Review Policies for Global Drug Development: Japan's Perspective

East Asian Pharmaceutical Regulatory Symposium 2008

April 15, 2008

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Pharmaceuticals and Medical Devices Agency (PMDA)

Why Global Drug Development?

- Objective of ICH
  - to ensure that safe, effective, and high quality medicines are **developed and registered in the most efficient and cost-effective manner**.
  - These activities have been undertaken to promote public health, **prevent unnecessary duplication of clinical trials in humans**, and minimize the use of animal testing without compromising safety and effectiveness.
- Drug-Lag Problem
  - Simultaneous multi-national drug development, NDA review, and approval etc...

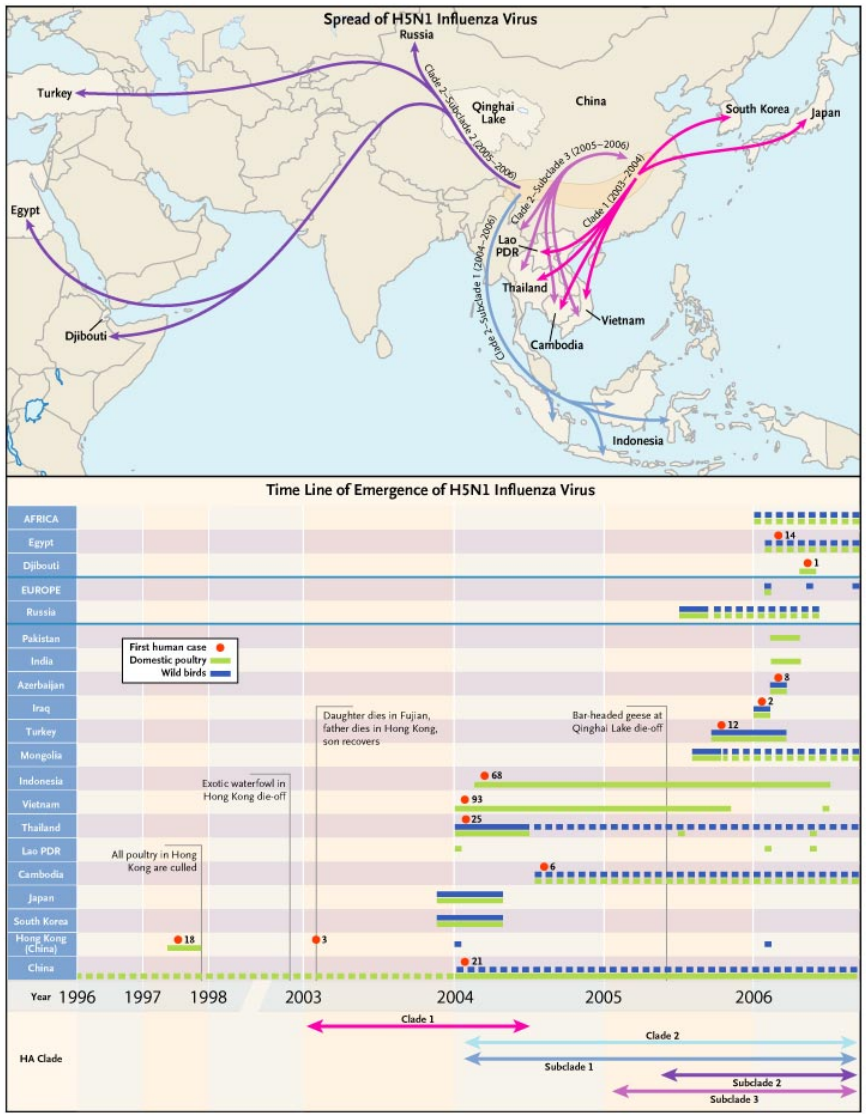
Why Global Drug Development?

- Participation of Asian countries in global drug development
  - Contribution to the global study
  - Planning and conduct of Asian study
  - More useful safety & efficacy data collection of Asian population
  - **Innovative New drugs from Asian area**

