Review Policies for Global Drug Development : Korea's Perspective

April 15, 2008

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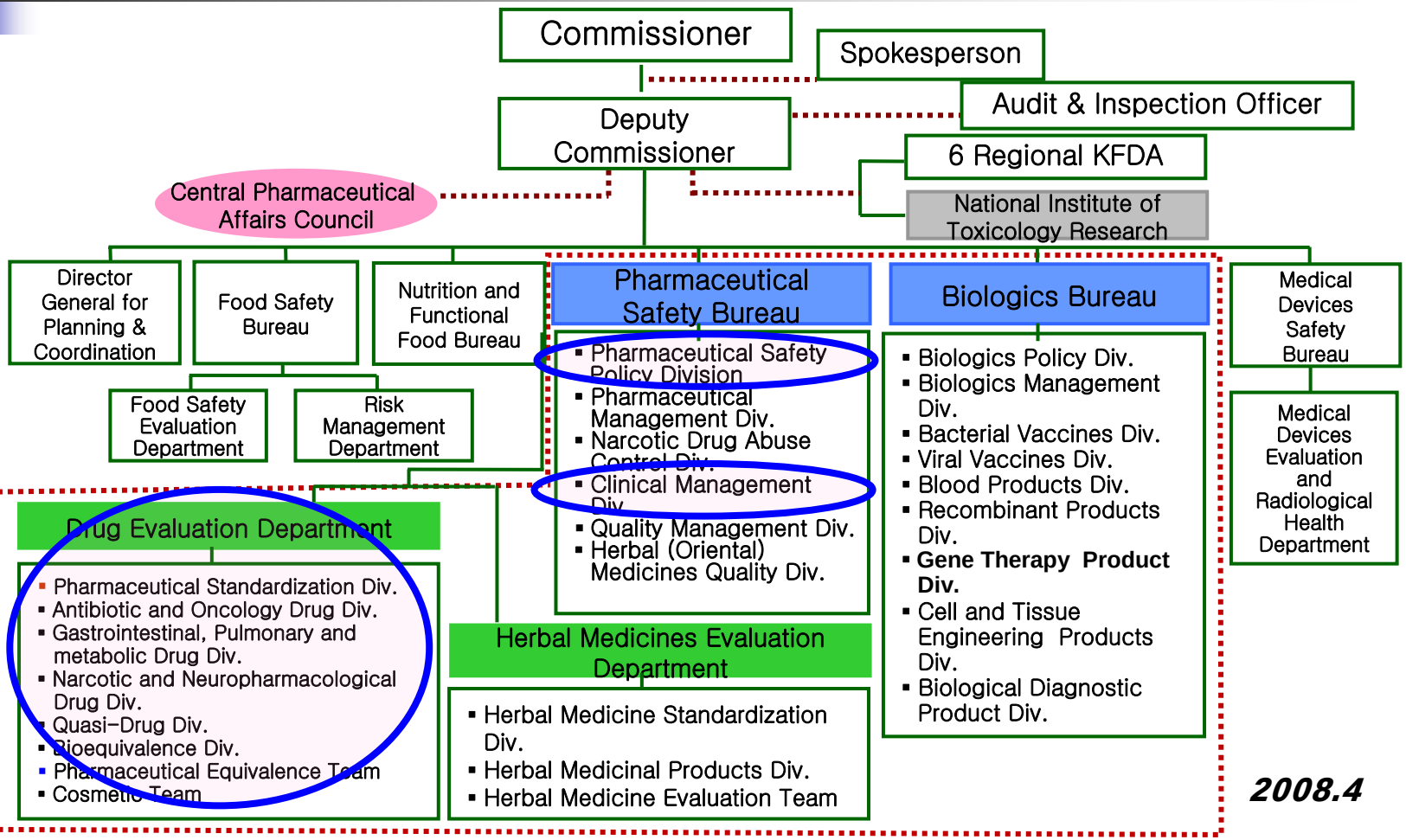

2008.4

Review Process in KFDA

All application documents could submit by KiFDA online system with electronical documents from Oct. 2nd, 2006

Major Regulatory Changes

Dec. 12, 1999 (enforced .Jul. 1, '00)	• **Adoption of the Bridging Concept** - Harmonized to ICH guideline E5 - Diverse bridging strategies were required
Jan. 4, 2000 (enforced Jan. 1, '01)	• **KGCP Amendment for Harmonizing with ICH GCP** - Harmonized with ICH guideline E6 - Protect the rights and safety of subjects - Responsibility of investigator
Dec. 3. 2002	• **Introduction of IND System** - Separation between developmental clinical stage and commercial product approval, such as IND and NDA - Participation in international study enabled
Jun. 30. 2006	• **Organization of Clinical management Division**
Jan. 4. 2007	• **Introduction of Joint-IRB**

Change of Clinical Trial Status

- Introduction of Bridging Concept and IND System

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- Increase in the Number of Domestic Clinical Trials Approved
- Increase of Participation in Multinational Clinical Trials

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- Change in Type of Clinical Trials
- Increase in Initial Clinical Trials

