New Strategy on Multinational Clinical Trials in China and Japan in consideration of Ethnic Factors

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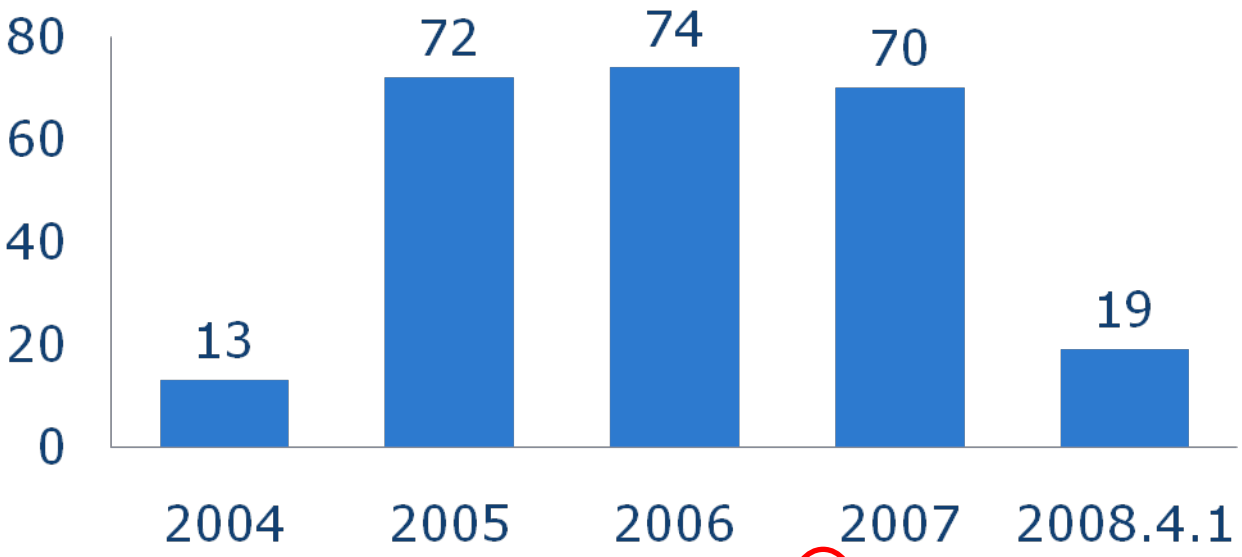
Trends of Multinational Clinical Trials in China

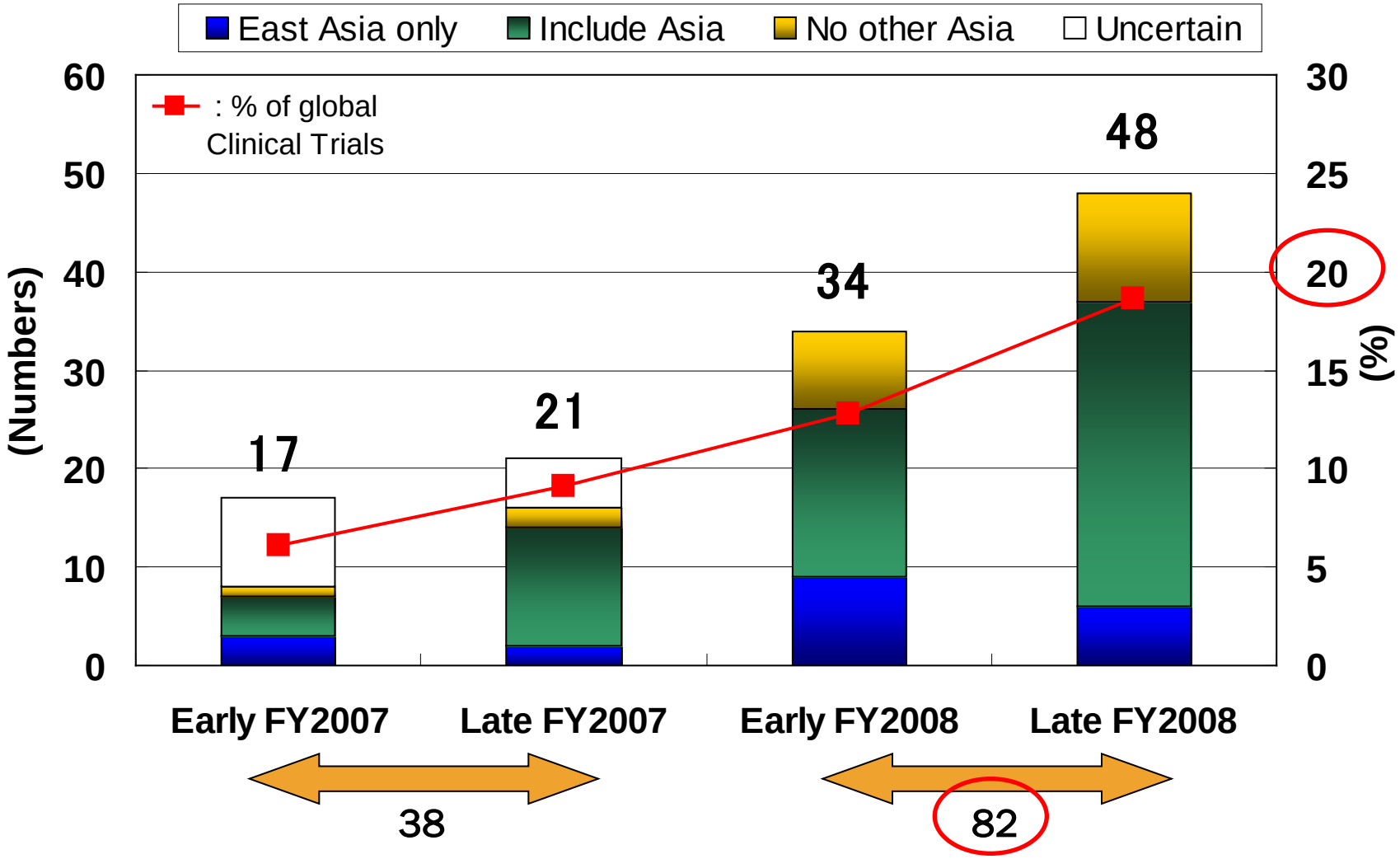


1. Applicants involved: 41, among whom 31 come from multinational corporations (European and American companies account for 83.9%, Asian companies 16.1% and 10 applicants are CRO corporate agents)
2. Indications involved 218 Chemical Drugs accounting for 87.9%, 30 biological drugs accounting for 12.1%.