Health Risk in Asian Region/Population

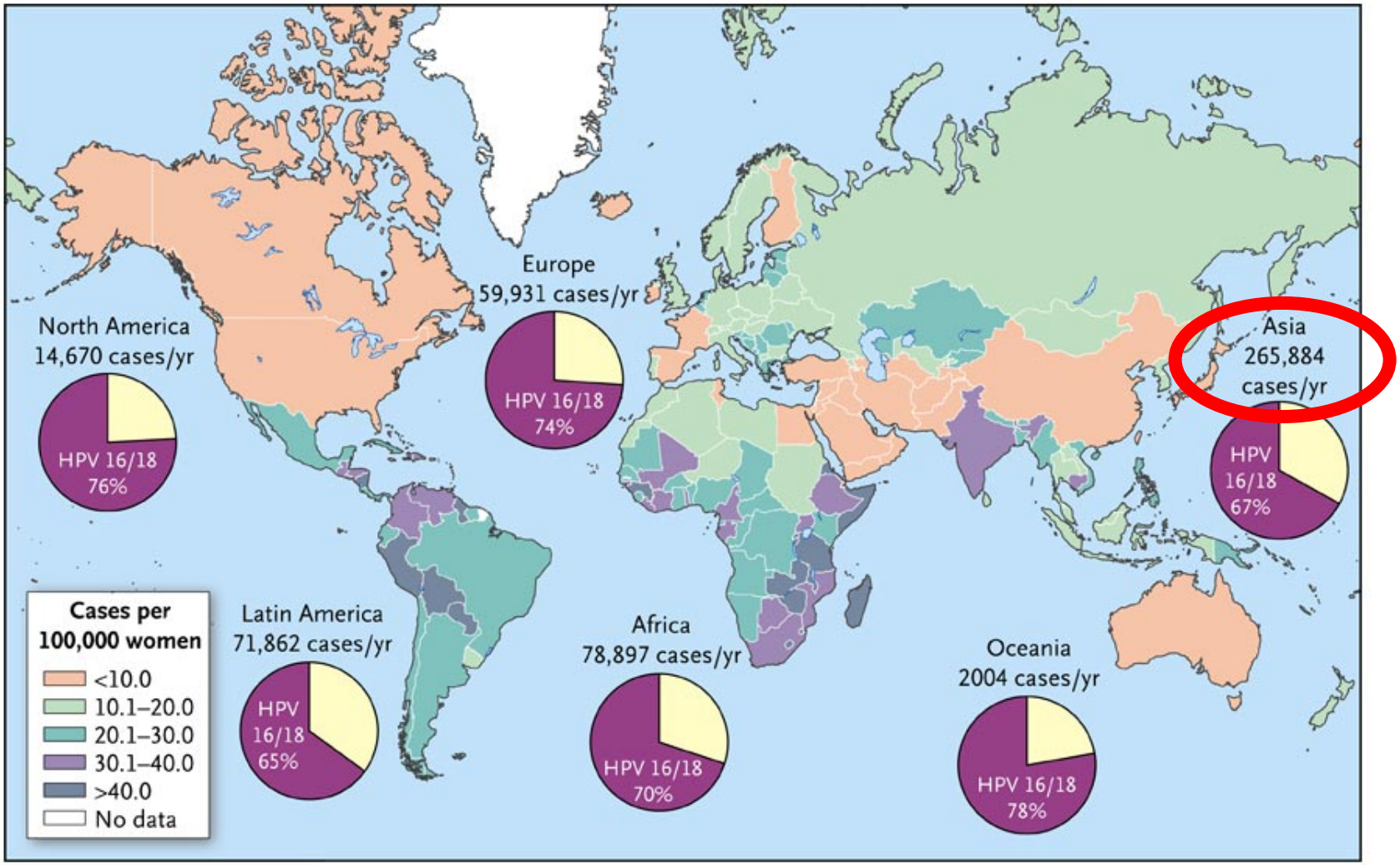
- Economic growth make people become health conscious
- Specific Health Risk in …..
  - Asian Region
  - Asian Population
- Aging population → lifestyle disease
- Emerging (rapid and/or steady) diseases

Asia as a Hot spots of Avian Flu (H5N1 influenza)



Webster R and Govorkova E. N Engl J Med 2006;355:2174-2177

Cervical Cancer and HPV vaccine
Big impact in Asian public health



Agosti J and Goldie S. N Engl J Med 2007;356:1908-1910

Asian participation in global drug development

- From the beginning of 21st century, East Asian countries took part in the multi-national clinical trials (MCTs)
- Korea, Taiwan, Hong-Kong, Singapore, etc. have much experience in planning and conducting the multi-national clinical trials
- Japan is running after….. But!