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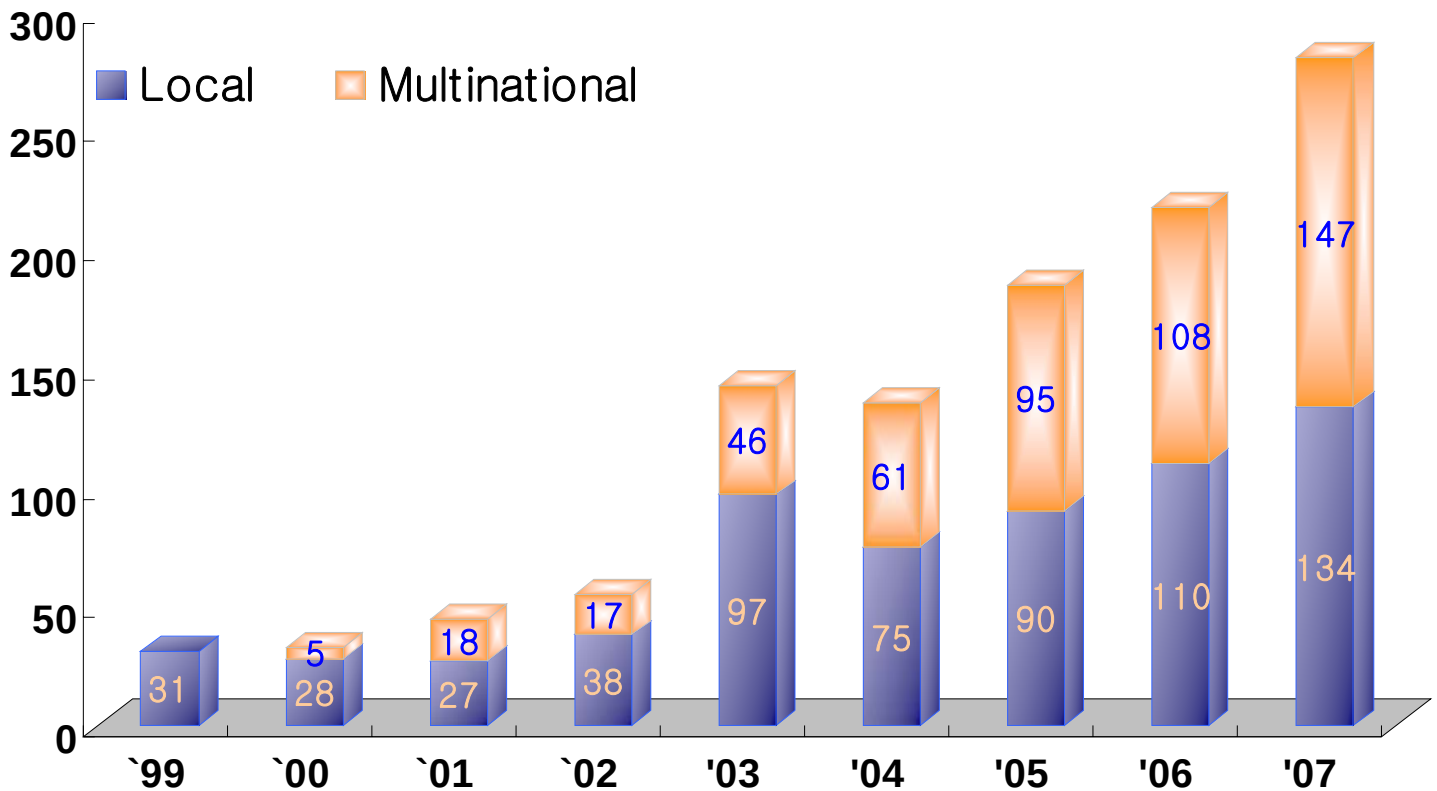
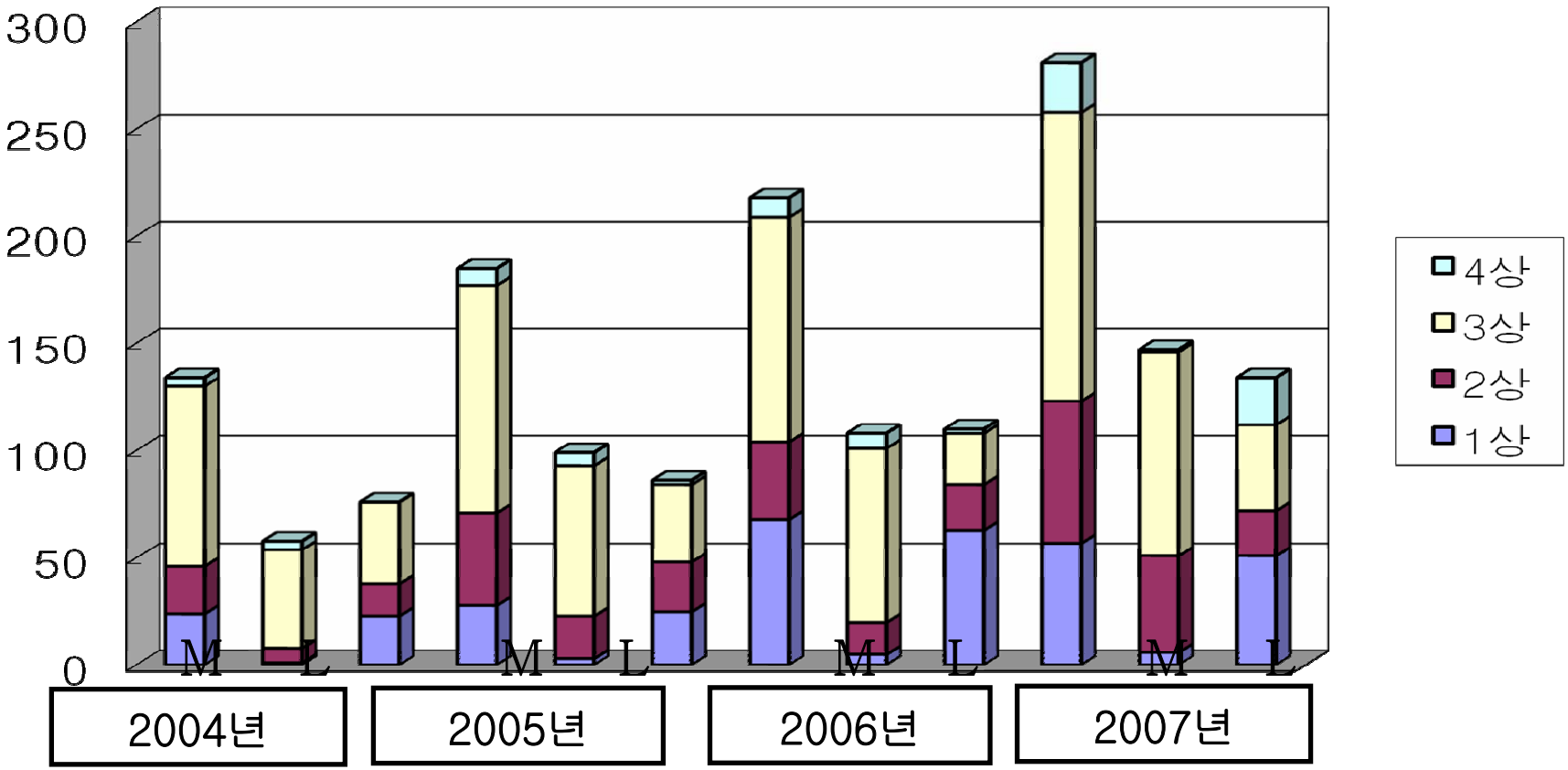
- Demand the Necessity of Amending Guidelines of Bridging Data Evaluation

