Global Clinical Trial and Development
Japanese Sponsor's Perspective

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East Asian Pharmaceutical Regulatory Symposium 2008

Tokyo, April 15, 2008

Disclaimer

The views in this presentation are those of the speaker and do not necessarily represent those of JPMA, Astellas or its management.

AGENDA

1. Global Development Organization & System in Astellas

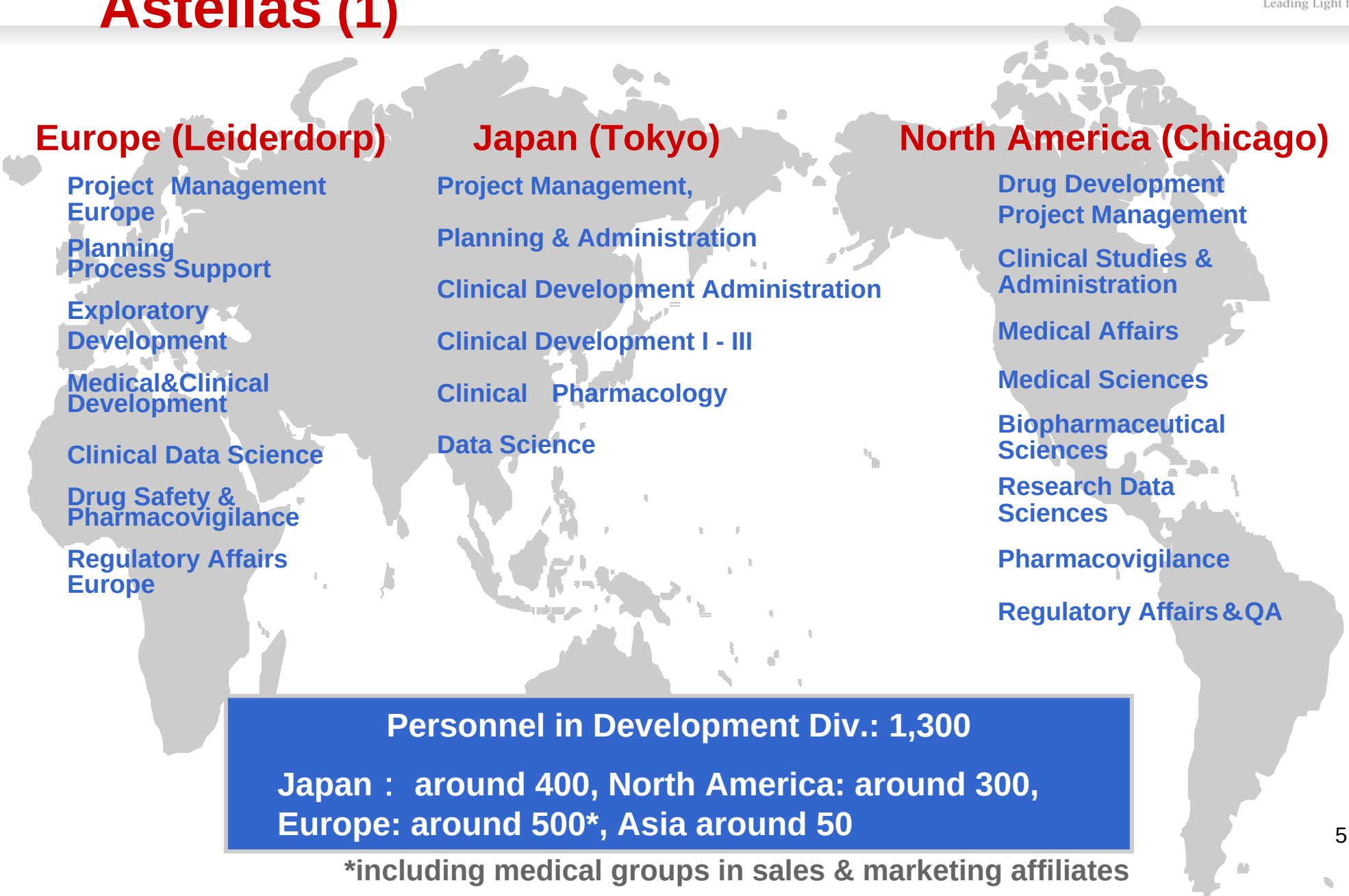
2. Asian Organization & Business in Astellas

3. Status of Asian Multinational Clinical Studies in Astellas

4. Challenging Issues and Requests to Asian Authorities

1. Global Development Organization & System in Astellas

Global Organization of Development in Astellas (1)



Europe (Leiderdorp)

- Project Management Europe
- Planning Process Support
- Exploratory Development
- Medical&Clinical Development
- Clinical Data Science
- Drug Safety & Pharmacovigilance
- Regulatory Affairs Europe

Japan (Tokyo)

- Project Management,
- Planning & Administration
- Clinical Development Administration
- Clinical Development I - III
- Clinical Pharmacology
- Data Science

North America (Chicago)

- Drug Development Project Management
- Clinical Studies & Administration
- Medical Affairs
- Medical Sciences
- Biopharmaceutical Sciences
- Research Data Sciences
- Pharmacovigilance
- Regulatory Affairs&QA

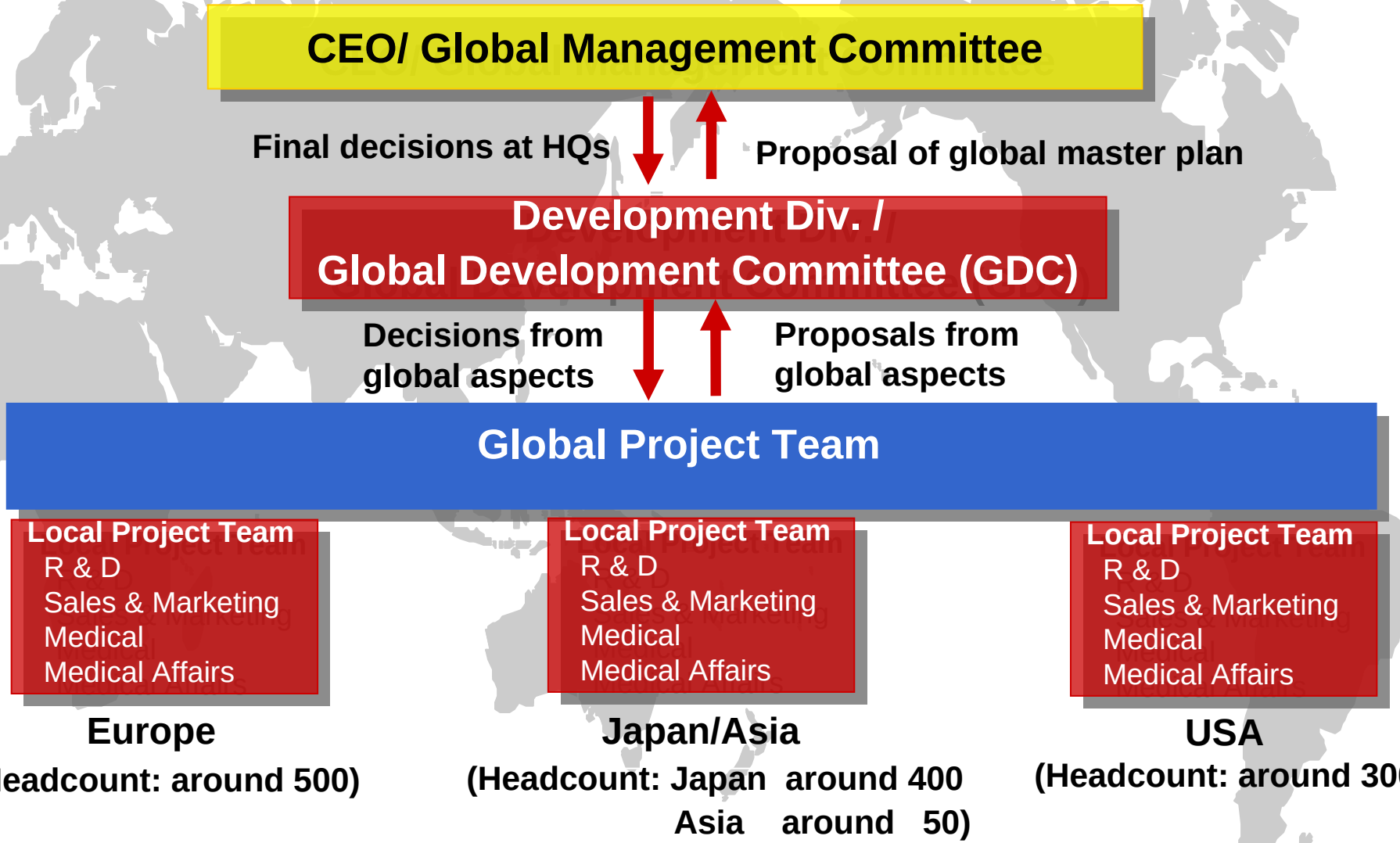
Personnel in Development Div.: 1,300

Japan： around 400, North America: around 300, Europe: around 500*, Asia around 50