The indications are lined up in a descending order: Antineoplastic Agents, nerve drugs, Drugs to cure heart and kidney problems such as hypertension and hyperlipemia, antidiabetic medicine, Anti-Infective Agents, antihepatitis drug, slimming drugs, medicine for respiratory system, drugs for external use, drug used in Gynecology and radiopharmaceuticals

Zhang Wei, SFDA, 1st DIA China Annual Meeting (02/Nov/2009)

Trends of Multinational Clinical Trials in Japan



Tatsuya Kondo, PMDA, JP-KR-CN Symposium (18/Dec/2009)

Trends of Multiregional Clinical Trials in Taiwan

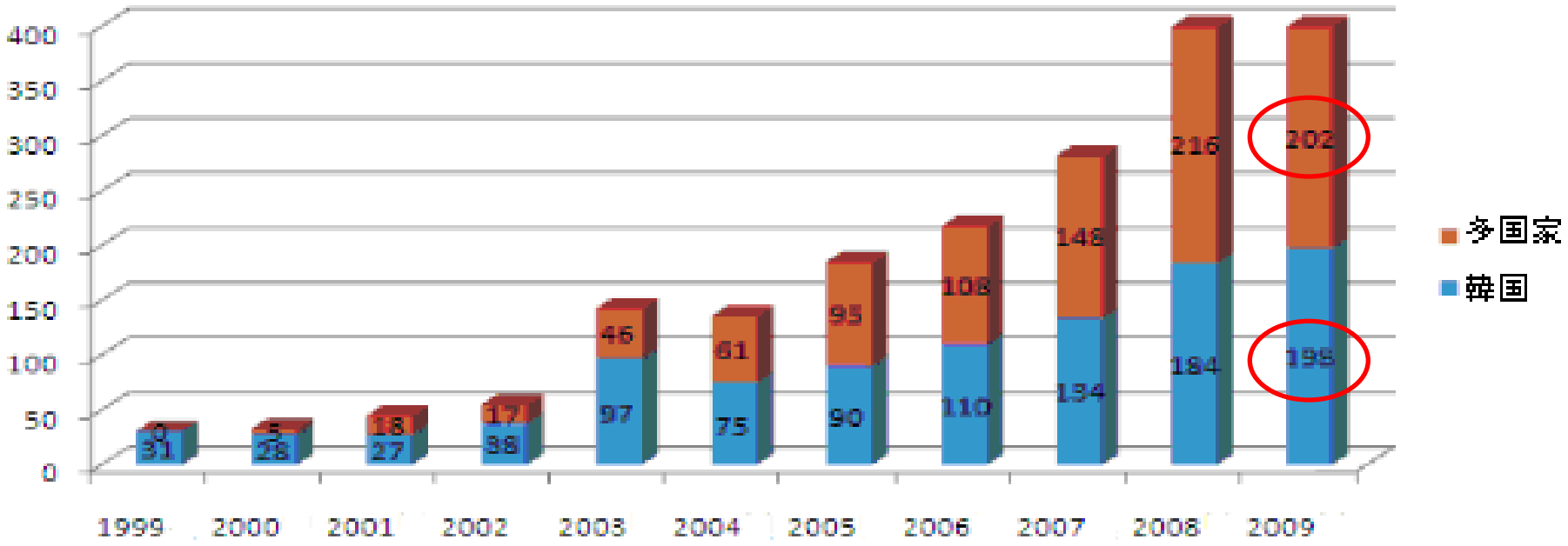
	2004		2005		2006		2007		2008		2009	
	P	S	P	S	P	S	P	S	P	S	P	S
TW single site	32	32	24	24	11	11	21	21	34	34	38	40
TW multiple sites	25	88	10	43	22	74	20	81	16	49	9	35
MR trials	62	196	86	284	100	337	127	479	155	599	140	537
% of MR trials, P	52.1%		71.7%		75%		75.6%		75.6%		74.9%	
Total	119	316	120	351	133	422	168	581	205	682	187	612

Partially modified

(P: Protocol, S: Sites)

Herng-Der Chern, Taiwan CDE (12/Apr/2010)