Clinical Trials approved by KFDA



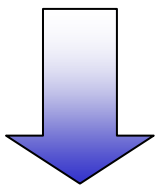
Clinical Trial Status



Bridging Concept

"Bridging Data" = "Korean Data"

"Bridging Study" = "A trial conducted in Korean"



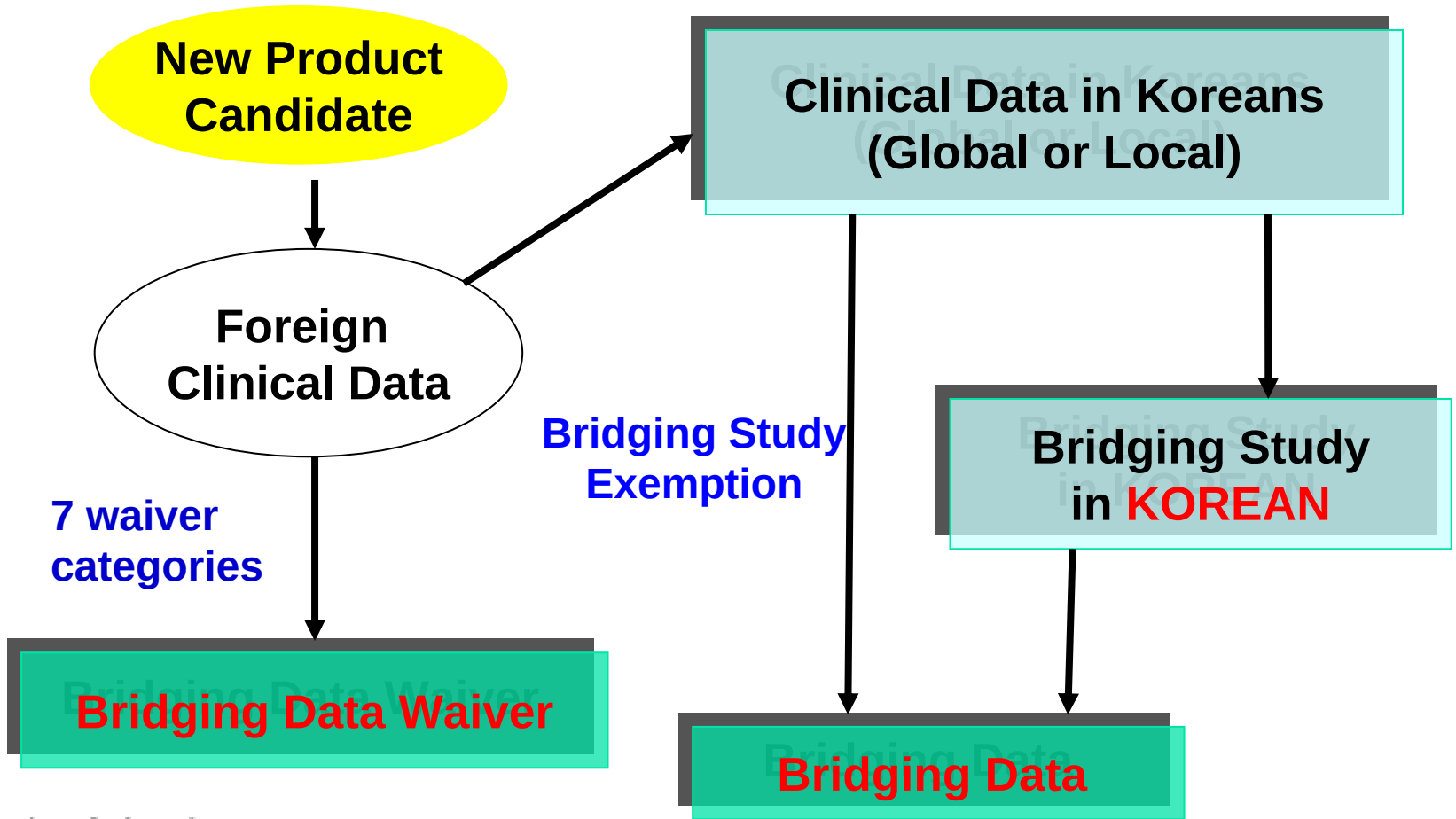
Ethnic Factors
(Ethnic difference)