*including medical groups in sales & marketing affiliates

Global Organization of Development (2)

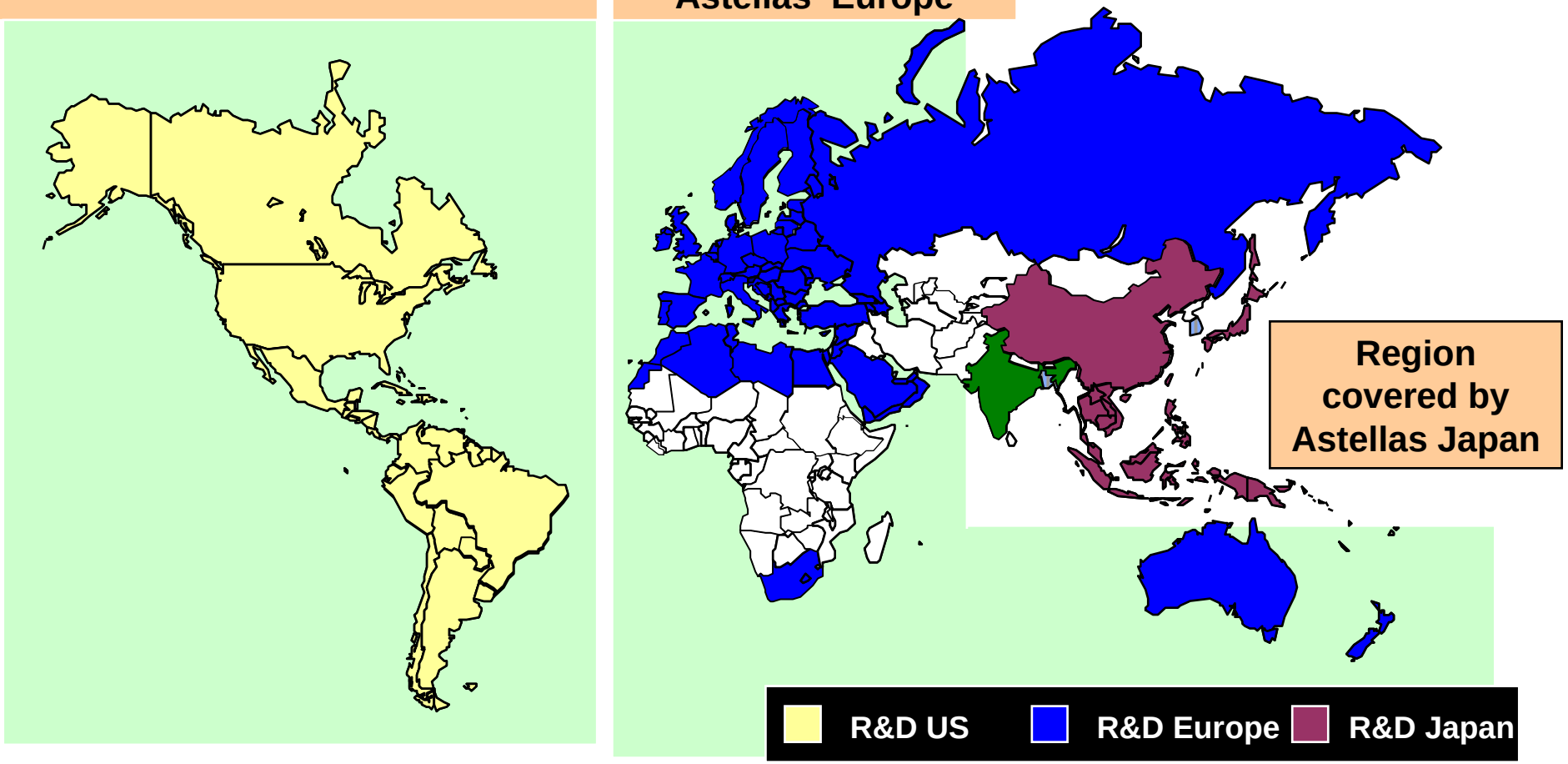
Global development operations fully integrated since April 2005



