe and Korea**

RA: Rheumatoid Arthritis
OA: Osteoarthritis
SLE: Systemic Lupus Erythematosus
CNS: Central Nervous System
HIV: Human Immunodeficiency Virus
HCV: Hepatitis C Virus
HSV: Herpes Simplex Virus

The Importance of Asia-Pacific Region in Early Clinical Research

Growth in Asia in Biomedical R&D Spending



Compound Annual Growth Rate of Biomedical R&D Expenditures by Country, Adjusted for Inflation, 2007–2012.

The compound annual growth rate was calculated on the basis of total inflation-adjusted biomedical R&D expenditures in U.S. dollars for 2007 and 2012.

J. Chakma et al. NEJM 370(1)3-6, 2014

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 clinical trial centers need access to global pharma study opportunities and best operating practices for running efficient operations

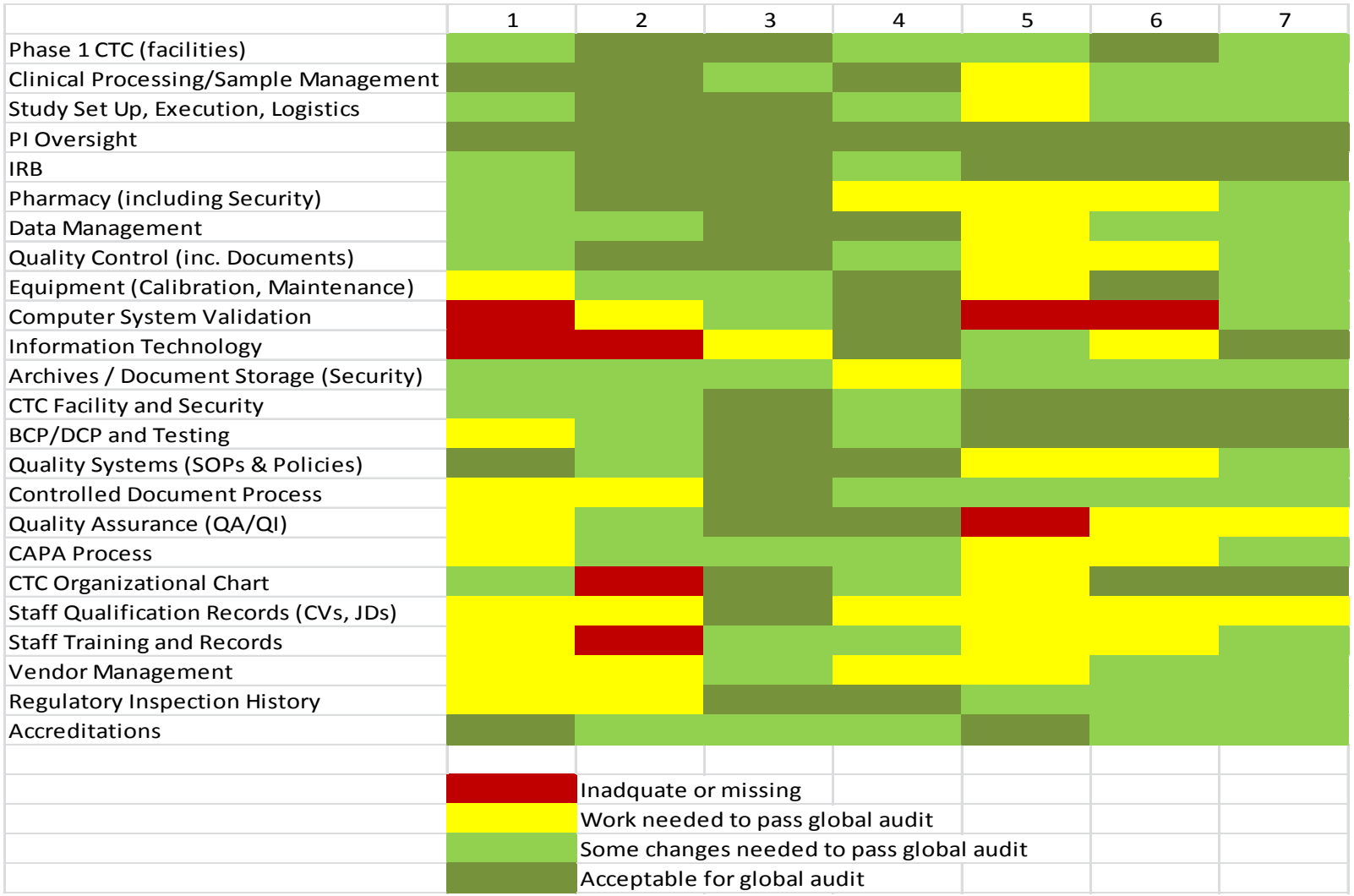
PK/PD: Pharmacokinetics / Pharmacodynamics