- **Intrinsic factor (genetic)**
- **Extrinsic factor (culture, environment)**

Evaluation

- Ethnic Sensitivity
- Foreign clinical data
- Bridging Data

New Product Approval



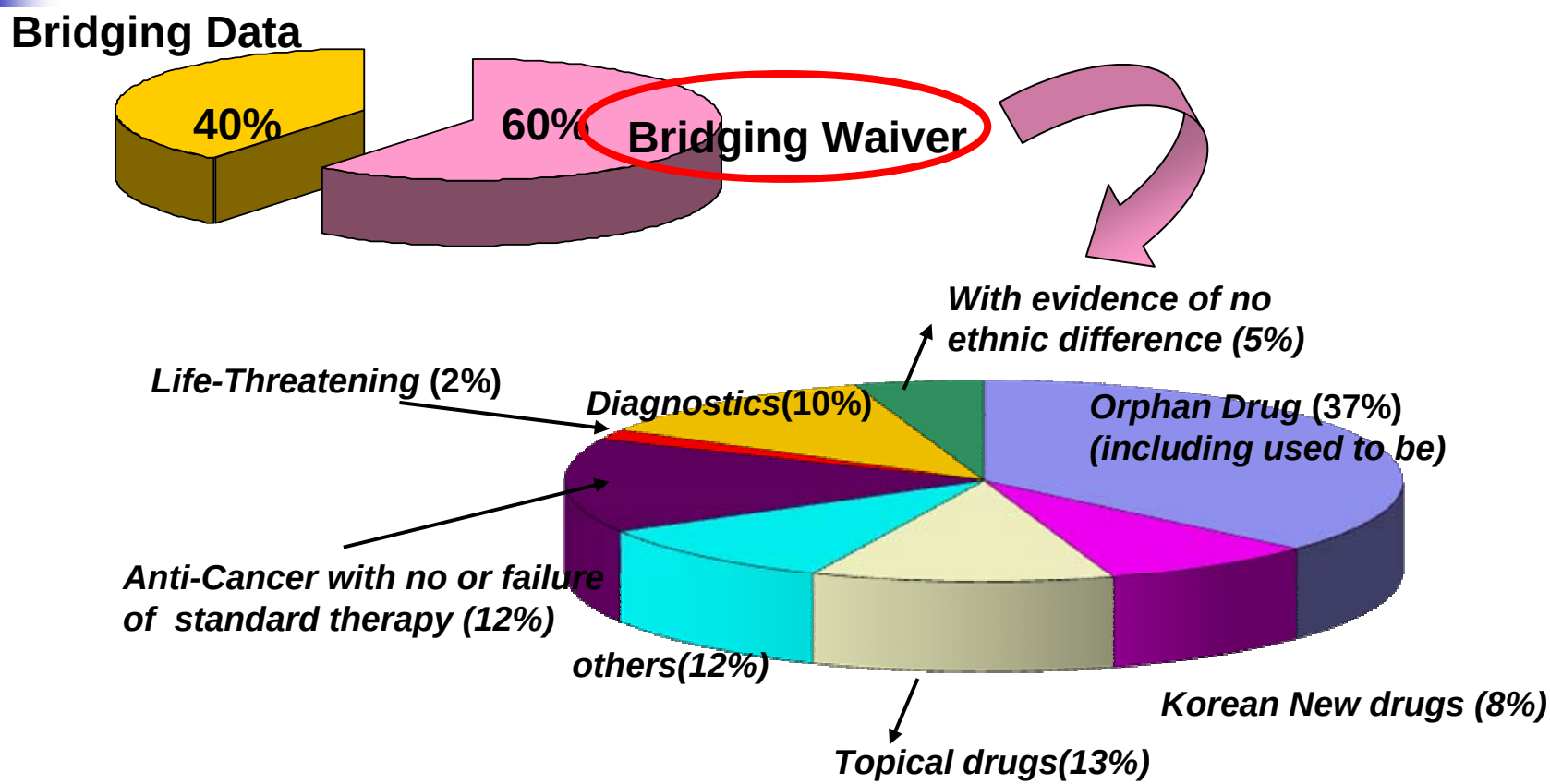
Bridging Waiver Categories

- Orphan drugs (or used to be orphan drugs)
- Drugs for life-threatening disease or AIDS
- Anticancer therapy for the following
  - No standard therapy
  - Therapy after failure of a standard therapy
- New drugs for which clinical trials conducted on Koreans
- Diagnostic or Radioactive drugs
- Topical drugs with no systemic effect
- Drugs that have No ethnic differences

Case of Bridging Waiver

- Renagel (Sevelamer, Tab., Che-il, renal dysfunction)
  - ✓ Polymer, Excretion with binding of Phosphorous in renal dysfunction Patient
- Travatan (Travaprost, Ophthalmic sol., Alcon, Glaucoma)
  - ✓ Drug Conc. & receptor : Less in systemic body
- Elidel (Pimecrolimus, Cream, Novartis,)
  - ✓ No systemic effect Local effect etc.
- Arixtra (Fondaparinux, Inj., Sanofi-Synthelabo, Antithrombotic)
  - ✓ Low MW Heparins, enough experiences in Korea
- Invanz (Ertapenum, MSD, Antibiotics)
  - ✓ Susceptibility test in Korean and western population: similar
- Cancidas (Caspofungin, Inj., MSD)
  - ✓ Life-threatening disease

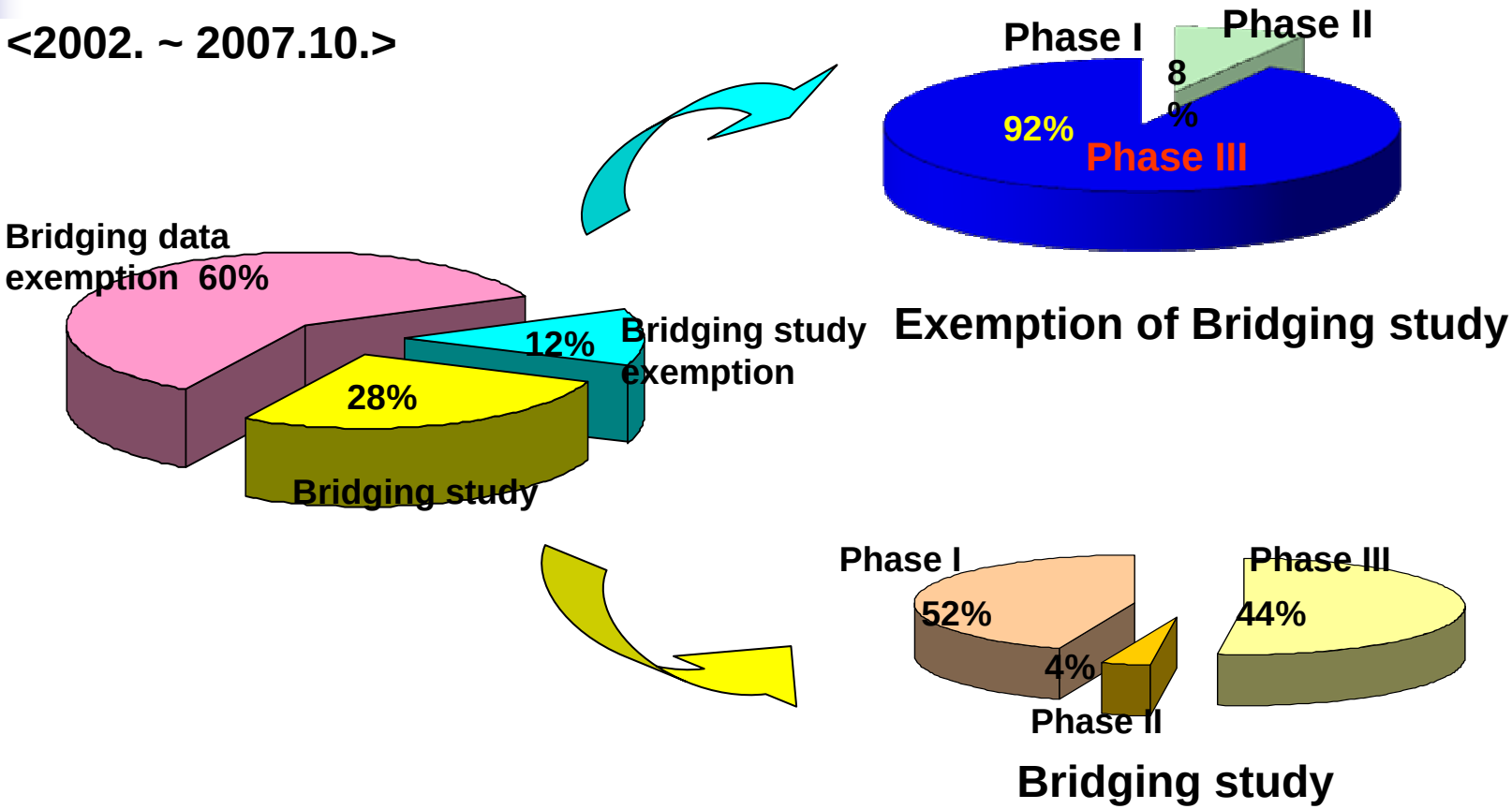
New Drug based on Bridging Strategy (1)