Geographic Responsibilities for Multinational Clinical Studies in Astellas

Region covered by Astellas US

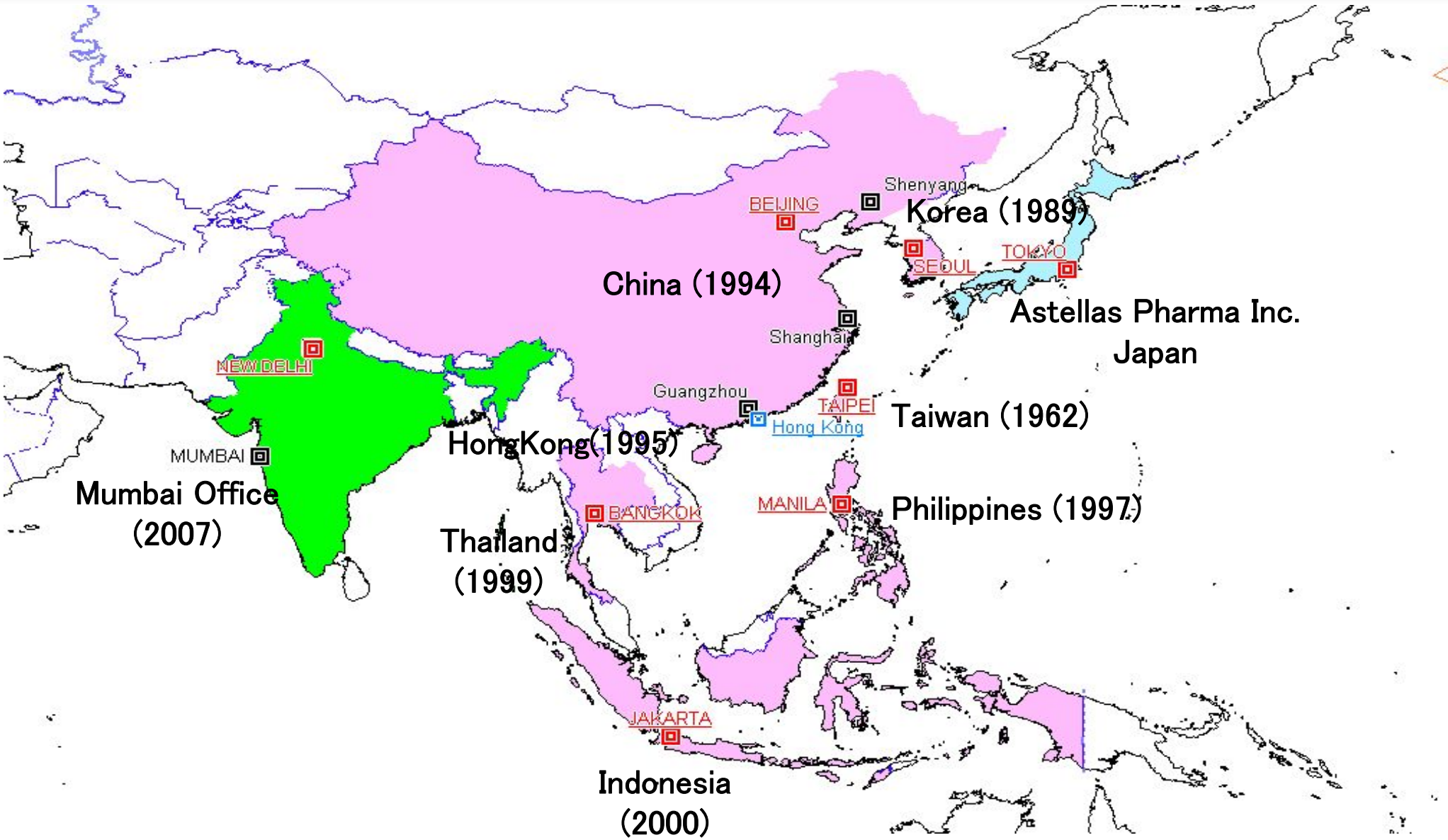
Region covered by Astellas Europe



Astellas Europe and US to jointly approach India, via common CROs

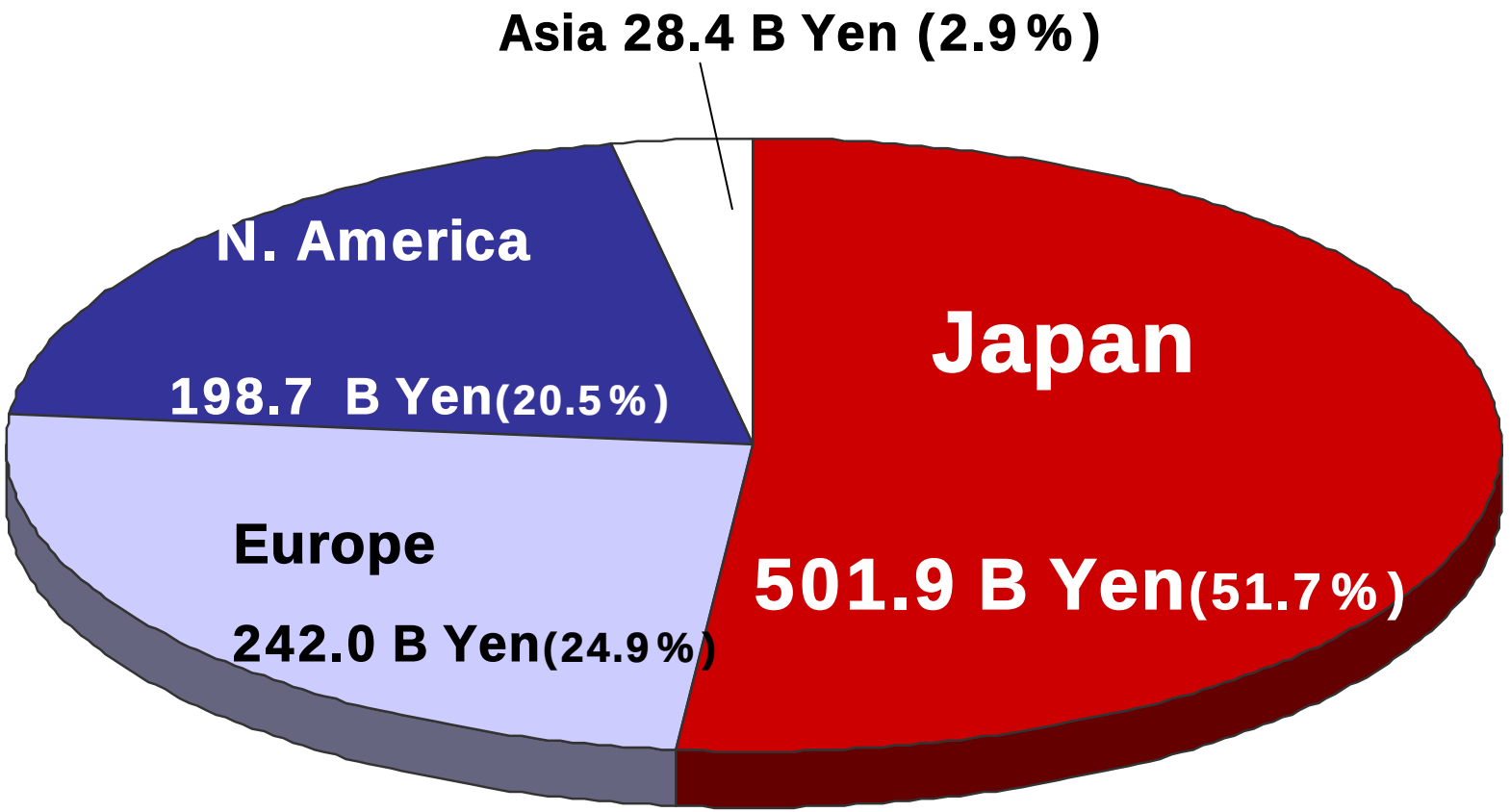
2. Asian Organization & Business in Astellas

Present Astellas Business Area in Asia

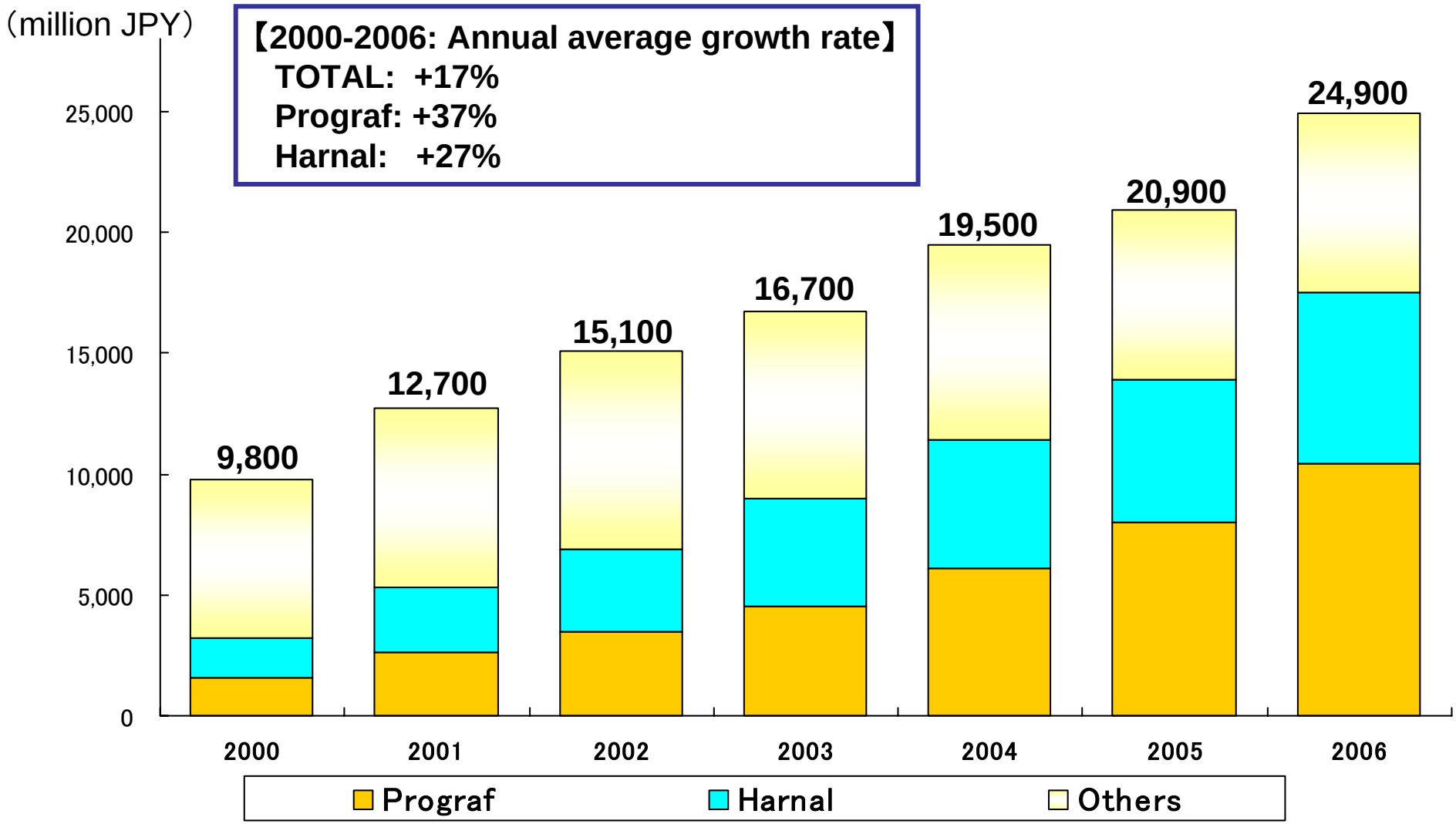


Sales by Regions (FY2007/Estimated)

