Global Development in Asia

-a JPMA perspective-

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Presentation

1）Current Status of Clinical Trials in Japan and Foreign Countries

2）Ethnic Differences and Similarities
（US/EU and Asia)

3）New Drug Development Strategy
（Critical Path)

One Strategy for Clinical Trials in Japan

1) Infra-structure for Clinical Trials in Japan

In Japan, we need pivotal Japanese data for approval. Therefore, we need sites which can conduct the global standard clinical trials.

2) Using the data from abroad.

Multinational study with EU, USA or Asian countries

Change in situation of clinical trial in Japan

- CRCs are well-established
- Participation of Small-scale Clinics (Clinical Trial Network)
- Central IRB
- Outsourcing (CRO/SMO)
- Patient Recruitment
  Newspaper, Magazine, Internet, etc

(1) Infra-structure (Clinical Trials)

(2)Expansion of CRO/SMO

Action Plan in other countries

(1)UK : In order to overcome the economic recession (shipbuilding) in 1980 , clinical trials business, especially of Phase I, were supported

(CTX : requirement) : Scotland

(2)Singapore：Reflection from Asia Economic Crisis

Setting up Clinical Research Center

collaborated with global company

Southeast Asia(6 countries) :Asia CTD

(3)China mainland

Evaluation of China-mainland sites

including Hong Kong sites

(4)Taiwan/Korea

Setting up Clinical Research Center

(based on University hospital)

Asian Clinical Trials

Trials in other countries

1)Singapore (comments in ICH6）:HSA(Health Sciences Authority)

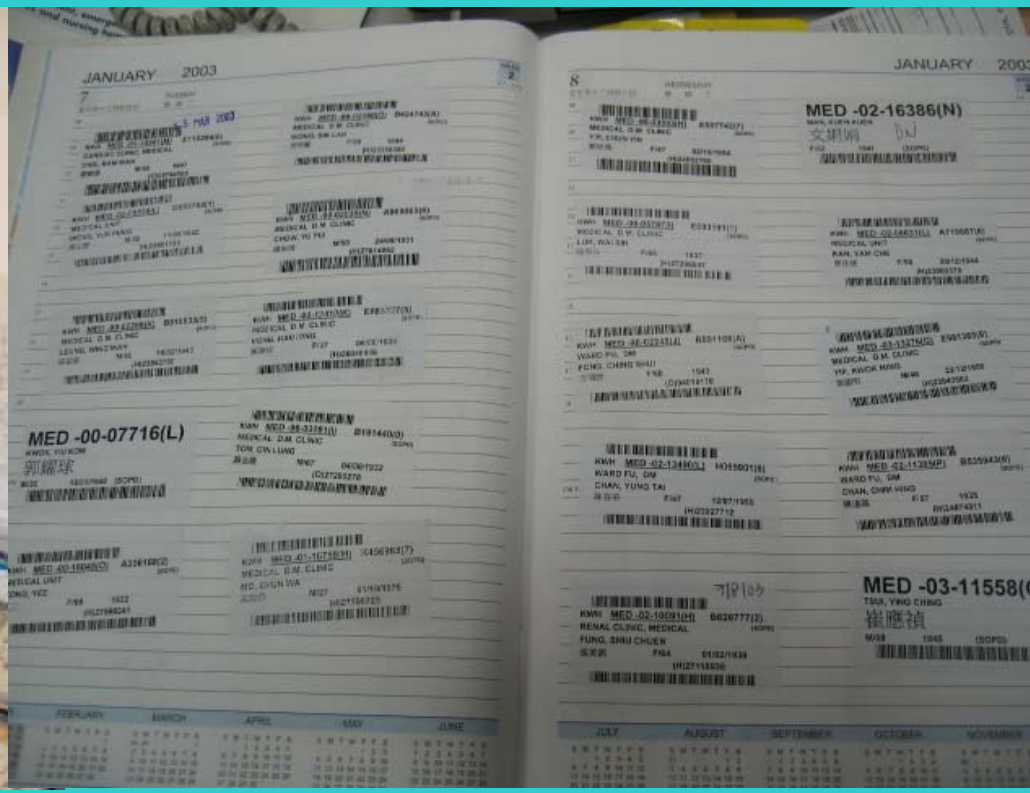
The lists of patients are prepared in the Public-Public Hospitals or Private-Private Hospitals.

2)Hong Kong： Hospital Authority Clinical Management System

Electronic Patients Records： In each cluster, one site can check all records in the hospitals which are in the cluster.

Even if a patient goes to another hospital, the doctor in that hospital recognizes this patient is in the clinical trial.