Current status of Japan

- ICH-E5 guideline (bridging study)
- ICH-E5 Q&A (Q11 for multi-national trials)
- Drug lag problem
- **Basic principles on global clinical trials**

  (Sep. 28th 2007)
- Rapid increase in planning MCTs (including Asian study)
- NDA approval by MCTs including Asian area

Guidance document for global studies

Japanese version

薬食審査発第0928010号
平成１９年９月２８日

各都道府県衛生主管部（局）長　殿

厚生労働省医薬食品局審査管理課長

国際共同治験に関する基本的考え方について

従来、我が国においては、ＩＣＨ－Ｅ５ガイドラインに基づく「外国臨床データを受け入れる際に考慮すべき民族的要因について（平成10年8月11日医薬審第762号 厚生省医薬安全局審査管理課長通知）」により、いわゆる「ブリッジング」による海外臨床試験成績を承認申請資料として活用することを認めており、また、欧米諸国における市販後調査等の結果についても必要に応じ承認審査に際して活用しているところである。

http://www.pmda.go.jp/operations/notice/2007/file/0928010.pdf

English version

September 28, 2007
Notification No.0928010

Attention to:
Commissioner of Prefectural Health Supervising Department

From Director of Evalution and Licecing Division,
Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

Basic principles on Global Clinical Trials*

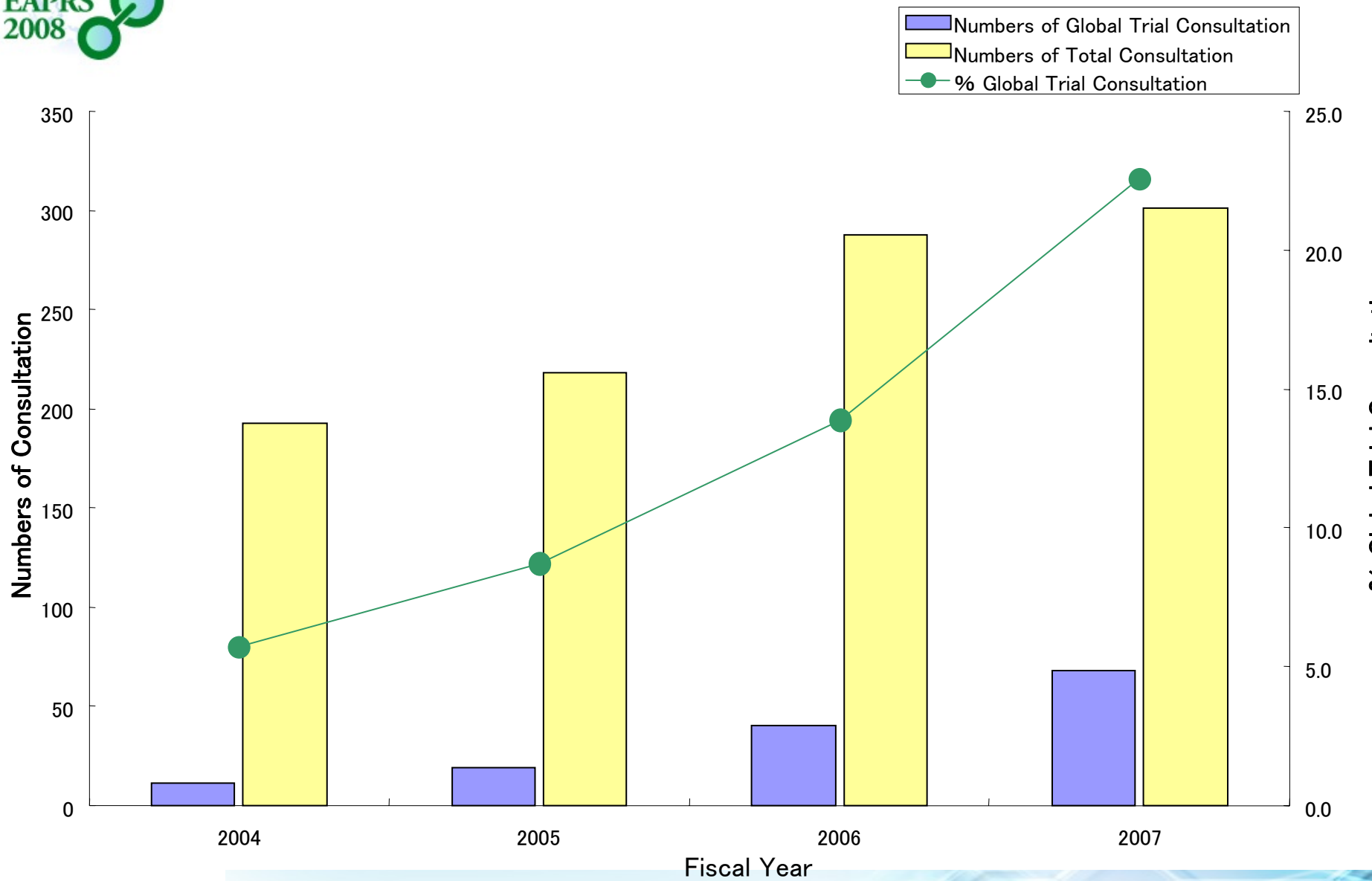
Up to the present according to "Ethnic Factors in the Acceptability of Foreign Clinical Data" based on ICH-E5 guideline (Notification No. 762, Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health and Welfare, dated August 11, 1998), utilizing foreign clinical trial data in a new drug application what is called "Bridging" has been accepted in Japan, and post-marketing data in USA and EU have been taken into consideration in a review for regulatory approval where necessary.