Trends of Multinational Clinical Trials in Korea

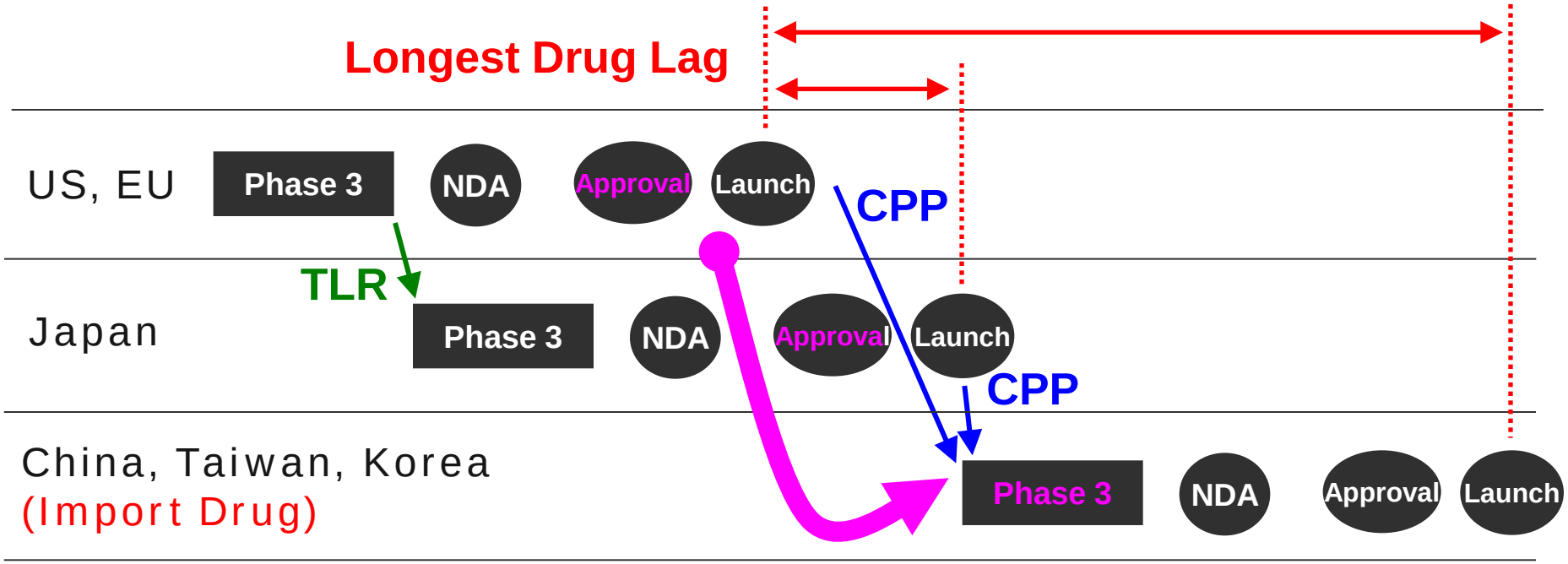


KFDA Press Release (09/Feb/2010)

Timing of Clinical Studies and NDAs of JP Pharma in East Asia (1 of 4)

JPMA

1. Super Old Fashion (E Asian P3 start after ICH approval)



TLR: Top Line Result

CPP: Certificate of a Pharmaceutical Product

Timing of Clinical Studies and NDAs of JP Pharma in East Asia (2 of 4)

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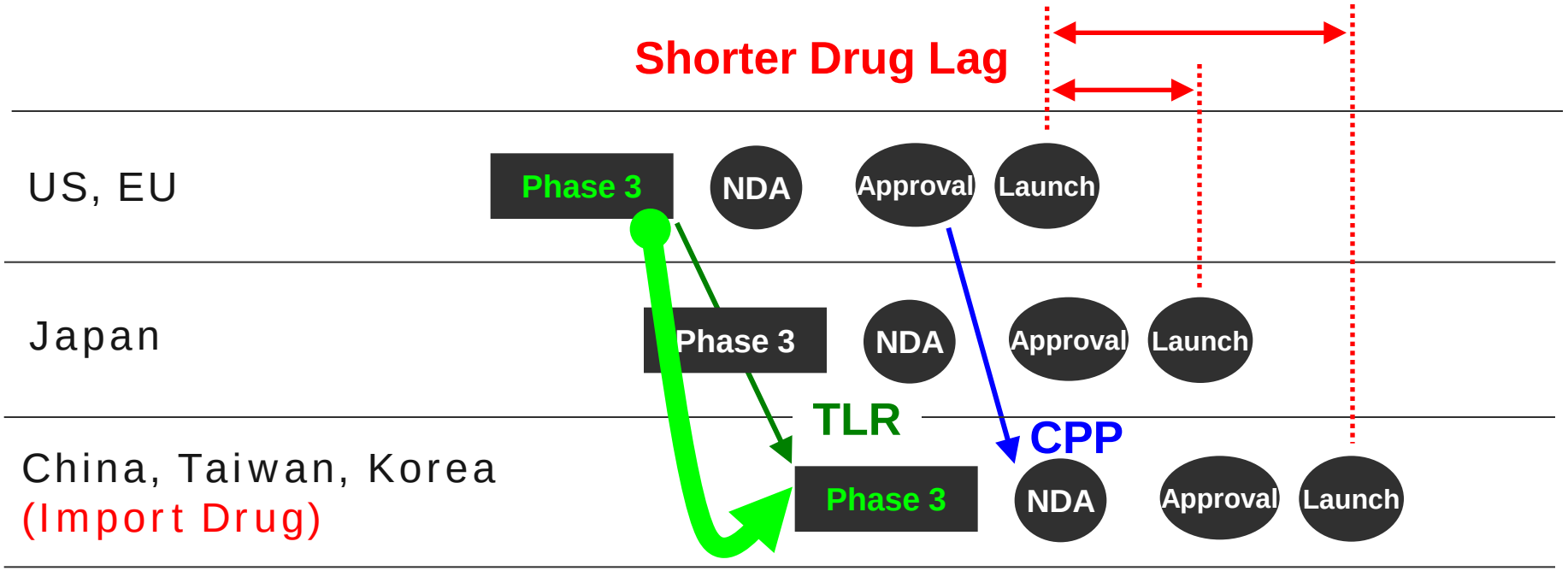
2. Old Fashion (E Asian P3 start after ICH P3 completion)



TLR: Top Line Result

CPP: Certificate of a Pharmaceutical Product

Timing of Clinical Studies and NDAs of JP Pharma in East Asia (3 of 4)