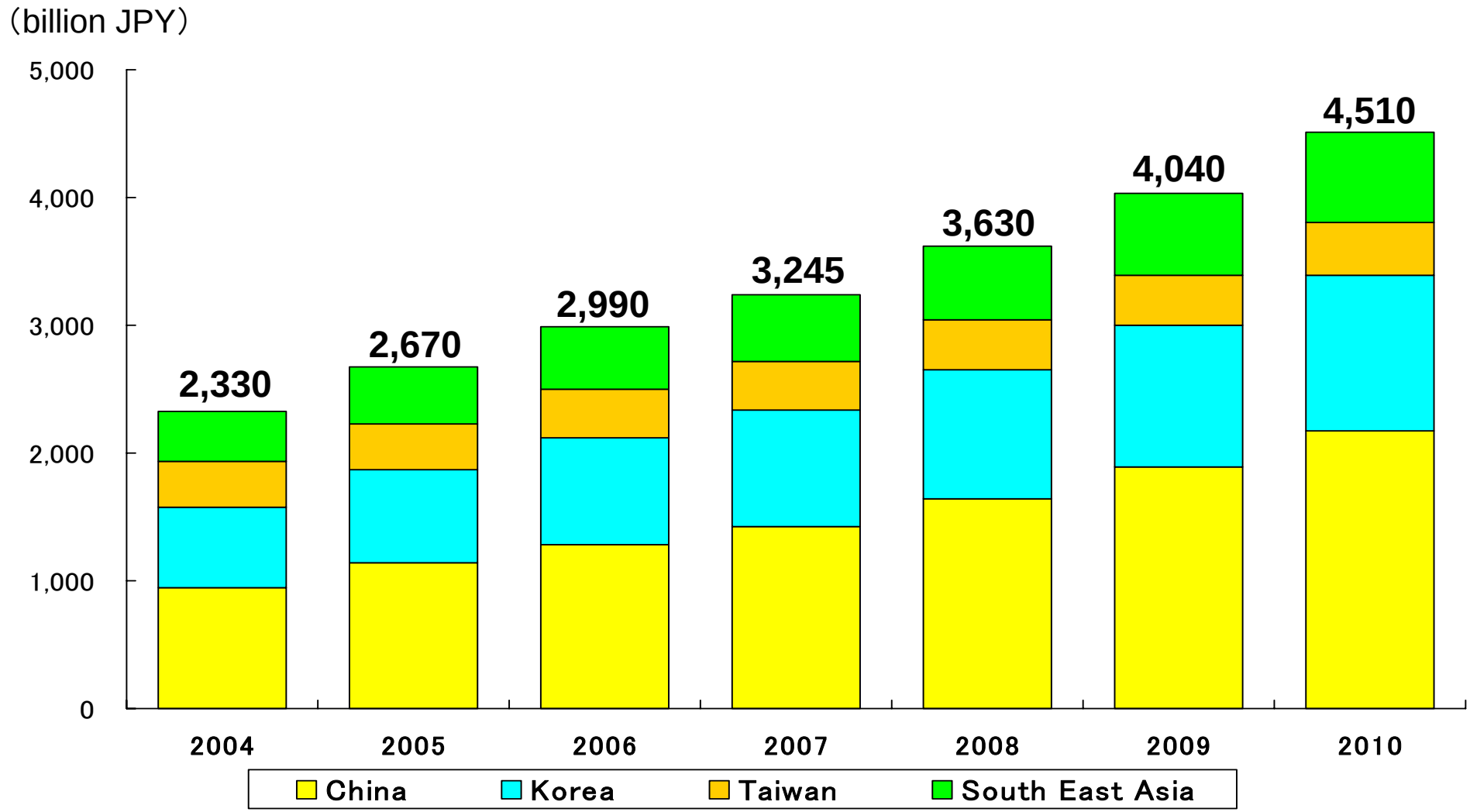
Total 971.0 Billion Yen



Sales of Asian Affiliates in 2000-2006



Total Asian Market Size - with Forecast to 2010 -



3. Status of Asian Multinational Clinical Studies in Astellas

Significance of Asian Multinational Clinical Studies

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1) Targeted Disease Area

- **Hard Endpoints (Cardiovascular, Osteoporosis etc)**
- **High Prevalence in Asia (Hepatitis, Stomach cancer etc)**
- **Orphan Diseases**

2) Contribution to Early Launches in US/EU/Japan
(from Global Development viewpoint)

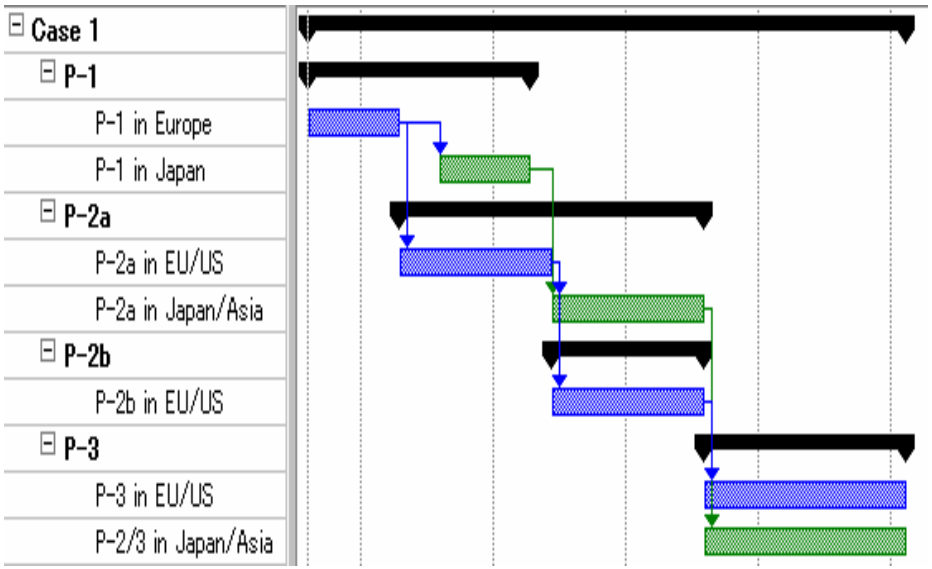
- **Faster Enrollment**
- **Lower Cost**

3) Contribution to Early Launches in Asian Countries
(from Local Development viewpoint in Asia)

3-1) Strategy from Global Development Viewpoint

Case 1 (development preceding in the EU/US, followed by JPN/Asia)

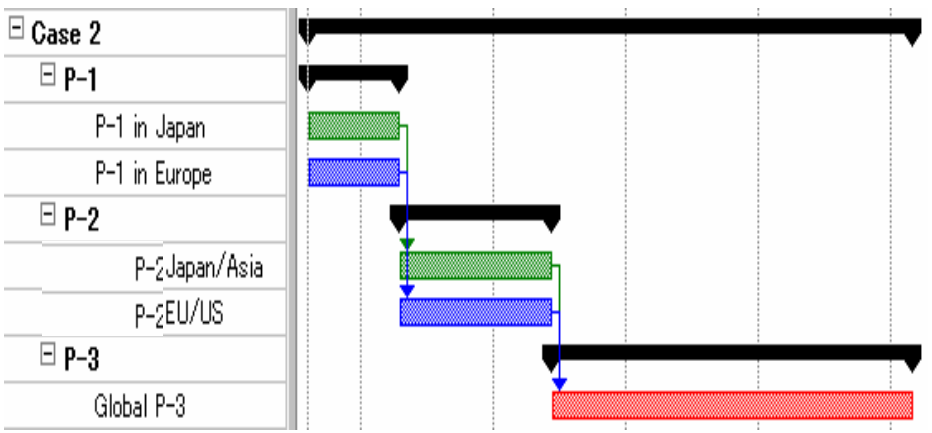
- **Conduct P-I in Japan during an EU/US POC study.**
  →Start P-IIa as a JPN/Asia multinational study after the POC establishment in EU/US,
  →followed by P-II/III JPN/Asian study



Case 2 (simultaneous development in EU/US/JPN/Asia)

- **Continue the development up to P-II as parallel studies in JPN/Asia and EU/US.**
  --> Start P-III as a multinational study in EU/US/JPN/Asia region.