- *Based on the New chemical entity approved by KFDA from 2002 to Sep. 2007*

New Drug based on Bridging Strategy(2)

<2002. ~ 2007.10.>



- *Based on the New chemical entity approved by KFDA from 2002 to Sep. 2007*

Type of Bridging Study

- Pharmacokinetics
- Pharmacodynamics with pharmacological endpoints
- Dose-response
- Phase III confirmatory study
- Phase III with surrogate marker

Reasons for the failure of bridging study

- **Phase III study**
  - ✓ Active controlled study, Single arm study
  - ✓ Power Deficiency
  - ✓ No sufficient in the statistical theory
  - ✓ No evidence on the no ethnic difference between ethnics
- **PK study**
  - ✓ No consistency between single and multiple dose result
  - ✓ No ethnic similarity

Overall Evaluation of Bridging Data

- Application of foreign clinical data to Korean population without changes in dosage
- Application of foreign clinical data to Korean population (;PMS recommended)
- Application of foreign clinical data to Korean population with modification of the dosage (;PMS recommended)
- Additional clinical trials are required.

Evaluation on Foreign Clinical Data and Bridging Data (1)

- Comparative analysis between the Korean data and non-Korean data with proper statistics methods, if possible
- Data of PK and PD correlate well,
- Safety and efficacy end points are predictable from PD end points
- There is sufficient experience with application of confirmatory studies conducted in the given country to Korea, and
- Medical practice, design and conduct of clinical trials are similar between two ethnic groups

Evaluation on Foreign Clinical Data and Bridging Data (2)

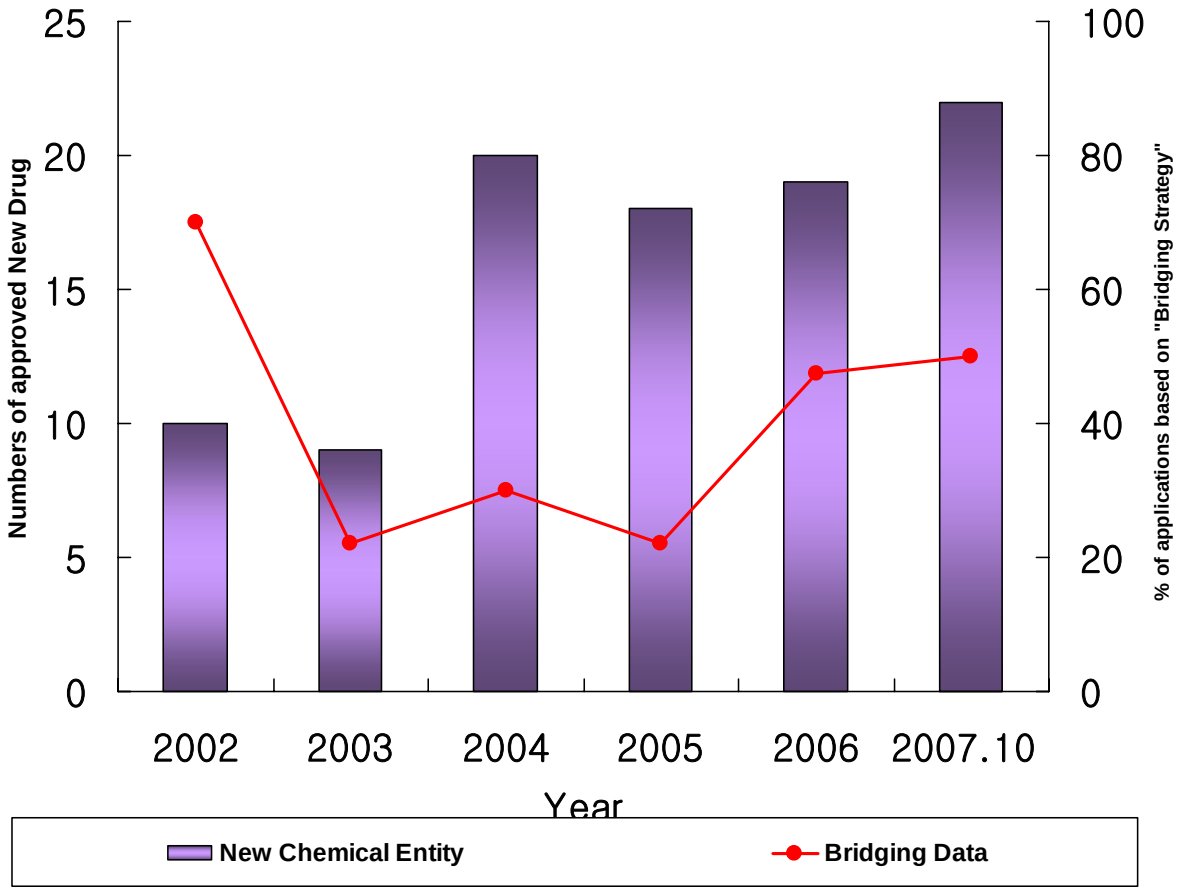
- Well-established PK-PD and dose-response relationships are necessary for PK study for bridging
- GCP Compliance
- In case Korean population participate in the multi-national clinical trials: Comparative analysis of the whole study result with the Korean subgroup included

  (; Sufficient sample size is needed) .