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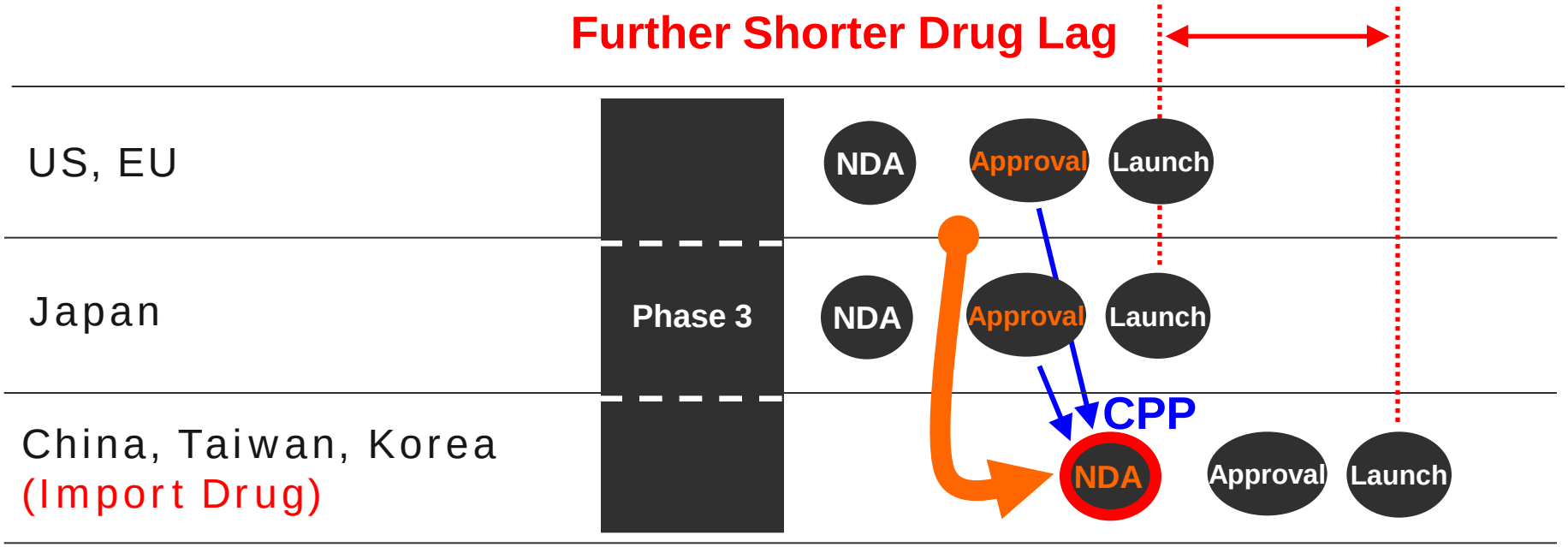
3. Multinational Trial, but E Asian NDA after ICH CPP
- Current Chemical Category 1 & 3 in China -



CPP: Certificate of a Pharmaceutical Product

Timing of Clinical Studies and NDAs of JP Pharma in East Asia (4 of 4)

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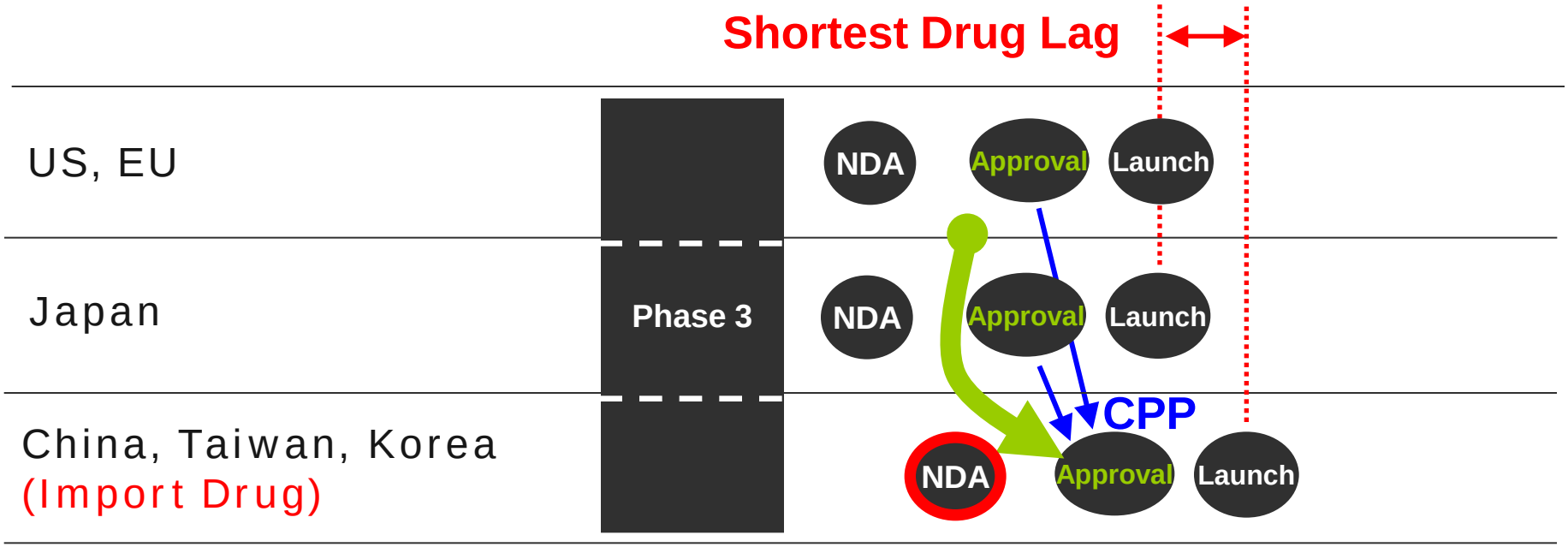
4. Multinational Trial, and E Asian NDA before ICH CPP
- Proposed Chemical Category 1 in China -