http://www.pmda.go.jp/operations/notice/2007/file/0928010-e.pdf

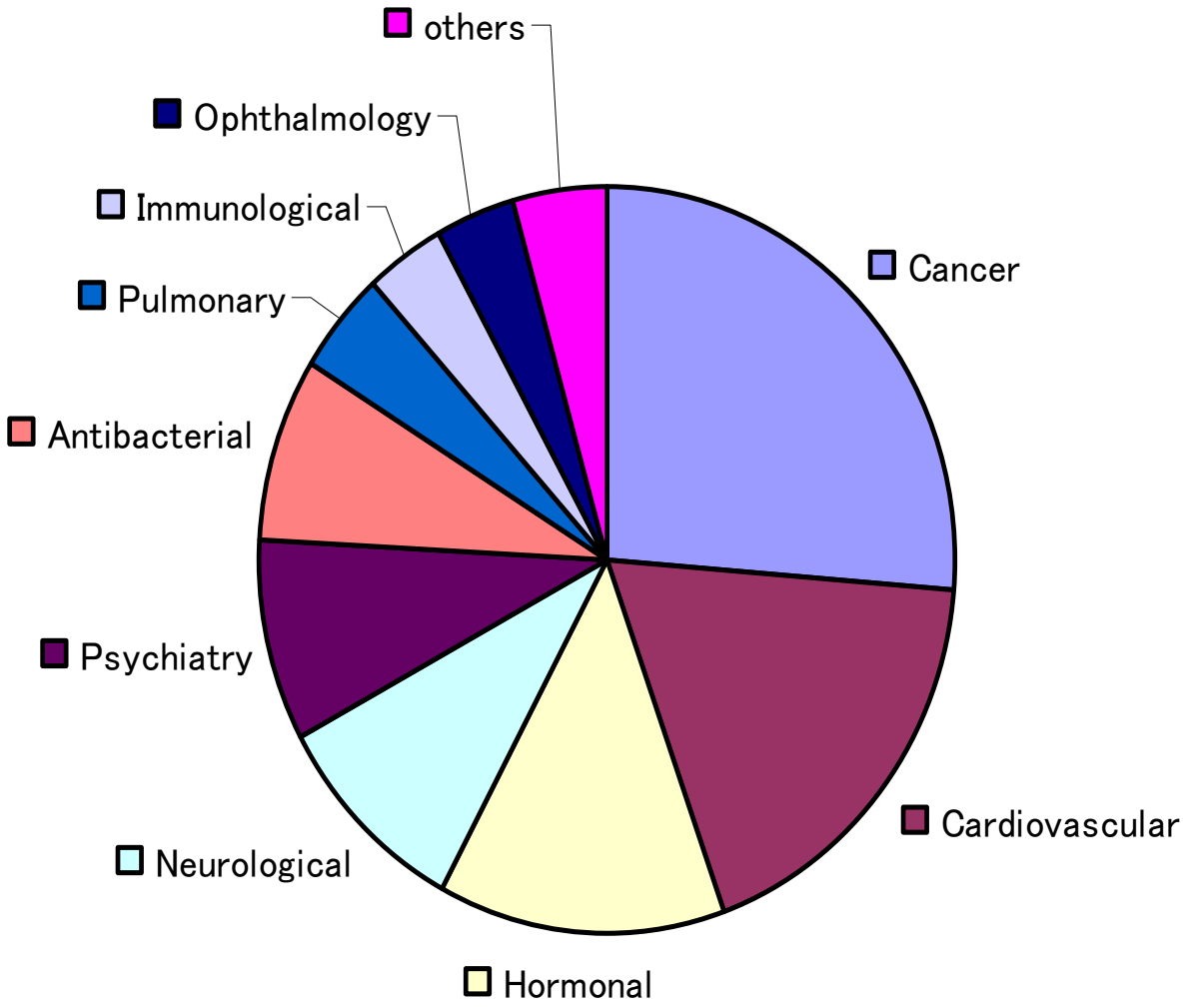
Message of the document

- Both regulatory authority and industry would like to participate global drug development in a timely manner
- Recommends to participate earliest possible timing in clinical development
- Pro-Active, Constructive, Scientific, flexible discussion with PMDA is encouraged

Global clinical trials consultations



Global clinical trial consultations (by therapeutic area)