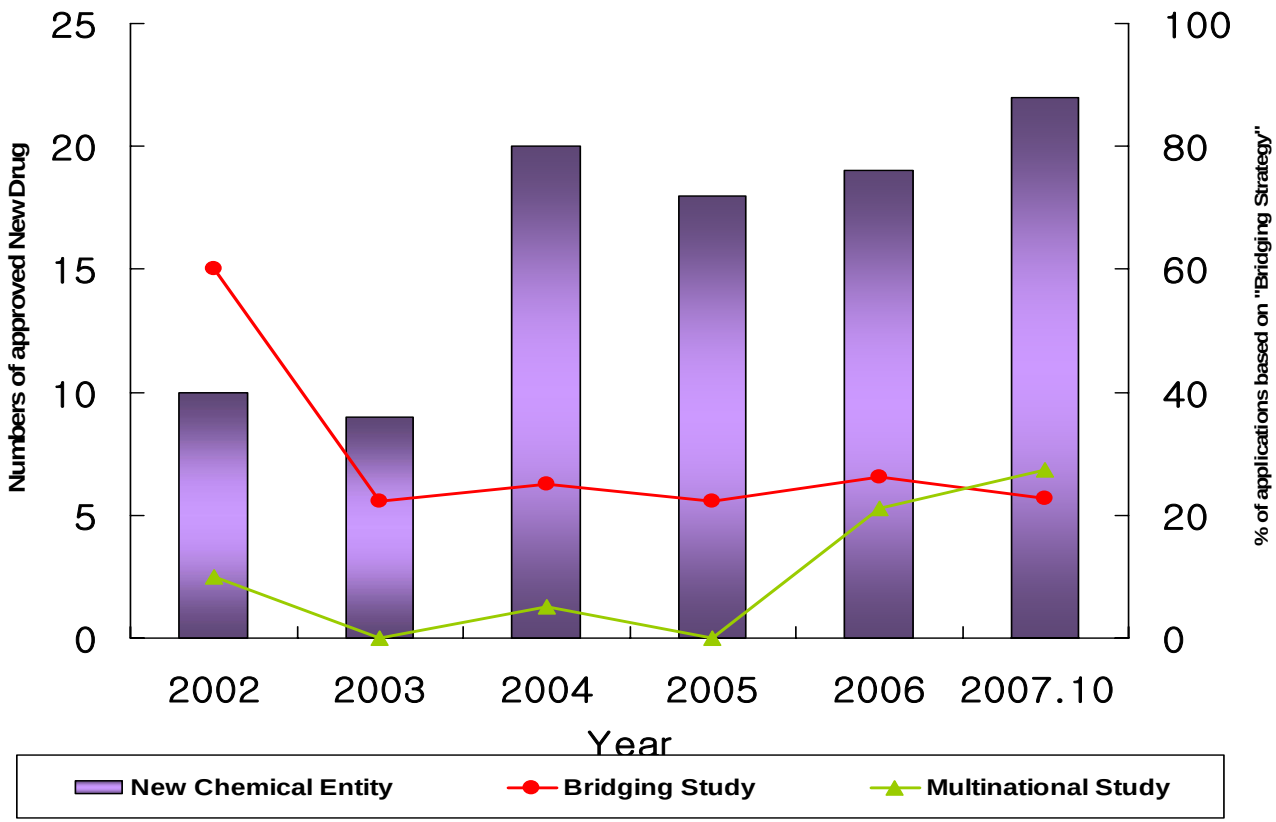
Case of Dose Adjustment

- **Actos (Pioglitazone, Tab, Lilly, Diabetics)**
  - ✓ Pharmacokinetics study with healthy Korean volunteers (n=24)
  - ✓ Adjusted Dosage in Korean
    - Mono-therapy : 15 mg, 30 mg
    - Combination therapy : 15mg
- **Morniflu (Morniflumate, Tab, Kolon, Analgesics & Antipyretics)**
  - ✓ Phase III study with Korean patients
  - ✓ Dose Adjustment to ½ with Safety issued of NSAID
- **Crestor (Rosuvastatin, Tab, Astrazeneca, Hypercholesterolemia)**
  - ✓ Phase III study with primary hypercholesterolemia
  - ✓ Dose Adjustment by Asian PK data different from Caucasian

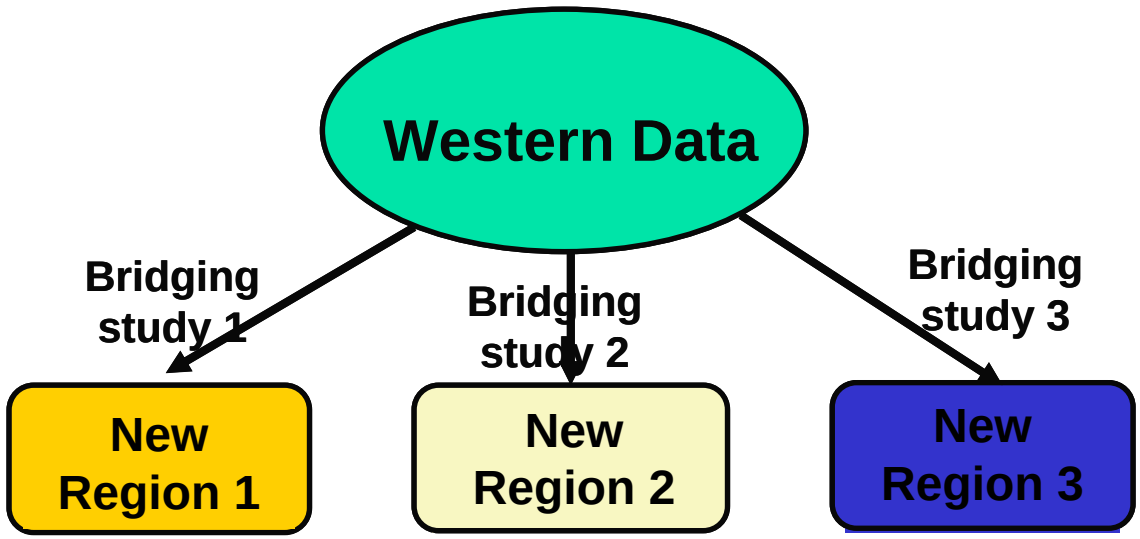
New Drug based on Bridging Strategy(3-1)



New Drug based on Bridging Strategy(3-2)