CPP: Certificate of a Pharmaceutical Product

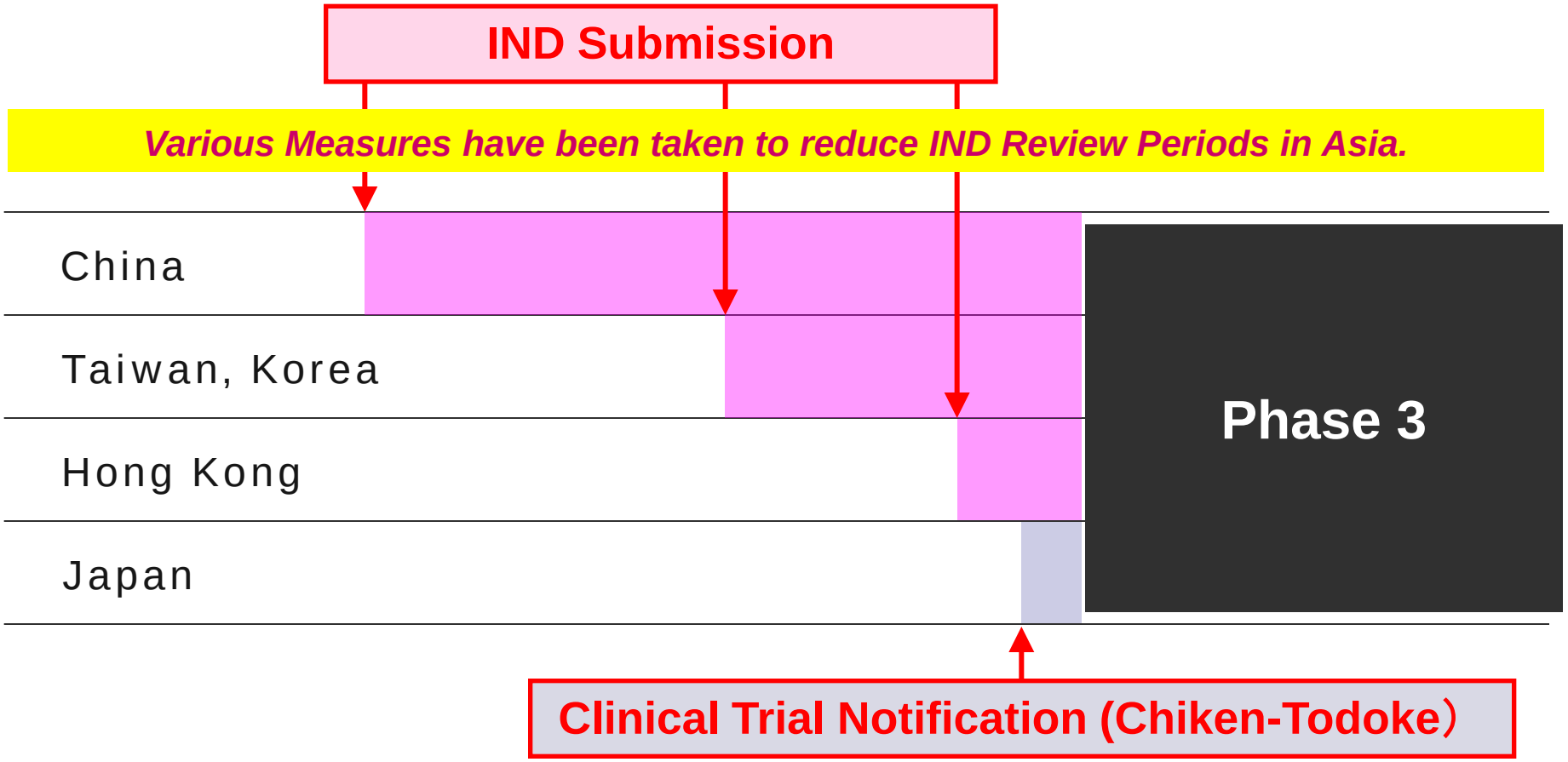
Speeding-up Approval for Anti-tumor Drugs in Past Five Years in China

- Drug Applications for Oncology indications: Constantly about 33% of the new Chemical Drugs classified as “Registration Category 1” from 2005 to 2009
- Special Review Procedures: 7 of 28 were Antitumor Drugs

Xiao-Yuan Chen, J. China Prescription Drug: No. 95, Page 10-12 (2010.02)

Timing of IND Submissions in Asia

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



IND Review Periods of Multinational Clinical Trials in China (2004–2008)

所用审评时间(月)*	品种数量
4	19
5	21
6	32
7	45
8	17
9	11
10	9
11	9
12	5

finished the calculation of statistics for 168 varieties and the time for review is from four to eight months. The average time and neutral position is 7 months

Not including the time of waiting for the review meeting and updating of materials by enterprises

Zhang Wei, SFDA, 1st DIA China Annual Meeting (02/Nov/2009)

Contents

Background Changes leading to New Strategy in East Asia

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1. East Asian regulatory agencies already have capability to evaluate innovative drugs
2. Skilled, talented & dedicated people in 産官学 (industry, agency, academia) of JP/CN
3. Ethnic Factors
   - Ethnic Differences between East & West
   - Ethnic Similarities in East Asia

Change of Purposes of Multinational Clinical Trials in Asian Countries

- **Contribute to Registration Studies for ICH Countries**
  - Speedy Enrollment
  - Low Cost
  - High Efficiency
- **Contribute to Early Launch in the Asian Countries**

Recently added

- **Contribute to Speedier and Further Progress of Life Science in the Asian Countries**
- **Contribute to Full (early through late) Phases of Asian/Global Development**
  - Challenges (Risk burden, Further investment)
  - Benefit (R&D knowledge and experience, Further improvement of national healthcare, Expansion of opportunities for industry/academia)

New Strategy in China and Japan

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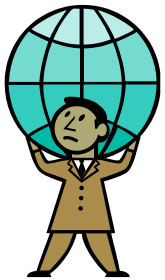
Essential Factors:

- Accumulation of Knowledge and Skills in East Asia

- Further East Asian Contribution to Local, Regional and Global Healthcare



1. **Simultaneous Approval with US/EU**
2. **Further Contribution to Early Stage R&D**
3. **Global Studies led by JP/CN**
4. **Asian Studies led by JP/CN (Collaborative Asian PK, POC, Dose Finding and P3 studies)**

with

- **「産⇔官⇔学」(industry⇔agency⇔academia) 連携 (collaboration) in Each East Asian Country**
- **「産⇔産」・「官⇔官」・「学⇔学」連携 in East Asia**

Contributions of China & Japan to Multinational Clinical Trials

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< Current Options>

- Global Studies led by US ← EU/JP/CN participation
- Global Studies led by EU ← US/JP/CN participation

< Future Options>

- Global Studies led by US ← EU/JP/CN participation
- Global Studies led by EU ← US/JP/CN participation
- Global Studies led by JP/CN/Asia ← US/EU participation
- Asian Studies led by JP/CN ← Asian countries' participation

Current Real Situation of Global Studies for Gastric Cancer

National Policy which supports New Strategy

- 医薬品産業は高度な知識集約型産業であるとともに健康面での国防産業である
- **Healthcare industry is an advanced knowledge-intensive industry and the national defense industry for human body.**

- 医薬品産業は国家安全保障の根幹を成す
- **Healthcare industry is located in the center of the national security.**

- 国民の命は自国で守る（外国への頼り過ぎは禁物）
- **Citizen’s life is guarded by each nation. Exceeded reliance on foreign countries should be avoided.**

NDA Strategies of Import Chemical Drugs in China

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< Old Fashion>

- Category 3 with Local PK/P3 (IND submission with CPP)