IND notification of MCTs

- FY2007: 508 IND notice (total)
- 18 company notified to conduct 38 MCTs
  - Japan based 5 company 8 protocol
  - **Global pharma 13 company 30 protocol**
- Development Phase
  - P-I : 1, P-II : 5, **P-III : 32**
- Therapeutic area
  - **Oncology: 17**, CV: 5, CNS: 4, Respiratory 3

Example from approved NDA

Approved on **Apr. 20th 2006**

- **Detrusitol (Tolterodine tartrate)** （Pfizer）
  - Korea-Japan study for bridging (n≒600)
  - OAB
- **NU-LOTAN (Losartan potassium)** （BANYU）
  - RENAAL study as global study (n≒1500)
  - Nephropathy in Type 2 Diabetic Patients

Approved on **Feb. 29th 2008**

- **Herceptin (Trastuzumab)** (Chugai)
  - HERA study as global study (n≒3400 asian≒400)
  - Adjuvant therapy for HER2-positive breast cancer

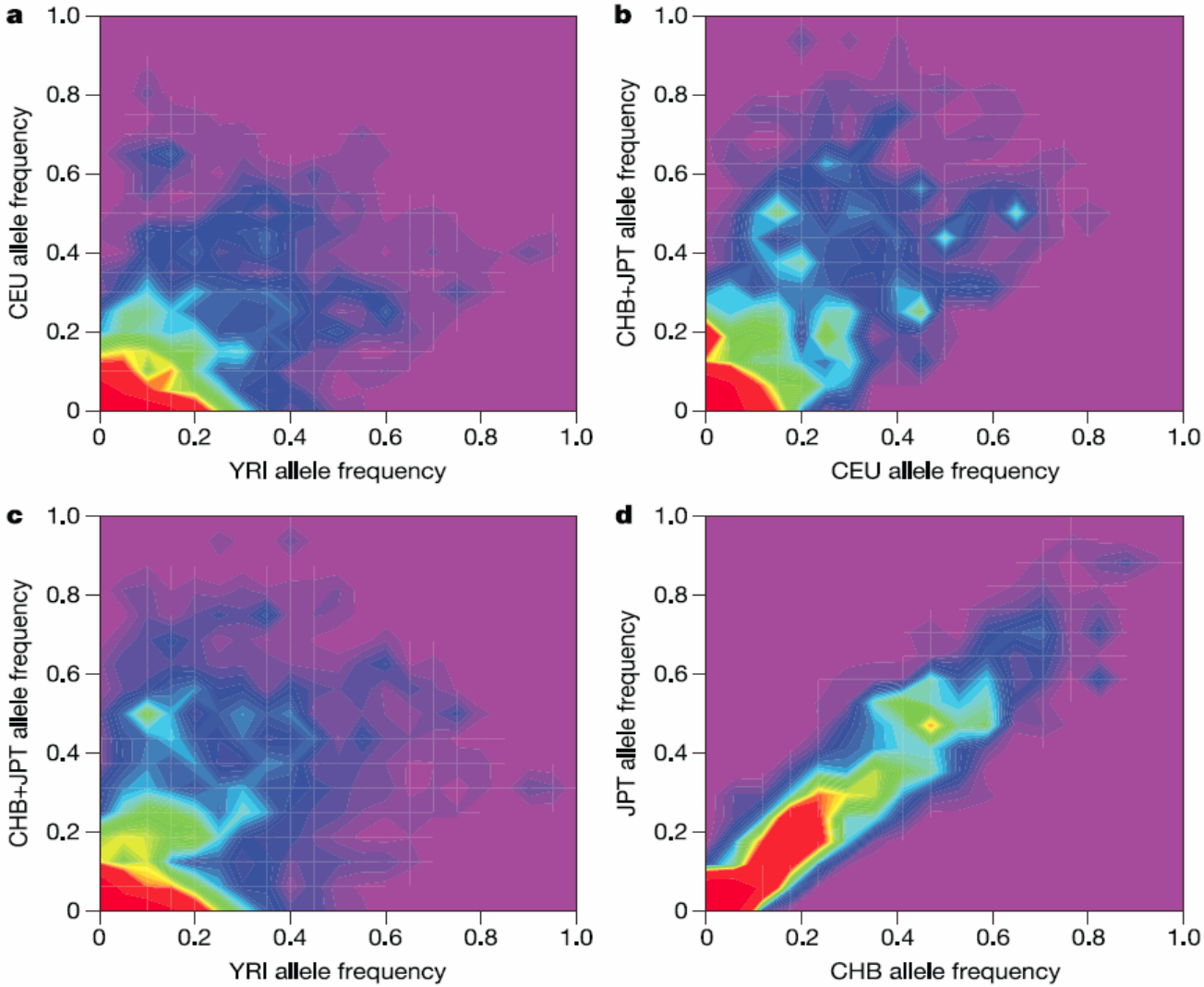
Review report

http://www.info.pmda.go.jp/shinyaku/r07/0104/45004500_21300AMY00128_A100_1.pdf

Scientific/Practical discussions

- Ethnic similarities
- Ethnic differences
  - Caucasian vs. Asian
  - Within Asian populations
- Various cultures, languages, religions, medical practices
- Standardized practice between trial sites (hospitals, medical institutes, etc…)