Electronic Patients Records : Key-point (clinical trials)


JANUARY 2003
MED -00-07716(L)
JANUARY
MED -02-16386(N)

Infra-Structure of Global Clinical Trials

Asia/Eastern Europe/South America/India

- Global Sponsor and CRO support regional hospitals to set up the IRB and to educate the investigators and CRCs.
- They conduct the clinical trials there and request FDA for inspection.
- FDA evaluates the performance in previous trials and compliance with GCP.

How to inspect (FDA) (DIA Annual Meeting)

- (1)1 week , Checking IRB documents and SDV for Patients Records
- (2)The most important issue is the interview of IRB members and investigators/CRC
  1. understanding of GCP
  2. independence from CRO and Sponsor

The status of IRB

1) In Japan ：Site 90 ：IRB 88

The document for Each IRB : Preparation (20 sets)

(1)How long dose it take for review?

(2)very often monitoring

(approval of some adjustments : informed consent)

2) In USA : 10years ago

Investigator meeting ：Investigator / CRC attended for 2 days

：Site 44 ：IRB 3（42sites share one central IRB)

3) In UK and Hong Kong

Cluster system（Each site attend the IRB of each Block(Cluster).

Hong Kong (population of 7 million) has 7clusters. If the IRB of one cluster approves it, those of other clusters will review based on the approval documents. (Mutual Recognition Procedure)

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Ethnic Difference/Similarity

1.Discussion Items
Internal Factor：Drug Metabolite, Height, Weight etc.
External Factor :Culture, Lifestyle, Treatment Method etc.

2.Efficacy：E12a
Protocol:
1)Titration from low-dose vs Fixed dose treatment from high-dose
2)Treatment time： At peak level vs At trough level
3)Primary endpoint： Responders' rate vs BP change from baseline

3.Safety
1)Identification and Detection method：E2
2)Results (Our Experiences)
Symptom : almost similar
Laboratory AE : ???

Safety data - Gaps between Japan and West -

Laboratory AEs

	Japan	US
Drug-related laboratory AEs	18.3	1.8
BUN increased	1.9	0.2
Uric acid increased	2.9	0.0
K increased	1.9	0.0
AST increased	1.9	0.9
ALT increased	4.8	0.9
		% of patients

--> Really more AEs in Japan ?

Safety data - Gaps between Japan and West -

Eg. Shift table for Uric acid

	Japan	24W				
		M:<2.5 F:<2.1	M:2.5-7.5[a] F:2.1-7.5	>7.5-10	>10-13	Total
0 W	M:2.5-7.5 F:2.1-7.5[a]	0	96.1	1.3	0	97.4
	>7.5-10	0	1.3	1.3	0	2.6
	>10-13	0	0	0	0	0
	Total	0	97.4	2.6	0	100
[a]Normal range (mg/dL)						% of patients

	US	24W				
		M:<2.5 F:<2.1	M:2.5-7.5[a] F:2.1-7.5	>7.5-10	>10-13	Total
0 W	M:2.5-7.5 F:2.1-7.5[a]	0.3	80.2	7.4	0	87.9
	>7.5-10	0	4.1	7.7	0	11.8
	>10-13	0	0	0	0.3	0.3
	Total	0.3	84.3	15.1	0.3	100
[a]Normal range (mg/dL)						% of patients

--> more changes in the US ?

Safety：Laboratory AE (Japanese, US/EU study)

1）General treatment by Investigators (Culture)

- Japan: Investigators treat and diagnose using full laboratory test
- U　S：Investigators examine laboratory test in case of clear symptom in Patients, cost-consciously

2）Monitoring by the sponsor

- Japan: Request the comment in case of the change (From normal range to abnormal range)
- U　S: Adverse Events based on clinical significance (eg,3-fold change)

This is the culture issue. In our case, the change value from pretreatment to posttreatment in Japanese data was not different from that in US data.

If studies in Japan and the US were conducted similarly, the incidence of AEs would be similar.