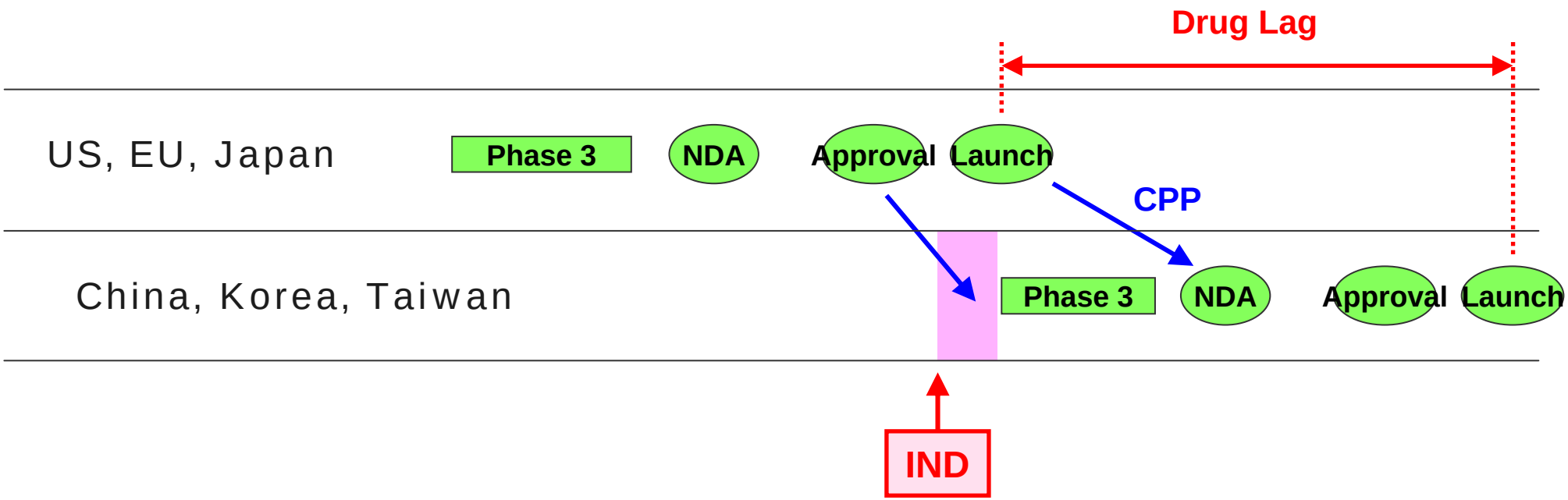
- **The fastest timeline.**



3-2) Strategy from Local Development Viewpoint in East Asia

Timing of Clinical Studies in East Asia (1)

Case A. Conventional (Lowest Risk, but Slowest)

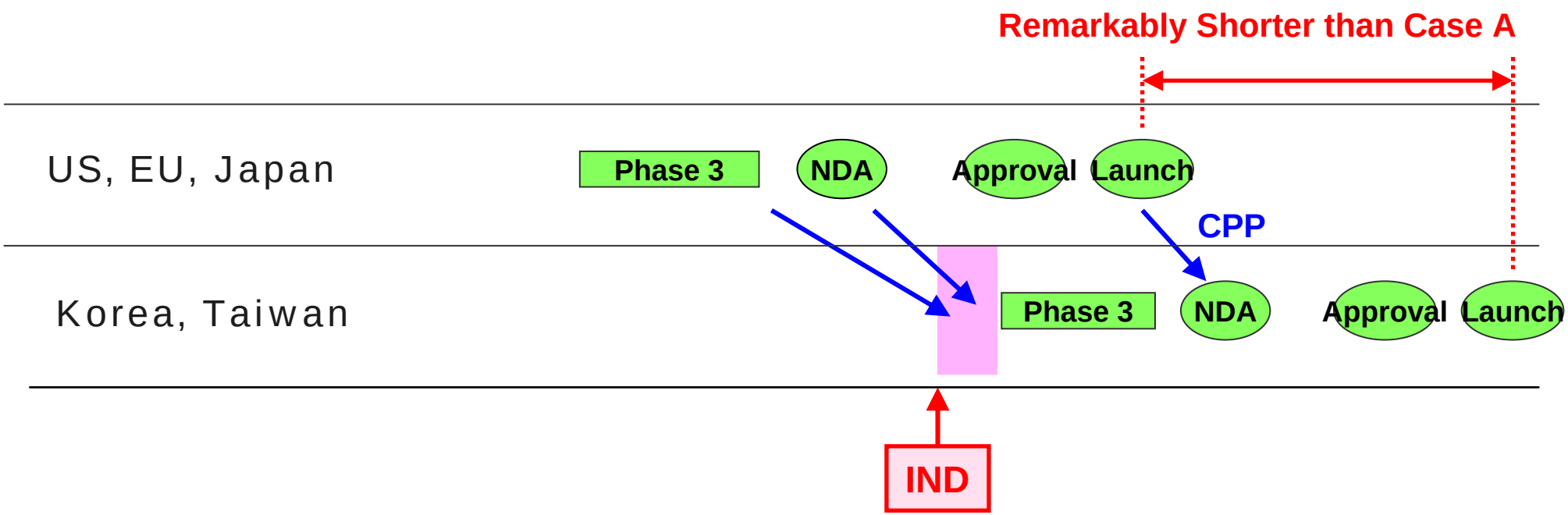


CPP: Certificate of a Pharmaceutical Product

3-2) Strategy from Local Development Viewpoint in East Asia

Timing of Clinical Studies in East Asia (2)

Case B. Advanced (Faster Launch Possible in E Asia)