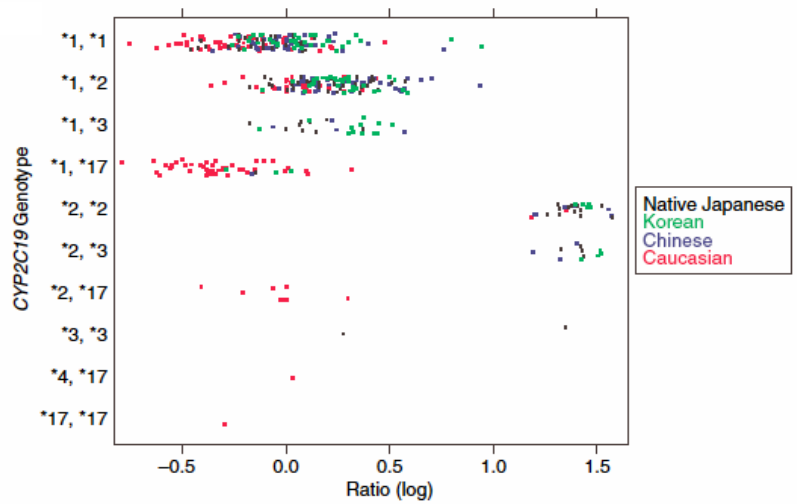
Japanese genome look alike Chinese

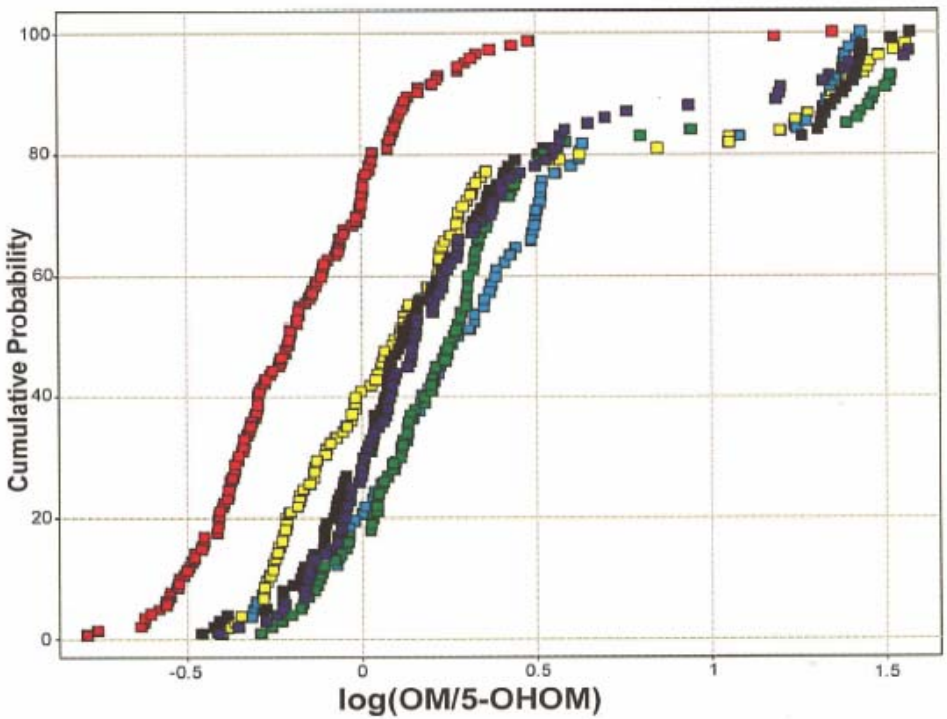


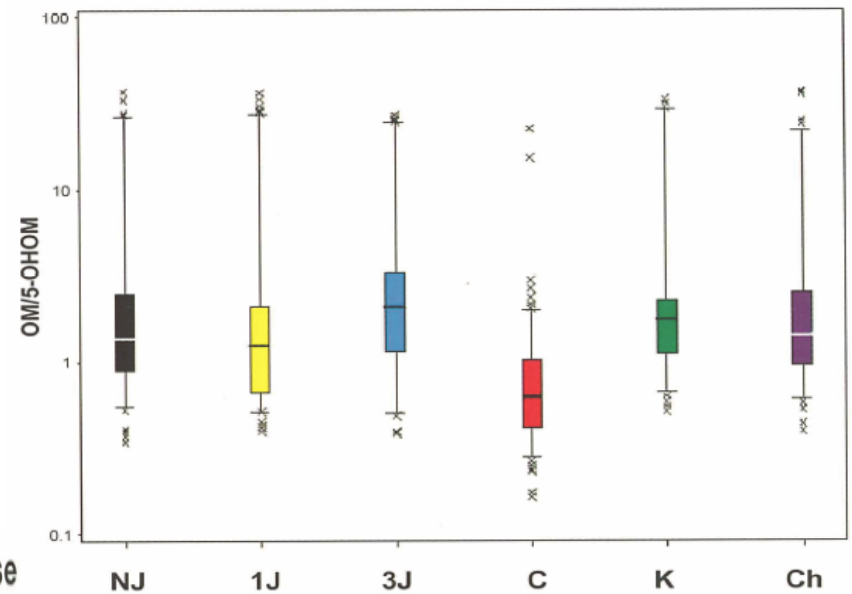
The International HapMap Consortium. A haplotype map of the human genome. Nature 2005;437:1299-320

Ethnic difference in CYP2C19

- Asian ≒ Japanese
- Asian ≠ Caucasian







Native Japanese, 1G-Japanese, 3G-Japanese, Caucasian, Korean, Chinese

Myrand SP et al, Clin Pharmacol Ther, Jan 30th, 2008

Relationship between SJS/TEN and HLA alleles

Table 1 **Frequency of *HLA* alleles in patients with Stevens–Johnson syndrome**

HLA allele	*CBZ–SJS*	*CBZ-tolerant*	*Normal*
*B*1502*	44 (100%)	3 (3%)*	8 (8.6%)†
*Cw*0801*	41 (93.2%)	17 (16.8%)	13 (14%)
*A*1101*	36 (81.8%)	51 (50.5%)	53 (57%)
*DRB1*1202*	33 (75%)	12 (11.9%)	18 (19.4%)
*B*1502, Cw*0801*	41 (93.2%)	3 (3%)	7 (7.5%)
*B*1502, A*1101*	36 (81.8%)	2 (2%)	6 (6.5%)
*B*1502, DRB1*1202*	33 (75%)	1(1%)	5 (5.4%)
*B*1502, Cw*0801, A*1101, DRB1*1202*	29(66%)	0 (0%)	3 (3.2%)