High Patient Incidence in Several Countries

US/EU : Heart disease / High-cholesterol

Asia : Stroke / Hypertension

Japan : Stomach cancer

South-East Asia: Liver dysfunction

Conduct : high incidence area

/ decreasing patient number for trials based on Biostatics

(1)High-cholesterol: Europe (WOS study, Helsinki study)

(2)Hypertension: China Mainland (Syst-China)

(3)Liver dysfunction: Hong Kong, Singapore

Medical Data between Japan and Hong Kong

Span of life

Japan		Hong Kong	
male age 77.6	female age 84.6	male age 78.0	Female age 83.9

Cause of Death

	1	2	3	4	5
Hong Kong	Cancer (33.0%)	Heart Disease (16.3%)	Stroke (10.5%)	Pneumonia (8.9%)	Accident/ poison (5.6%)
Japan	Cancer (31.0%)	Heart Disease (15.3%)	Stroke (13.6%)	Pneumonia (8.8%)	Accident (4.1%)

Height and Weight

		Male		Female	
		Height	Weight	Height	Weight
Japan	Forties	169.3cm	68.2kg	155.7cm	54.5kg
	Fifties	165.7cm	64.6kg	153.0cm	54.6kg
China		169.7cm	67.7kg	158.6cm	59.6kg

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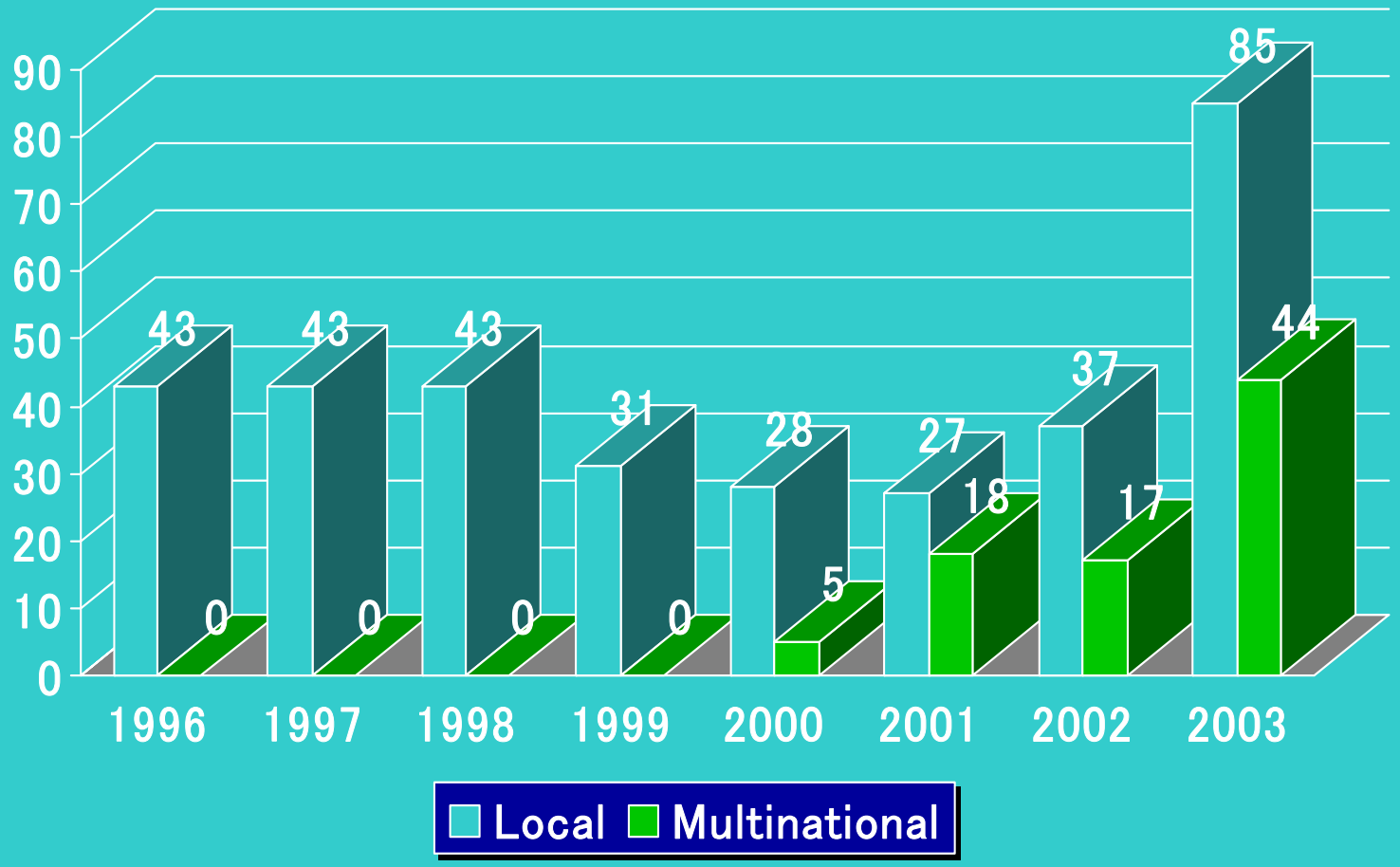
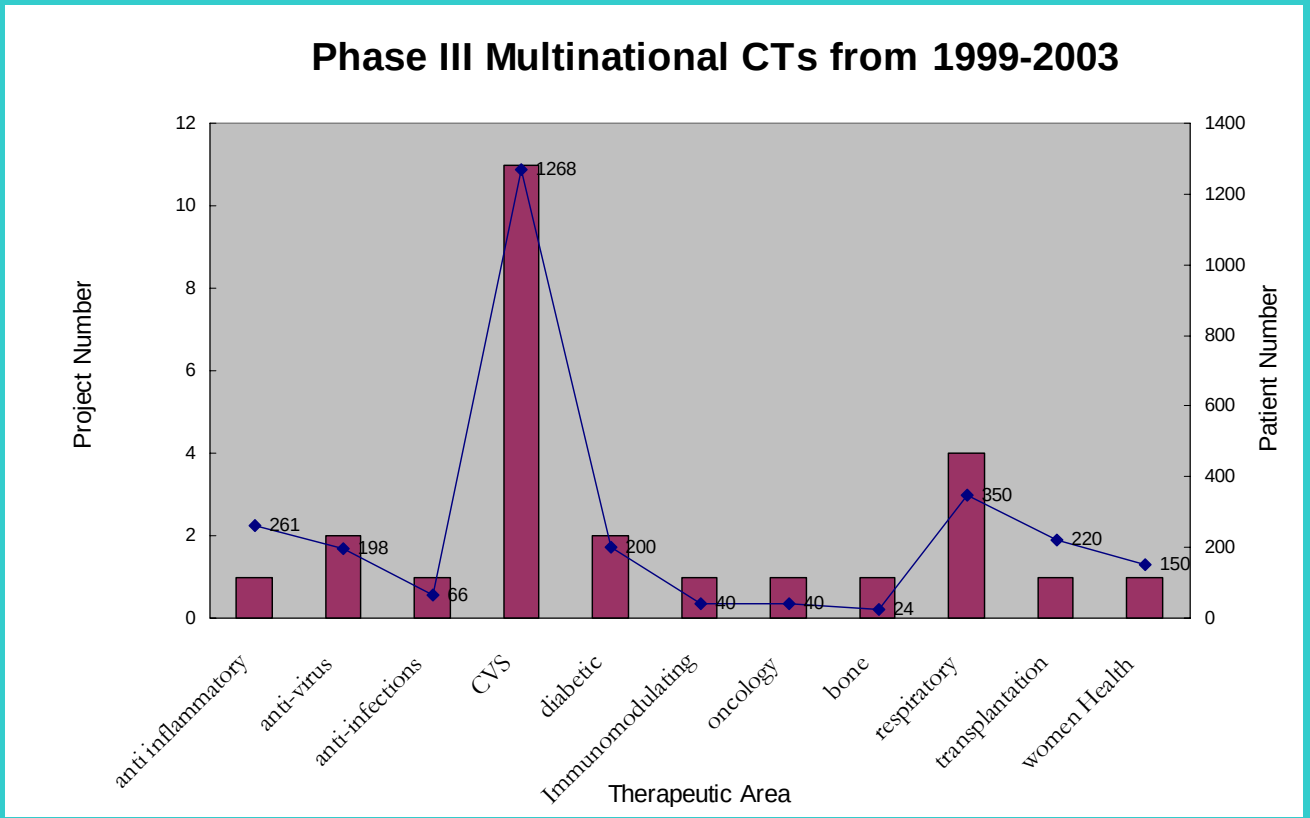
(Critical Path)