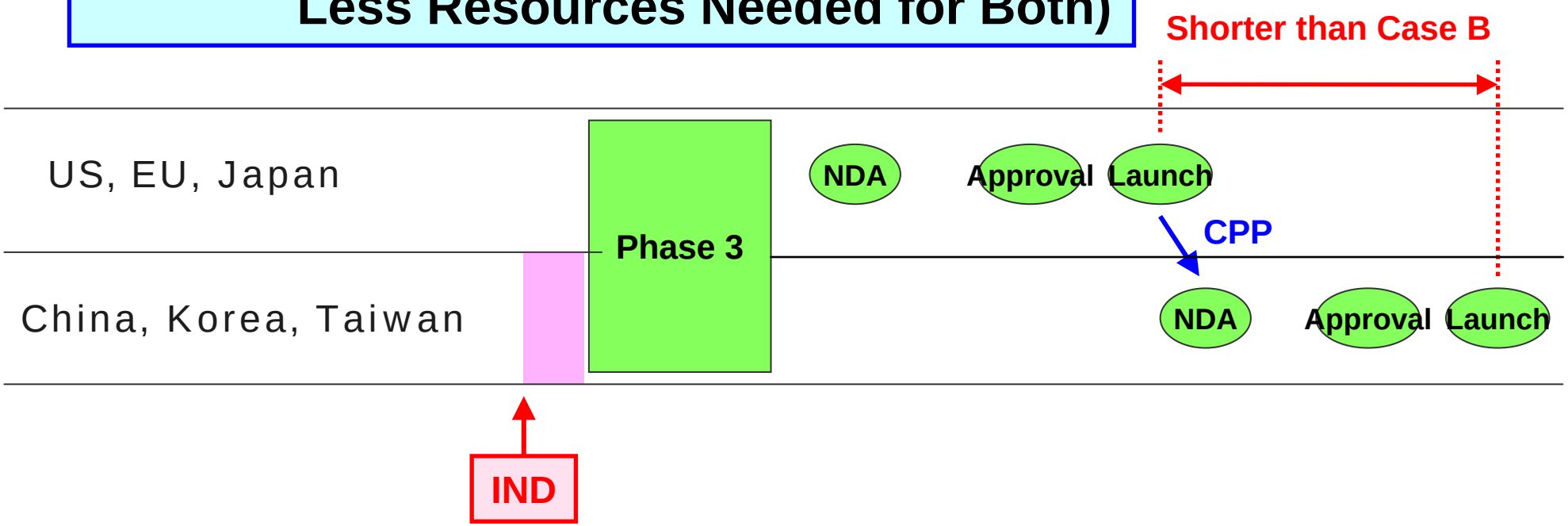


CPP: Certificate of a Pharmaceutical Product

3-2) Strategy from Local Development Viewpoint in East Asia

Timing of Clinical Studies in East Asia (3)

Case C. Multinational Study (Fastest, Less Resources Needed for Both)



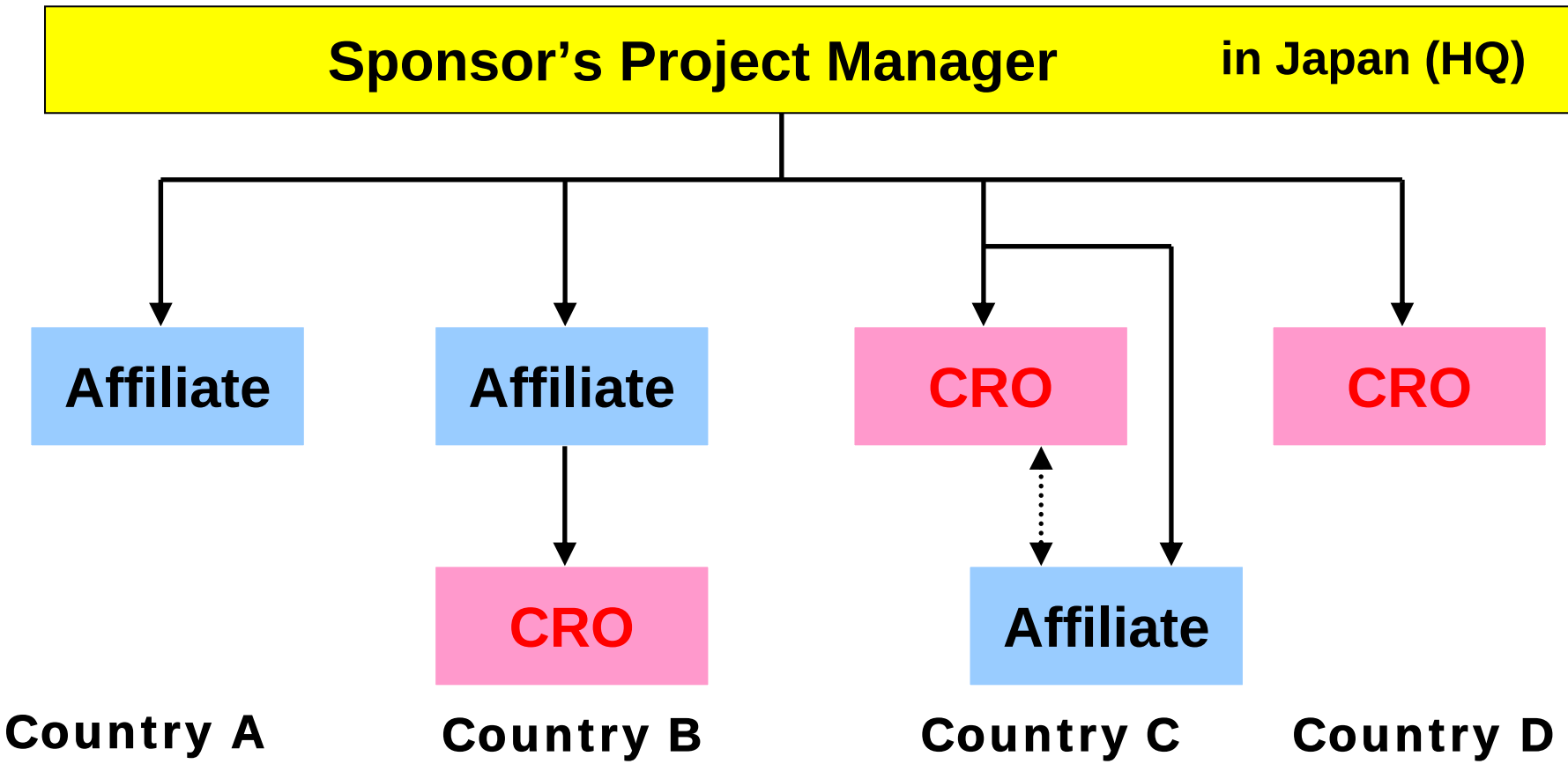
CPP: Certificate of a Pharmaceutical Product

3-3) Operation for Clinical Studies in Asian Regions

- **Seek Best Partner for Each Study**
- **Implemented by Affiliates**
  - ✓Astellas China
  - ✓Astellas Korea
  - ✓Astellas Taiwan
- **Implemented by CROs**
  - ✓Global CRO
  - ✓Asia-Pacific International CRO
  - ✓Local CRO

3-3) Operation for Clinical Studies in Asian Regions

Case1 - *Suit for Small Sample Size* -



3-3) Operation for Clinical Studies in Asian Regions

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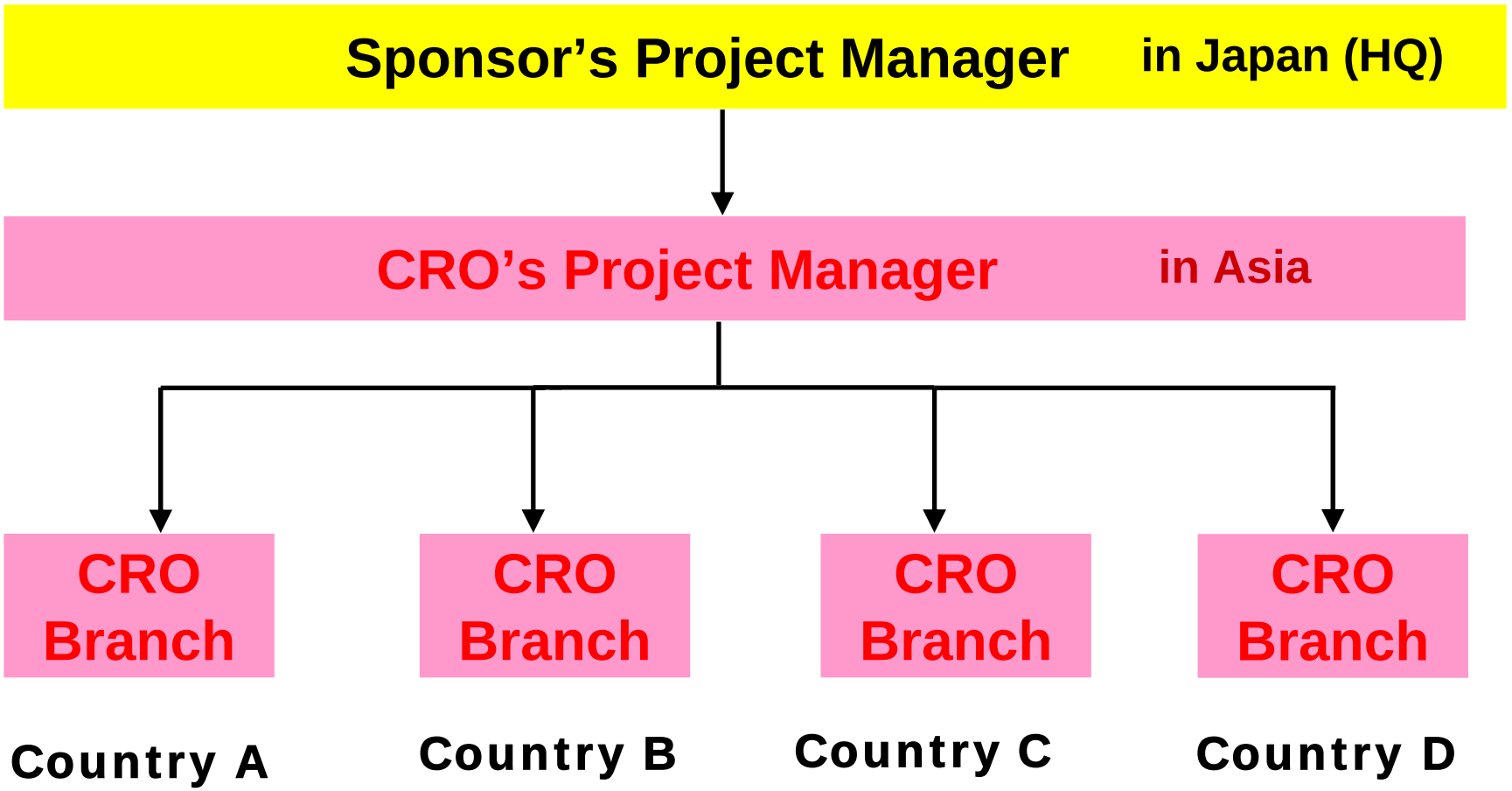
Case 2 ***- Suit for Large Sample Size -***