Frequencies (by number and percentage) of individual or combined loci of the *B*1502* ancestral haplotype are shown in patients with carbamazepine-induced Stevens–Johnson syndrome (CBZ–SJS; $n = 44$), and in carbamazepine-tolerant ($n = 101$) and normal subjects ($n = 93$). For methods, see supplementary information.

*Odds ratio (CBZ–SJS/CBZ-tolerant): 2,504 (95% CI, 126–49,522); corrected *P* value $P_c = 3.13 \times 10^{-27}$.

†Odds ratio (CBZ–SJS/normal): 895 (95% CI, 50–15,869); $P_c = 1.38 \times 10^{-21}$.

Chinese

WH Chung, SI Hung, HS Hong, MS Hsih, LC Yang, HC Ho, JY Wu, and YT Chen
Nature, Apr 2004; 428: 486.

TABLE. Frequency of HLA Class I Alleles in Patients with Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN)

	SJS/ TEN with Ocular Complications		Control Subjects				
HLA Allele	No.	%	No.	%	*P* value (χ^2)	Corrected *P**	Odds Ratio
Carrier frequency	(n = 40)		(n = 113)				
A*0206	19/40	47.5%	17/113	15.0%	0.00003	<0.0005	5.1
A*1101	1/40	2.5%	23/113	20.4%	0.0076	NS	–
Gene frequency	(n = 80)		(n = 226)				
A*0206	21/80	26.3%	19/226	8.4%	0.00005	<0.0005	3.9
A*1101	1/80	1.3%	26/226	11.5%	0.0055	<0.05	0.1

*: Corrected *P* is *P* after correction for multiple (9) comparisons.