< Current Trends>

- Category 3 with Multinational P3 (NDA submission with CPP)
- Category 1 with Delayed P1,2,3 in China after P2 in Foreign Countries (NDA submission before/with CPP)
- Change to Domestic Drug's Category 1 with Simultaneous P1,2,3 with Foreign Countries

< Future Expectations>

Relaxation of Drug Registration Regulation (Article 44) is Essential

- Import Drug's Simultaneous P1,2,3 with Foreign Countries
- Import Drug's Multinational P1,2,3 with Foreign Countries

Hurdle against Simultaneous Approval in China

Proposal for "NDA Submission without CPP" followed by "CPP Submission before IDL Approval" (RDPAC, Apr. 2010)

- Based on the spirit of the Article 84 of "Drug Registration Regulation (SFDA局令第28号)", import drugs with medical needs can be approved by SFDA without the precondition of obtaining approval from foreign countries, thus it can be seen that submission for import drug registration prior to obtaining foreign marketing approval conform to the current regulation requirement in China.

- With global simultaneous NDA submission independent to CPP, Chinese patients would have a chance to benefit from the import new drugs at least one year ahead.

CPP Required Timing for NDA of import drugs in Korea and Taiwan:
During the NDA review period as a requirement of IDL (Import Drug License) approval, not submission.

Clinical Study Collaboration between East & West (1 of 2)

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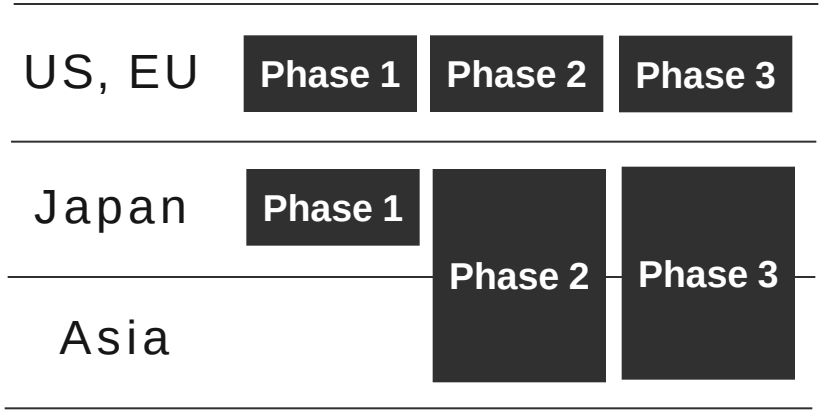
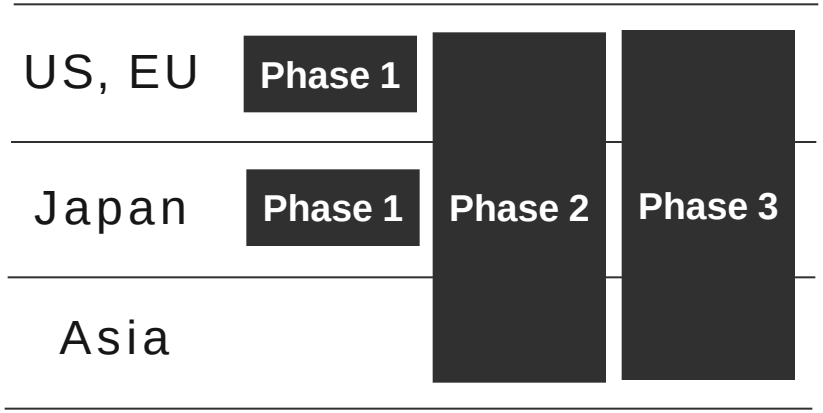
- JP Pharma's Point of View -

A. Fully Separated



- Considerable Ethnic Difference
- Much Time Difference
- Differences in Clinical Practice, Guideline, Dosage, Active Control, Concomitant Drugs

B. Joint in Phase 2 & 3



- No Ethnic Difference
- Huge Sample Size
- Very Small Population e.g. Orphan Drugs

Clinical Study Collaboration between East & West (2 of 2)

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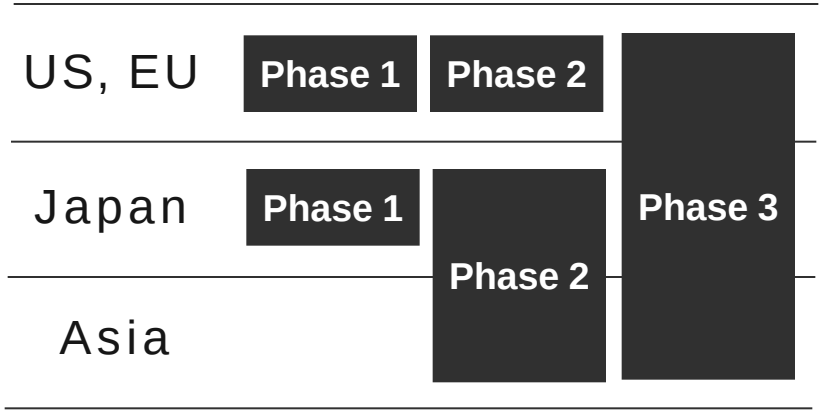
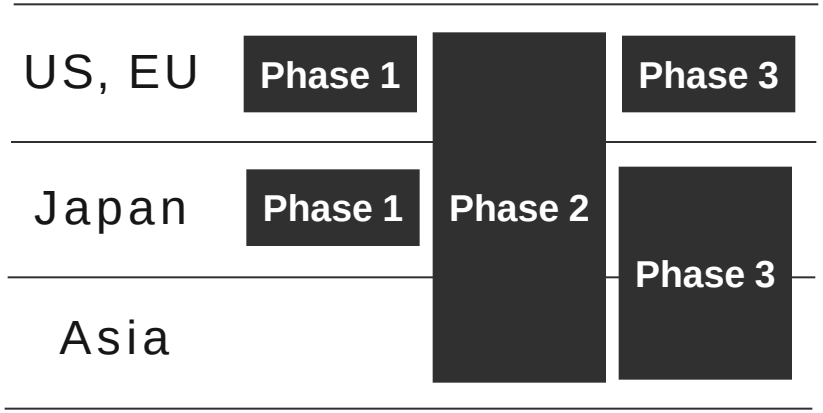
- JP Pharma's Point of View -