3-4) Experience from the First Asian Study by Astellas

- **Study Title: Prevention of Venous Thromboembolism in Total Knee Replacement (TKR) patients**
- **Stage：P-II is on going**
- **Countries: Japan, Korea, Taiwan, Singapore, Malaysia, Thailand, Philippines, Indonesia**
- **Document Languages**

  Investigator's Brochure /Protocol: English

  (along with local languages in Japan and Korea)

  ICF: English + local language

  (local language only in Japan, Korea and Taiwan)

  CRF/DCF: English only

3-5) Outstanding Issues for Sponsor

- Personnel Training
  - ✓Educate the clinical development staff to be capable of managing the multinational clinical studies
    (language skills, leadership, international sense and humanity)

- SOP/Manuals
  - ✓Prepare Global Clinical SOP
  - ✓Prepare manuals for Asian Multinational Studies

- Resource optimizations
  - ✓Optimize personnel assignment in PJ Mgt. Dept. and Clin. Dev. Depts.
  - ✓Optimize the staff composition in clinical development department at Astellas affiliates in Asia
  - ✓Establish CRO outsourcing policy for Multinational Studies

4. Challenging Issues and Requests to Asian Authorities

1-1) Required Documents for IND Submission

Documents		JP	CN	KR	TW	SG	TH	MY	PH
Protocol	English	V	V	V	V	V	V	V	V
	Local language	V	V	V					
Investigator's Brochure	English	V	V	V	V	V	V	V	V
	Local language	V	V	V					
CoA			V	V	V	V	V		V
GMP certificate			V			V	V	V	V
CPP			V*						

*** CPP is required in the case of local registration study on import drugs.**

JP: Japan, CN: China, KR: South Korea, TW: Taiwan, SG: Singapore,
TH: Thailand, MY: Malaysia, PH: Philippines,
CoA: Certificate of Analysis, CPP: Certificate of a Pharmaceutical Product

1-1) Requests about Requirement & Documents for IND Submission

To Chinese, Japanese, and Korean Authorities

- Accept the documents without local language translations (Investigator's Brochure, Protocol)

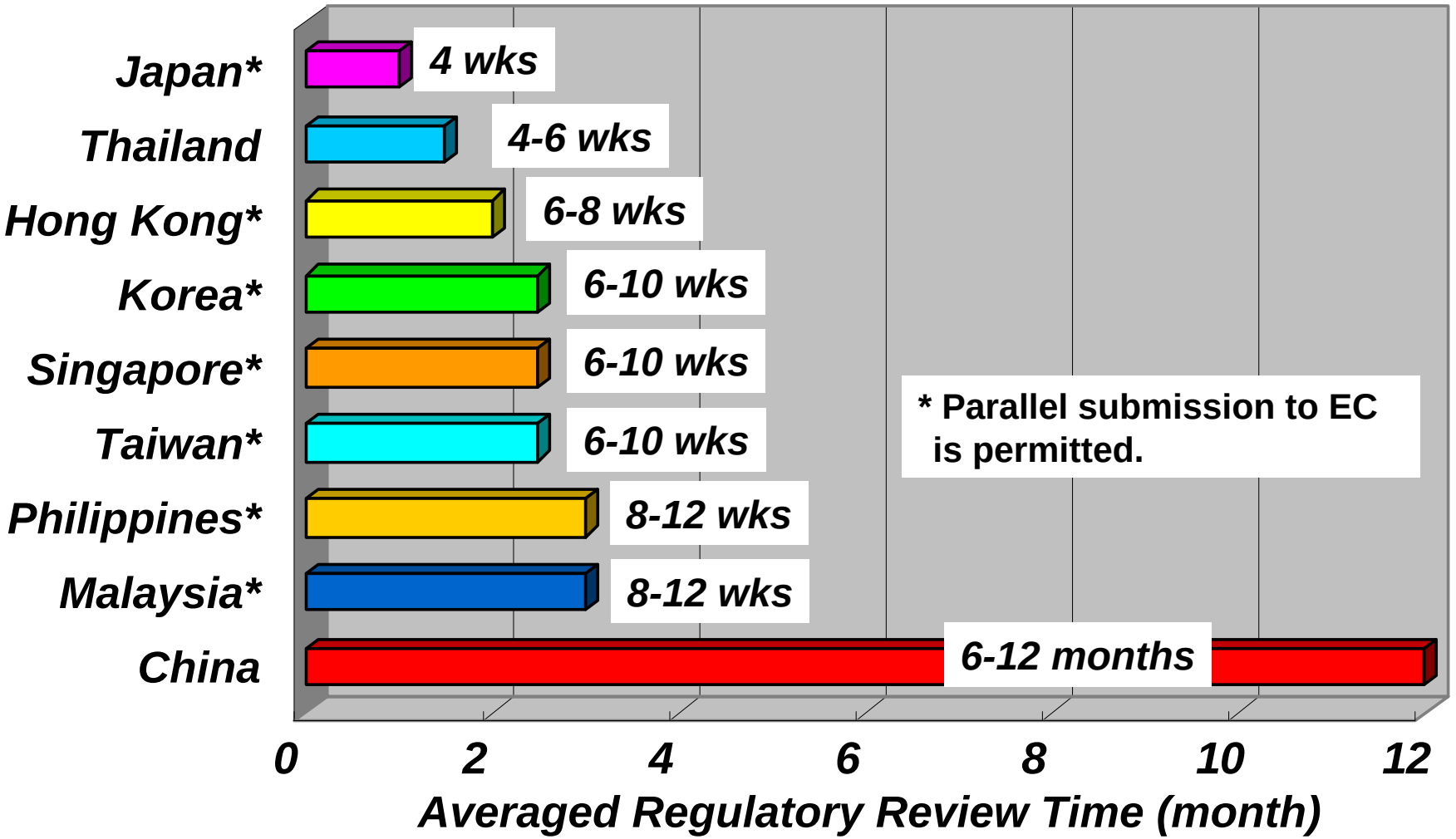
To Chinese Authorities

- Eliminate Certificate of a Pharmaceutical Product (CPP) from IND requirement (in the case of local registration study)

To All Asian Authorities

- Harmonize IND requirements for Asian Multinational Clinical Studies
- Introduce the standard format for IND submissions