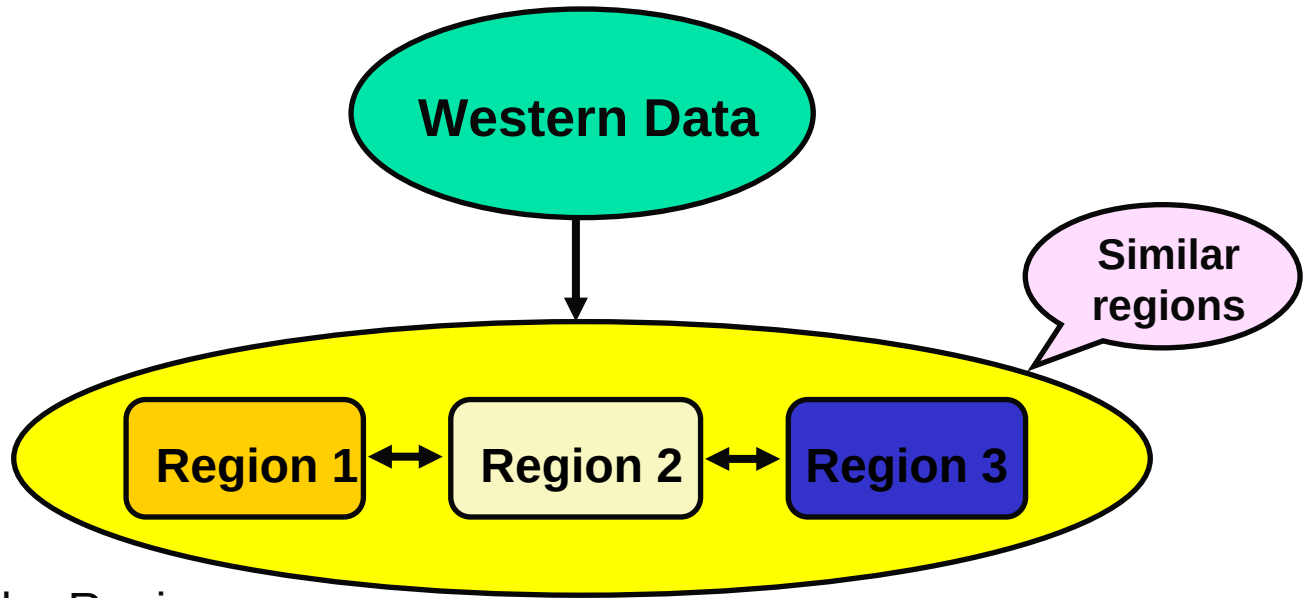
Past Experience



1. No clear scientific evidence regarding racial difference
2. No clear statistical approach-similarity, sample size
3. No unified regulatory authority requirements

- Presented by Masahiro Takeuchi in 2nd Kitasato University-Havard School -

Present & Future Application



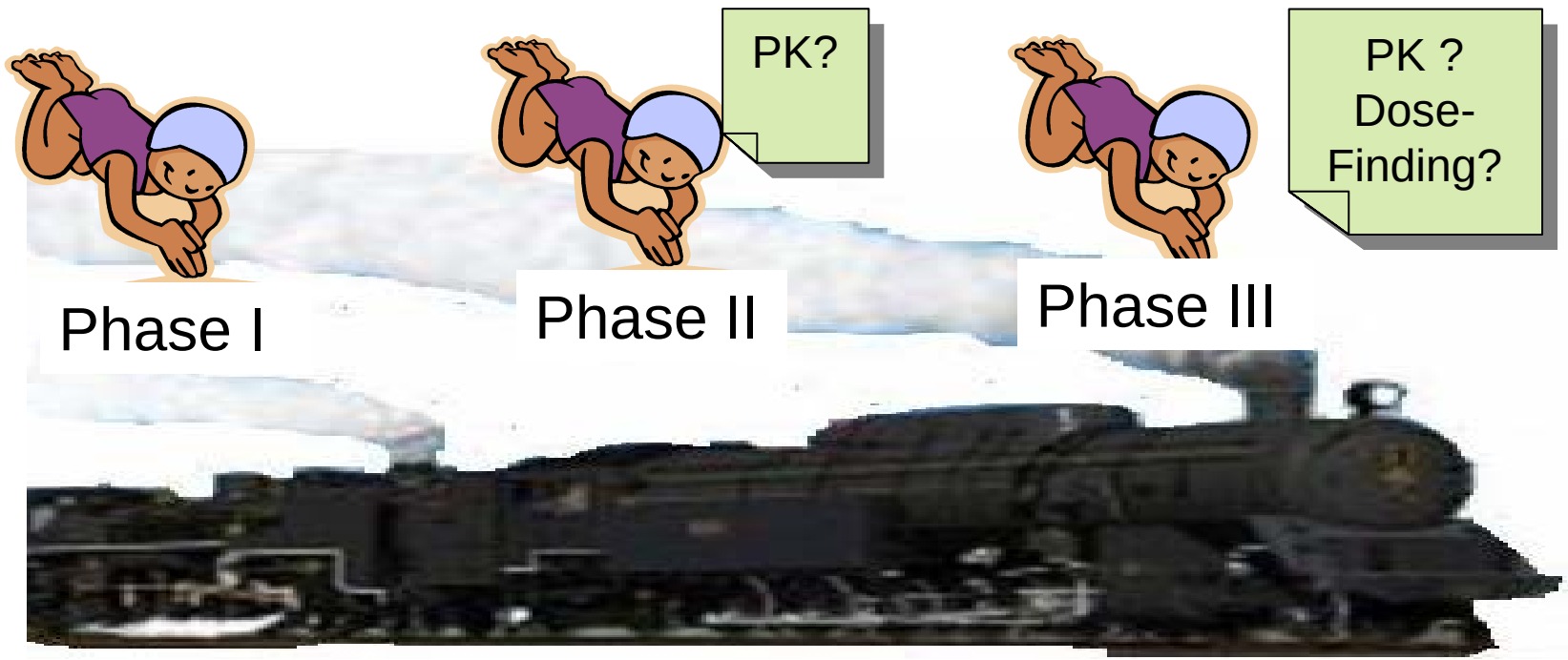
Similar Region :

- Intrinsic Factors
- Extrinsic Factors(medical practice, etc)
- GCP

One Gobal Protocol

- Presented by Masahiro Takeuchi in 2nd Kitasato University-Havard School -

When to jump into Global Clinical Development with what Data on own Population ?



Clarifying Ethnic Factors to enlarge Ethnic Basis should HELP !