Japanese

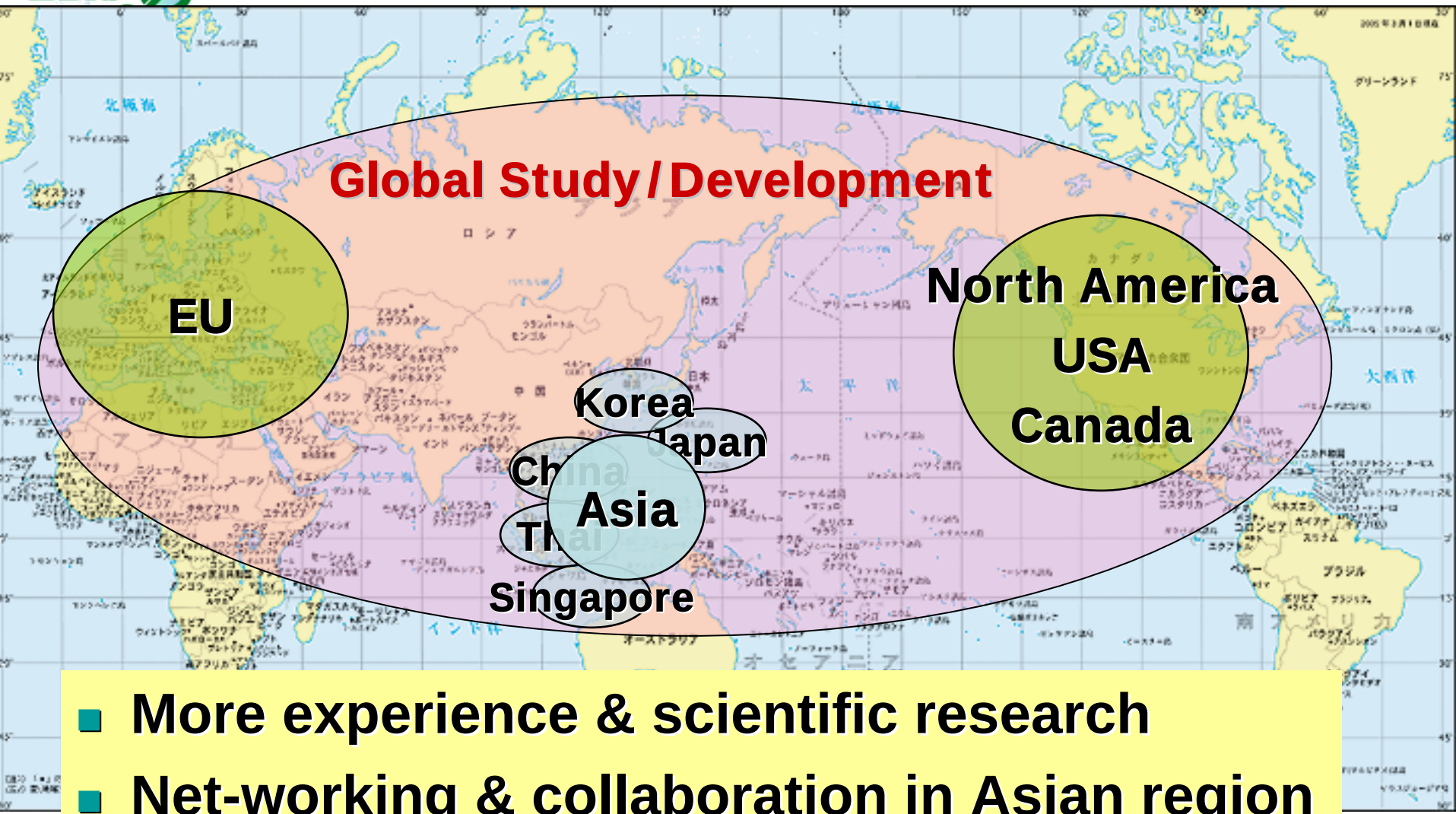
M Ueta, C Sotozono, K Tokunaga, T Yabe, and S Kinoshita
Am J Ophthalmol, Feb 2007; 143: 367-8.

Ethnic difference in HLA-B*1502

Ethnic group	prevalence
Chinese	1.9-7.1 %
Japanese	<0.3 %
Thailand	8.5 %
Singapore	5.7 %
Korean	0.2 %
Caucasian	0-1 %

- Difference exists within Asian populations

Asian drug development as global player



- More experience & scientific research
- Net-working & collaboration in Asian region
- Develop best fit drugs for Asian populations

Very near future style of Global Development (Asia + US + EU)

- Asian drug development as a part of global development is very important
- Positive dialog about Asian Clinical Trial Network for information/experience exchange
- Challenge to conduct **Asia**+EU+US Study
- Let's try for a win-win situation

Key message to industry

- **Join and contribute Global Drug Development**
  - Encourage to participate, plan, conduct MCTs
- **Patient Safety Ensuring (Vigilance system)**
  - Clinical Developing Phase (up to thousands, limited)
  - Post-marketing Phase (up to millions, unlimited)
- **Patient Benefit Ensuring**
  - Ensure patient's accesses to innovative products
- **Quality & Reliability of Data/Products**

was not built in one day! (GLP, GCP, GMP)

All the players in good harmony

"for the welfare of patient!"