1-2) Regulatory Review Time & Review Process

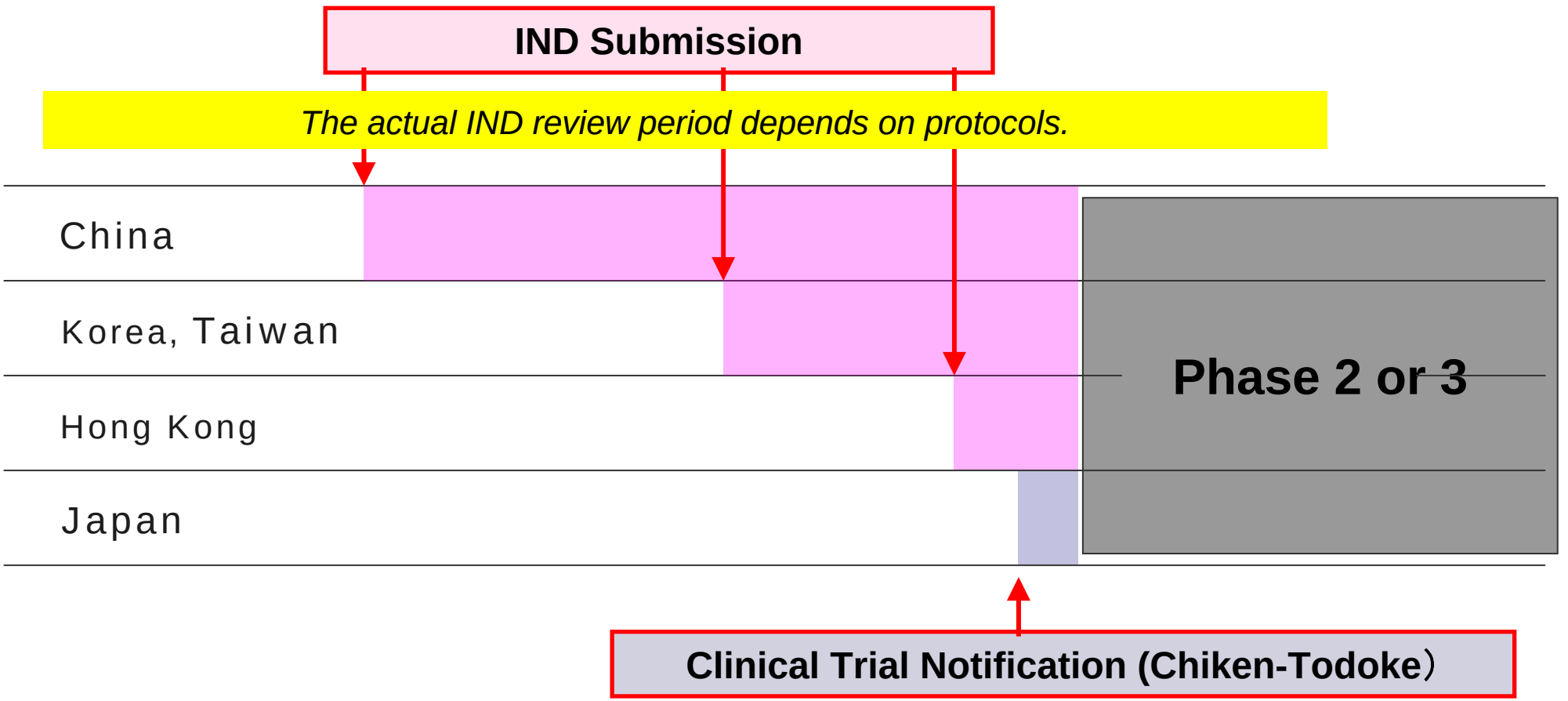


Ref. Presentation slide of a CRO (Received Dec 14, 2006)

1-2) IND Review Time & Review Process

Timing of IND Submissions in Asia

If you need Simultaneous First Patient Enrollment .....



1-2) Requests about IND Review Time & Review Process

To Chinese Authorities

- Shorten IND review time to those of other Asian countries

To All Asian Authorities

- Harmonize the IND approval process in Asian regions
  - ✓Mutual Recognition Procedure:
    In case Japanese authorities approves an IND,
    other Asian authorities accept and approve the IND with or even without brief review
- Encourage Japanese authorities to taken the initiative and the lead as an ICH member

2. SAE Reporting Rule

	SADR in domestic site				SADR in foreign site			
	Death or Life-threatening		Others		Death or Life-threatening		Others	
	Unexpected	Expected	Unexpected	Expected	Unexpected	Expected	Unexpected	Expected
ICH E2A	Y 7d	-	Y 15d	-	Y 7d	-	Y 15d	-
China	Y* 24h	Y* 24h	Y* 24h	Y* 24h	-	-	-	-
Korea	Y 7d	Y 7d	Y 15d	-	Y** 7d	Y** 7d	Y** 15d	-
Japan	Y 7d	Y 15d	Y 15d	-	Y 7d	Y 15d	Y 15d	-
Taiwan	Y* 7d	Y* 7d	Y* 15d	Y* 15d	Y*** 7d	Y*** 7d	-	-
Singapore	Y 7d	-	Y 15d	-	Y 7d	-	Y 15d	-
Thailand	Y* NA	Y* NA	Y* NA	Y* NA	-	-	-	-

Y: Yes, SADR to be reported.

Y*: Yes, SAE to be reported.

NA: No time line.

Y**: Yes, only foreign SADR in the same study to be reported.

Y***: Yes, only foreign death case in the same study to be reported.

2. Request about SAE Reporting Rule

- Differences in reporting rules among countries
  - ✓ SAE to be reported
    (Ex. All SAEs regardless of their expectedness // Drug-related only)
  - ✓ Reporting rules for foreign SAEs
    (Ex. Same as domestic SAEs // Drug-related, unexpected death only)
    (Ex. SAEs in the same study // Single rule for different studies on the same ingredient)
  - ✓ Reporting rules for comparative drug's SAEs
    (Ex. All SAEs including foreign cases // No reports needed)

To All Asian Authorities (except Singapore Authorities)

- **Harmonize with the unified SAE reporting rules based on ICH E2A and further consensus**
  - ✓**Simple SAE report process for Sponsor**

3. Requests about Requirement & Document for NDA Submission

To All Asian Authorities(except Japanese Authorities)

- Accept NDA submission without CPP, which to be submitted later
  - ✓Approval status of NDA products are disclosed at websites of health authorities in ICH countries.
  - ✓Sponsor can achieve NDA submission a few months earlier.

To Chinese Authorities

- Accept ICH-CTD as NDA format
  - ✓Sponsor can prepare NDA documents remarkably earlier.

To Chinese and Korean Authorities

- Accept NDA documents in English without local language translations
  - ✓Sponsor can save the workload and time to translate many NDA documents into local language.

4. Joint / Central IRB

➢IRB in Japan

- In multi-centered studies, Japanese sponsors have overwhelming tasks to meet requirements for various formats of documents and reply to similar deficiencies from each IRB.
- The revised GCP in Mar.26,2008, allows the establishment of central IRB for university-run and large-scale hospitals.

➢IRB in Korea

- There are no central IRBs so far and site IRBs only.
- The revised KGCP introduced in Jan. 2007 allows joint IRBs to review and approve jointly for multi-center studies.

➢IRB in Taiwan

- Joint IRB(JIRB) was established in 1997, which provides an efficient and high quality IRB review service for multi-center studies, on behalf of individual site IRBs.

4. Request about Joint / Central IRB

IRB	Japan	China	Korea	Taiwan	Singapore	Thailand
1.Local IRB 2.Central IRB	1,(2)	1&2	1	1&2	1&2	1&2
Parallel or Sequential with IND process	Parallel	Tandem	Parallel	Parallel	Parallel	Tandem

Request to Korean and Japanese Authorities

- Facilitate/ help to establish central/joint IRBs
  - ✓ Efficient IRB process for multi-center studies
  - ✓ Sponsor can save the workload and expect to start study earlier

Summary
Requests to Asian Authorities

1. IND
   1) Requirement and Documents for IND Submission
   2) IND Review Time & Process
2. SAE Reporting Rule
3. Requirement and Documents for NDA Submission
4. Central/Joint IRB

Thank you！

謝謝！

감사합니다！