Multinational Clinical Trials (Korea)



Multinational Clinical Trials (China Mainland)



Reports for Regulatory issues

1)FDA

(1)Challenge and Opportunity on the Critical Path to New Medical Products,March 2004

(2)Development strategy（report：FDA/Novartis）

(3)CPDER（Center of postmarket Drug Evaluation & Research)

2)ICH

(1)E5/Question11（Dr. Temple, Dr. O'Neill, PMDA、JPMA）

Flexibility for conducting the multinational clinical study

(2)E2e

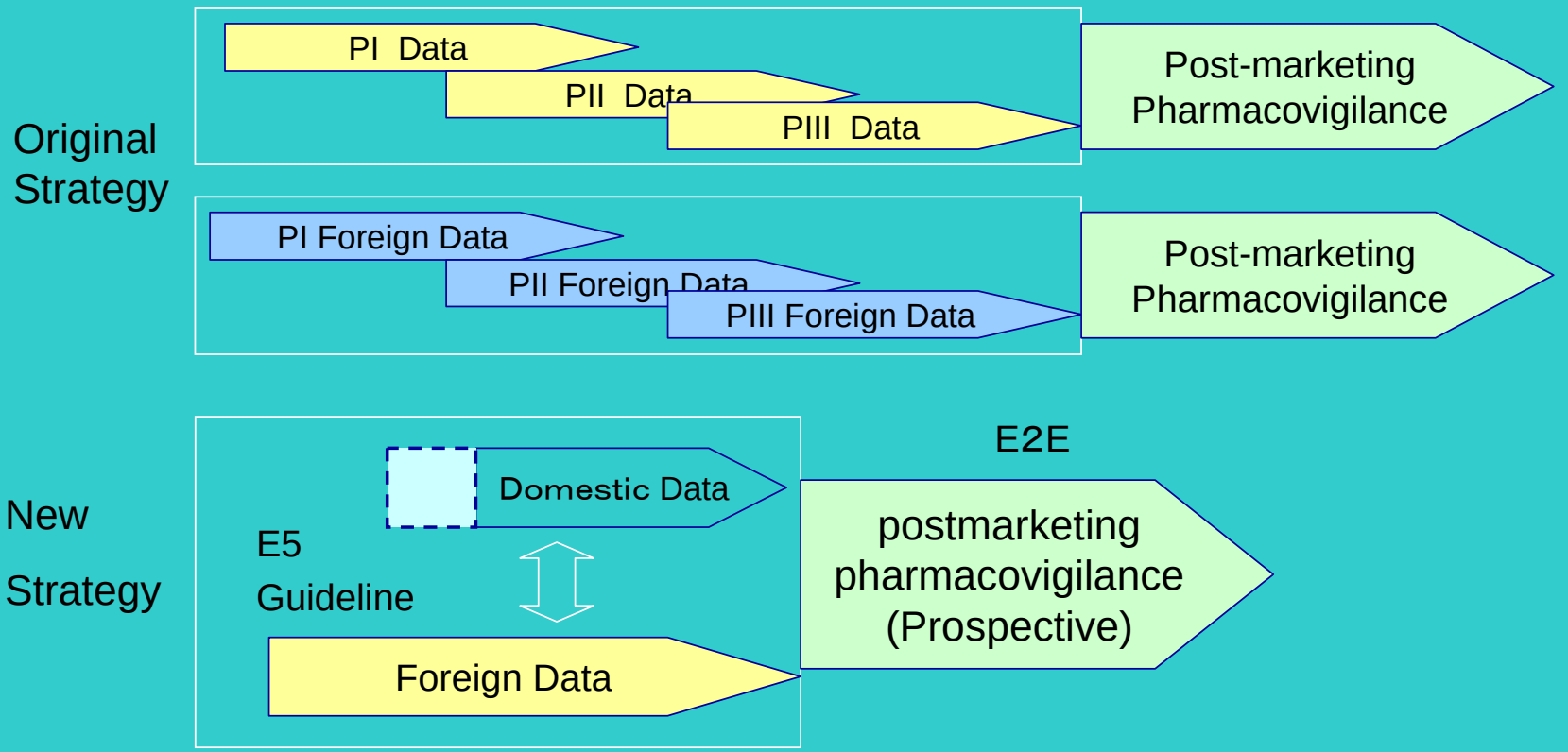
In the development strategy, the Post-market plan should be added.

New Drug Development Strategy

FDA/Norvatis(2006/5/16)

1. Development stage
   1）Phase Ⅰ: Set up model/Proof of Concept
   2）Phase Ⅱ: Confirm the model
2. Approval stage
   1）Monitored Release
   2）Full Release

Drug Development Strategy in Japan
(Tanigawara Proposal:2006/4/12)



- PK/PD study is important in New Strategy
- According to E2E guideline, we should discuss overall development strategy including postmarketing pharmacovigilance.
- In new strategy, multicenter clinical trials should be done in Japan.

New Drug Development Strategy in Japan

Importance of PK/PD study

- **PK/PD study should be recognized as Phase I/IIa study.**

Participation in Global Study

- **The experiences should be accumulated in Japan. Japanese sponsors should manage and take the responsibility for global clinical trials, with global CRO.**

Summary

1)We should understand and learn the activities in Asian/US/EU and continue to promote and improve the Japanese infra-structure (Clinical Network, Central-IRB). This is the requirement for attending global clinical trials.

2)Asian study may be the suitable study for NDA in Japan because of similar ethnic Factor. Asian countries have a lot of experiences, therefore, Japanese Sponsor should learn the operation skill with them. APEC and DIA are the suitable communication places.

3)The concept of ICH is “share the high-quality data” and “speedier supply for patients all over the world” , therefore, the mutual usage is very important concept.