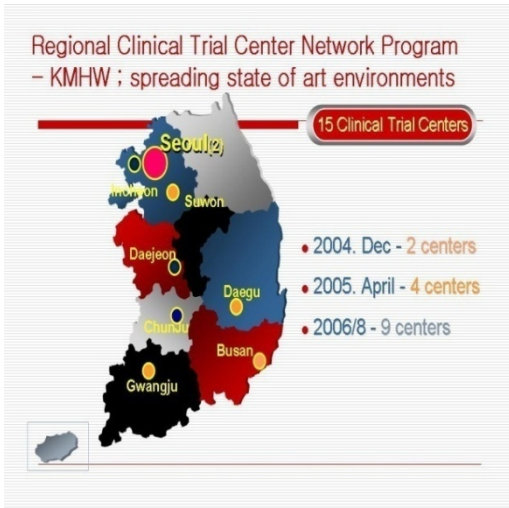
- Presented by Toshiyoshi Tominaga(MHLW) in Japan-Korea joint workshop, July, 18th, 2007 -

Challenges for implementation

- Qualification of Investigator
- Importance of IRB review
- Importance of SOP
- Need for Clinical Research Resources
- Need for Regulatory Service from Authorities
- Need for communication and harmonization with Foreign Authorities

Strong Supporting Plan

- **Supported plan for Clinical Centers by MOHW**
  - 9 Regional centers designated in 2004-2006
  - Support for Facilities, Operation systems, R&D etc.
  - $ 0.5 ~ 1 million/center/yr for 5 years



- **Ko-NECT**

(Korea National Enterprise of Clinical Trials)

  - Clinical Hub of North-East Asia
  - Regional centers will be increased by 15 centers until 2010
  - Regional centers will be network
  - Training center and Development center to support clinical trials

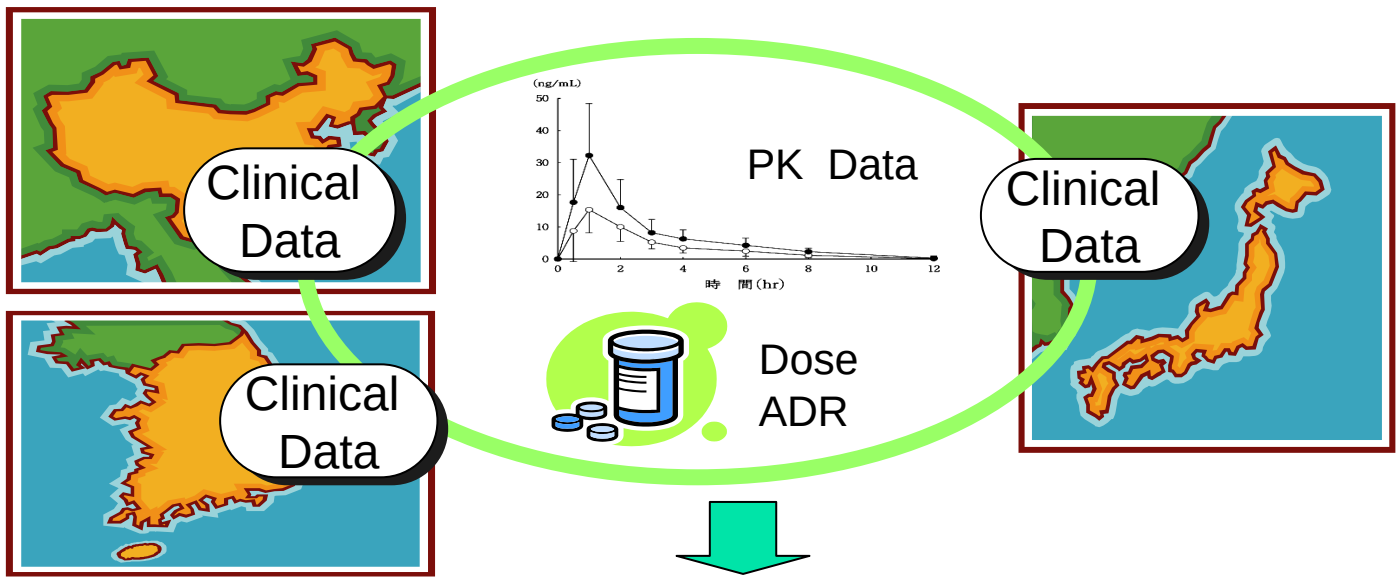
➢ MOHW : Ministry of Health and welfare

Korean Investigator's Contribution to Global Trials

More than these…..

- **Prof. Byung-Hee Oh: Cardiology, SNUH**
  Global PI of Aliskiren, Norvatis
- **Prof. Yoon-Ku Kang: Oncology, AMC**
  Global PI of Xeloda Phase III study in GC, Roche
- **Prof. Young-Joo Bang: Oncology, SNUH**
  Global PI of Sunitinib Phase II study in GC, Pfizer
- **Prof. Sun-Young Ra: Oncology, YUMC**
  AP PI of Sunitinib Phase II study in RCC, Pfizer
- **Prof. Sun-Woo Kim: Endocrinology, SMC**
  Global PI of Vildagliptin, Phase III study in T2DM, Norvatis
- **Dr. Jin Soo Lee: Oncology, NCC**
  Global PI of ZD6474 Phase III study for LC, AZ
- **Prof. Joon Soo Kwon: Psychiatry, SNUH**
  Global PI of 11286 Sertindole, Phase III study for schizophrenia, Lundbeck

Tripartite Cooperation to study Ethnic Factors



If Ethnic Factors are small,
Data from 3 Countries can be combined and analyzed
for quicker Delivery of Drugs in the Countries

- Presented by Toshiyoshi Tominaga(MHLW) in IFPMA, March, 12th, 2008 -

Cooperation among Korea, China and Japan

- Based on the currently available date, it is difficult to examine closely whether there is a difference in drug sensitivity caused by ethnic factors.
- Make a comparison of clinical data from Korea, China and Japan on the same products for the purpose of a more explicit comparison
- Establishment of action plan designed to collect sufficient data
  - Working group with tripartite reviewer and experts

Harmonization of East Asia

- Harmonization of International Standard
  - Korea isn't ICH member, but accepted ICH Guideline
  - Implementation of GLP, GCP, GMP, DMF
- Adoption of ICH CTD
  - step by step from New drugs(2009.3)
- Harmonization of Japan,US,EU
  → Harmonization of Japan,China,Korea
  - Compare the regulation, system, process etc

Evaluation of Multinational Clinical Trial Data

- Acceleration of participation in multinational clinical trials at the early stage
- Numerous participation simultaneously in multinational clinical trials with the same protocol
  - Acquisition of statistically significant figures
- Bridging study < Bridging data
- Change in evaluation policy based on accumulation of experience

Thank you!

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