Regulatory Environment in Five Asia/Pacific Countries

	Japan	China	South Korea	Singapore	Australia
Regulatory Review Time	**No queries – 30 days after CTN submission**	**11 Months**	**30-60 Days**	**15-30 Days**	**No approval for healthy subject studies**
Ethics / IRB Review Time	**Variable**	**60 Days**	**2-4 Weeks**	**1-4 Weeks**	**12-16 Weeks (patients)**
Parallel or Sequential	**Parallel**	**Sequential**	**Parallel**	**Parallel**	**Clinical Trial Notification acknowledged in days**
Clinical Trial Centers	**Hospital and CRO-owned**	**SFDA-accredited CTCs**	**15 Hospital-based CTCs**	**1 Pharma-owned and 3 Hospital CTCs**	**5 Academic hospital clinics**
Other Comments	**Government funding new CTCs**	**Difficult to ship samples out of China**	**MFDS built on US FDA model**	**Translational medicine focus**	**Less CMC and preclinical safety**

IRB: Institutional Review Board
CTN: Clinical Trials Notification
CMC: Chemistry, Manufacturing and Controls

Audit Results of 7 Asian CTCs 2013-2014



BCP/DCP: Business Continuity Plan/ Data Continuity Plan
SOPs: Standard Operating Procedures
CAPA Process: Corrective and Preventive Action

CVs: Curriculum Vitae
JDs: Job Descriptions
PI: Principal Investigator

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: Phase I CTC facility and Security, PI Oversight and IRB or Ethics Committee.
- 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)
  - CAPA process (3 of 7 sites)

celerion

Innovations in Early Clinical Research

- New Biomarkers of drug action and effect
  - Imaging (SPECT, functional MRI/PET), microRNAs, tracking genetic changes in tumors or microbiome, digital high resolution EEGs and ECGs
- Patient Recruitment
  - Social media tools to recruit patients
  - Electronic patient records to quickly assess impact of inclusion and exclusion criteria on recruitment and suitability of patients for a study
- Data Acquisition
  - Digital capture of data – real-time review and monitoring for quality
  - Video for remote viewing of study conduct in real time
  - Tablets and smart phones to capture patient data
  - Electronic tracking to confirm study compliance
- Data Analysis
  - Data repositories that allow comparison across studies and advanced modelling to predict drug response in specific patient settings

SPECT: Single-Photon Emission Computed Tomography

Brief Answers to Questions

- **How is early clinical research changing?**
  - Focus on Clinical Proof-of-Concept – fail early
- **What are some challenges and strategies for engaging patients in early clinical studies?**
  - Regional differences, patient networks
- **What are some challenges in conducting early clinical research studies in patients?**
  - Access to biomarkers, specialty equipment and specialist researchers
  - Sample logistics
- **Why is there increasing attention to Asia-Pacific region in early clinical research?**
  - Access to patients, modern clinical trial centers, educated staff, rapidly emerging biotechnology industry, large market
- **What innovations are making early clinical research more efficient and effective?**
  - Digital communications, real-time acquisition and access to data, apply complex analysis and modeling, new biomarkers

celerion

Thank You!

ありがとうございました。