C. Joint in Phase 3

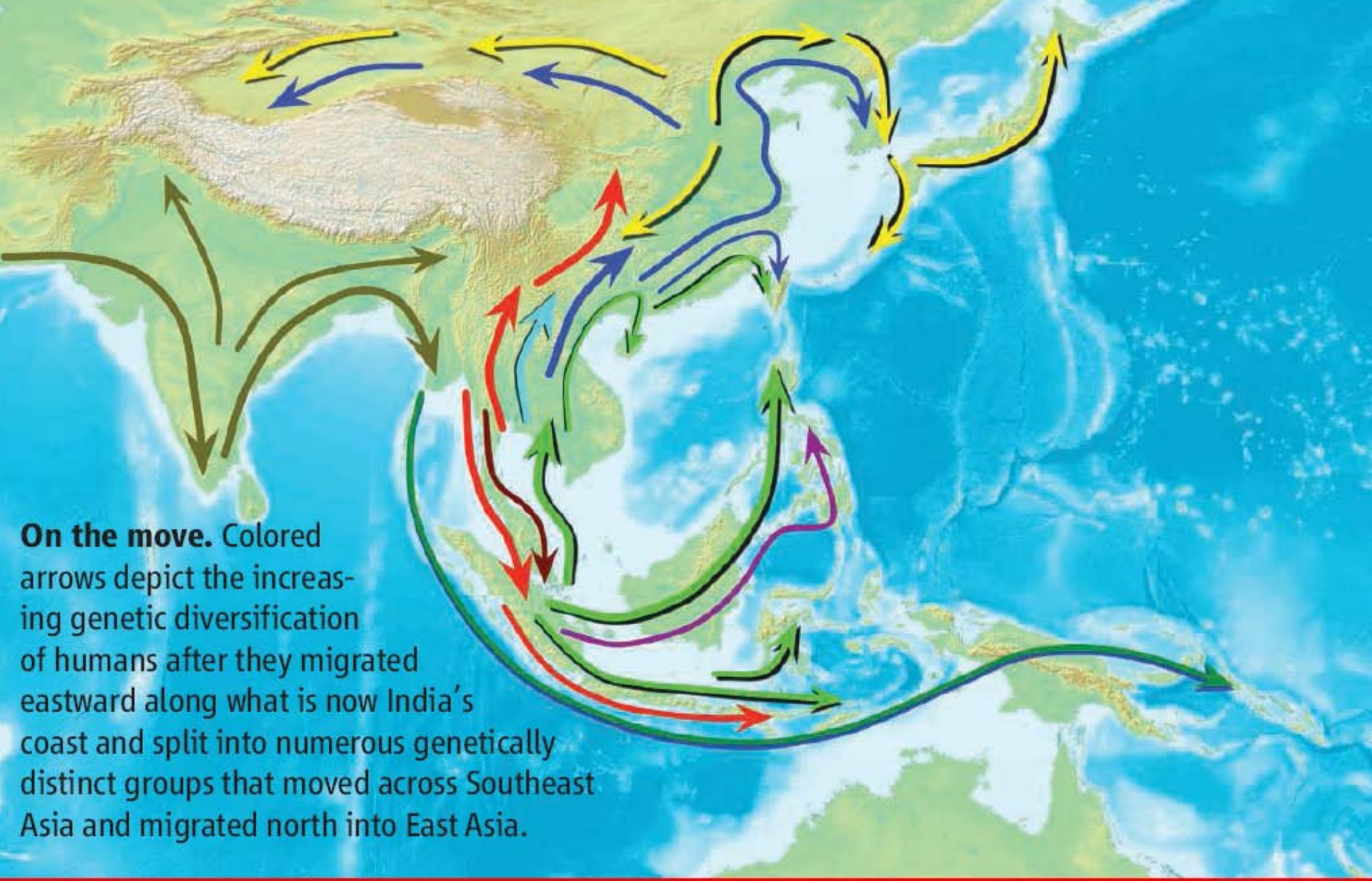


- Potential Ethnic Difference before the start of P2
- Large Sample Size
- Moderate Time Difference
- Required Adjustment at P2

D. Joint in Phase 2



- Newly Found Ethnic Difference after P2
- Critical Concern leads to re-separated P3



Dennis Normile, Science Vol 326, Issue 5959, Page 1470 (11Dec2009) www.sciencemag.org

Different Disease Pattern between China & USA

Non Oncology disease areas	China Morbidity (000s)	US Morbidity (000s)
Hepatitis (B & C)	166,000	5,100
Diabetes	30,000	12,000
Atherosclerosis	27,000	18,400
Affective and psychiatric disorders	20,000	19,700
Obesity	20,000	63,000
Alzheimer's Disease	5,000	4,500
RA & SLE	4,000	1,500
Oncology (Breast Cancer)	2,100	2,200
HIV	840	850
Solid organ transplantation	25	116

Yearly New Patients (000), Oncology	China Incidence	US Incidence
Breast Cancer	188	180
Lung cancer (including NSCLC and SCLC)	500	213
Hepacellular Carcinoma (HCC)	384	19
Gastric Cancer	376	21
Ovarian cancer	97	191

New Cancer Cases in Four Key Countries

CHINA	KOREA	INDIA	JAPAN
N = 2,190,623	N = 108,684	N = 851,901	N =570,598
Lung	Stomach	H&N	Stomach
396,368 (18%)	23,649 (22%)	160,030 (19%)	106,760 (19%)
Stomach	Lung	Cervix	Colorectal
392,938 (18%)	15,490 (14%)	132,082 (16%)	105,195 (18%)
Liver	Liver	Breast	Lung
345,844 (16%)	14,425 (13%)	82,951 (10%)	73,635 (13%)
Esophagus	Colorectal	Esophagus	Breast
253,752 (12%)	10,211 (9%)	50,457 (6%)	41,960 (7%)
Colorectal	Breast	Lung	Liver
150,656 (7%)	5,511 (5%)	35,495 (4%)	40,604 (7%)
Breast	Cervix	Stomach	Prostate
126,227 (6%)	4,949 (4%)	34,393 (4%)	29,345 (5%)
H&N	H&N	Colorectal	Pancreas
64,053 (3%)	3,536 (3%)	33,063 (4%)	21,386 (4%)
Leukemia	Esophagus	Leukemia	Gall / Bile duct
64,053 (3%)	1,985 (2%)	24,840 (3%)	17,876 (3%)

GLOBOCAN 2002, IARC

First in Man Studies in China & Japan

- Many First in Man (FIM) studies of Chinese Local Pharmas have been conducted in China.
- Many FIM studies of Japanese Local Pharmas have been conducted in Japan.
- Most of FIM Studies of Japanese Global Pharmas were conducted in Japan before the start of globalization.

Future Options of FIM Studies in China & Japan for Import Drugs in China

1. FIM in JP → PK in CN
2. FIM in CN → PK in JP
3. Collaborative FIM in CN & JP

Relaxation of Chinese Drug Registration Regulation (Article 44) is Essential

Advantages of Japan's R&D

- Long history of Universal Health Insurance Coverage (国民皆保険制度, 1961-) followed by the start of **Domestic R&D activities**
- **Primary Drug Discover Country** (US, UK, Japan, Swiss, France, Germany, Belgium, Denmark)
- **World's No. 3 Drug Discovery Power** from the viewpoint of No. of products (No.1: US, No. 2: UK)
- **14 Products of Blockbuster**, over JPY 10 billion sales per year, discovered in Japan (as of 2007)
- **ICH** Country
- Drawing up of **whole CDP (clinical development plan)**
- Long history of **Full Development (early through late phases)**
- Scientific capability, experience and expertise including protocol preparation activities in **PK, POC (proof of concept), Dose Finding and P3 studies**

Potential Collaboration among East Asian Regulatory Agencies

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[Step 1]

- ✓ Mutual understanding
- ✓ Personnel exchanges

[Step 2]

- ✓ Unification of IND requirements/procedures
- ✓ Unification of NDA requirements/procedures
- ✓ Unification of IND/NDA review timeline

[Step 3]

- ✓ Good review practice (GRP)
- ✓ Common training program
- ✓ Joint IND/NDA review
- ✓ Mutual recognition procedure (MRP)
- ✓ Centralized procedure (CP)

Contents

Conclusion

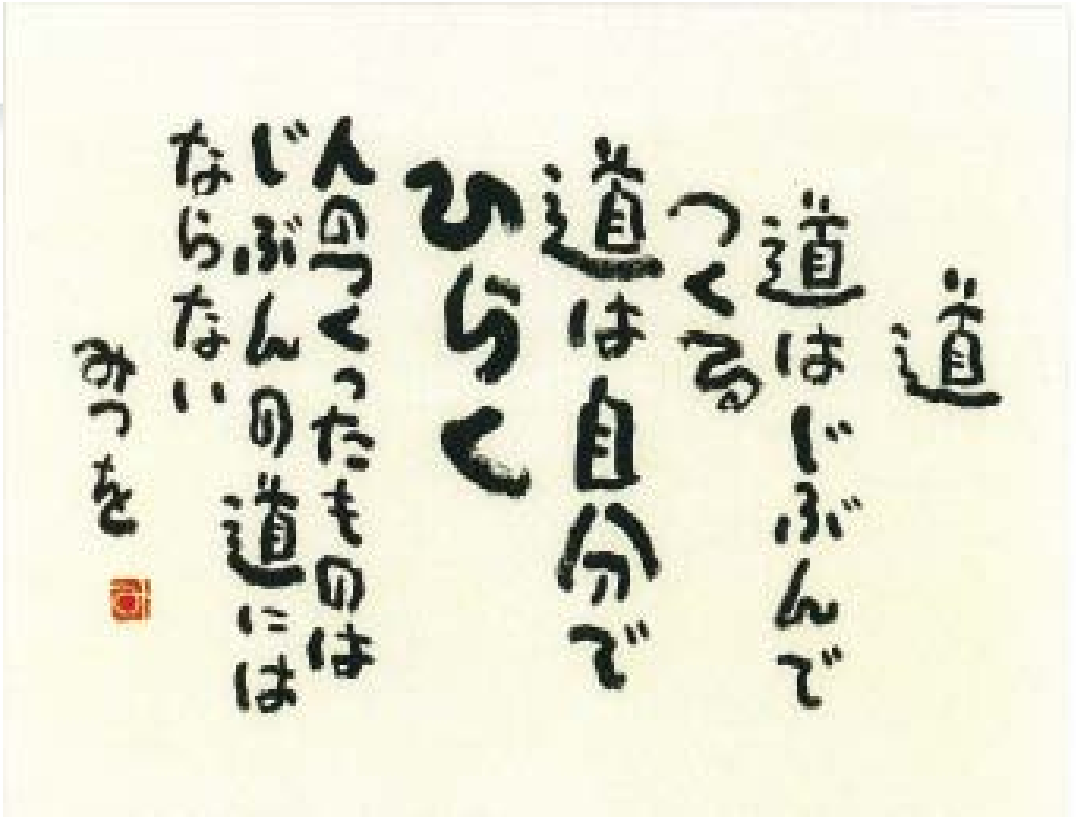
I. Accumulation of Knowledge and Skills in Drug R&D in East Asia is essential.

II. Further East Asian Contribution to Local, Regional and Global Healthcare is essential.

III. Next Strategy to be executed in China and Japan is.....
1. Simultaneous Approval with US/EU
2. Further Contribution to Early Stage R&D
3. Global Studies led by JP/CN
4. Asian Studies led by JP/CN (Collaborative Asian PK, POC, Dose Finding and P3 studies)

IV. In consideration of Ethnic Factors (Ethnic Differences between East & West and Ethnic Similarities in East Asia), Further Collaboration between China and Japan is very much reasonable.

China and Japan are ready to go!



相田みつを
（1924～1991）
書家・詩人

Road
Road is built by myself.
Road is developed by myself.
Other peoples' creations cannot be my own road.
- by Mitsuo Aida (1924-1991) -

 # Unofficial translation

JPMA

谢谢!

Win-Win Relationship between China and Japan

astellas
Leading Light for Life