Applications of PGx in PK at PMDA experience and expectations

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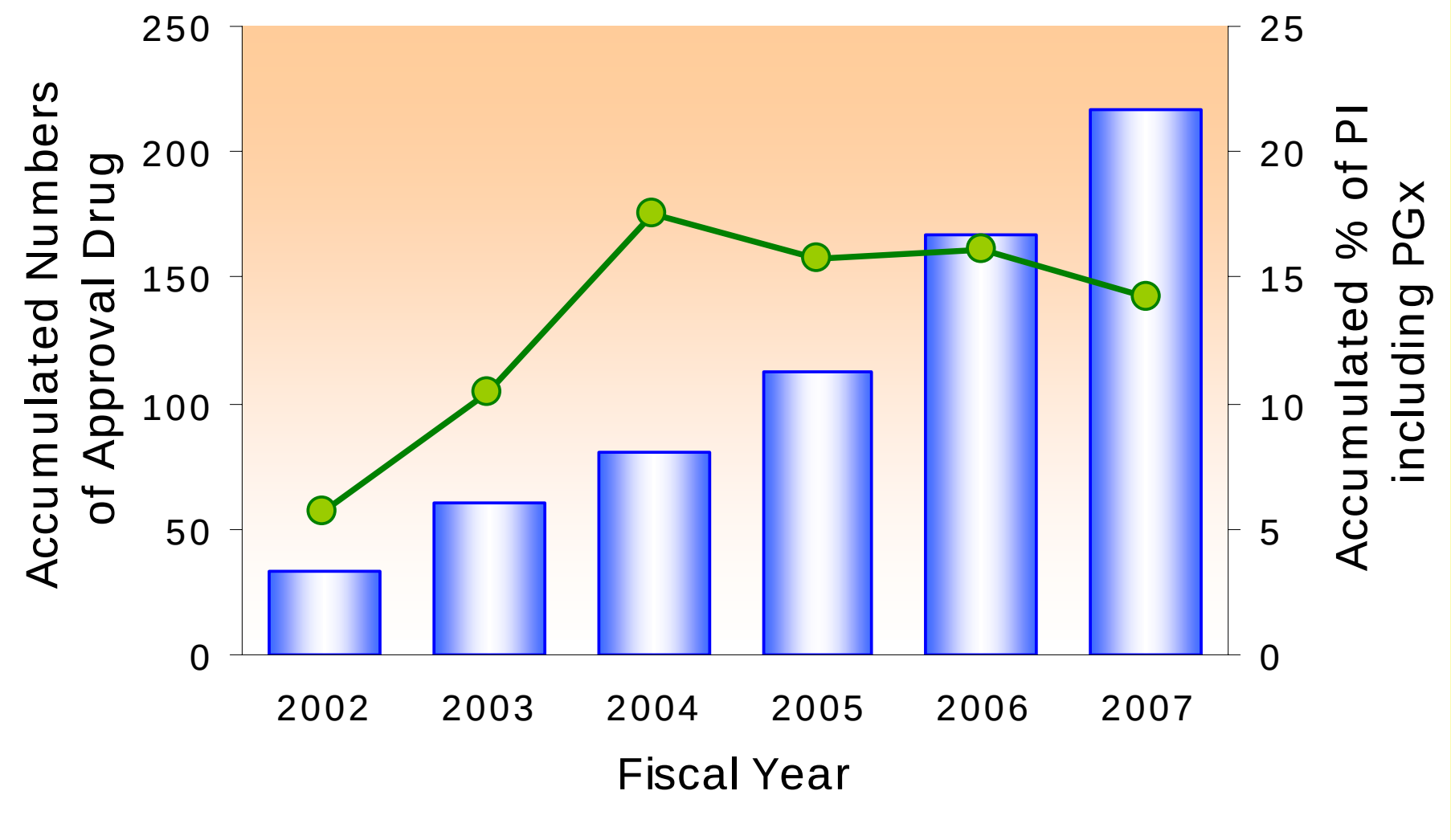
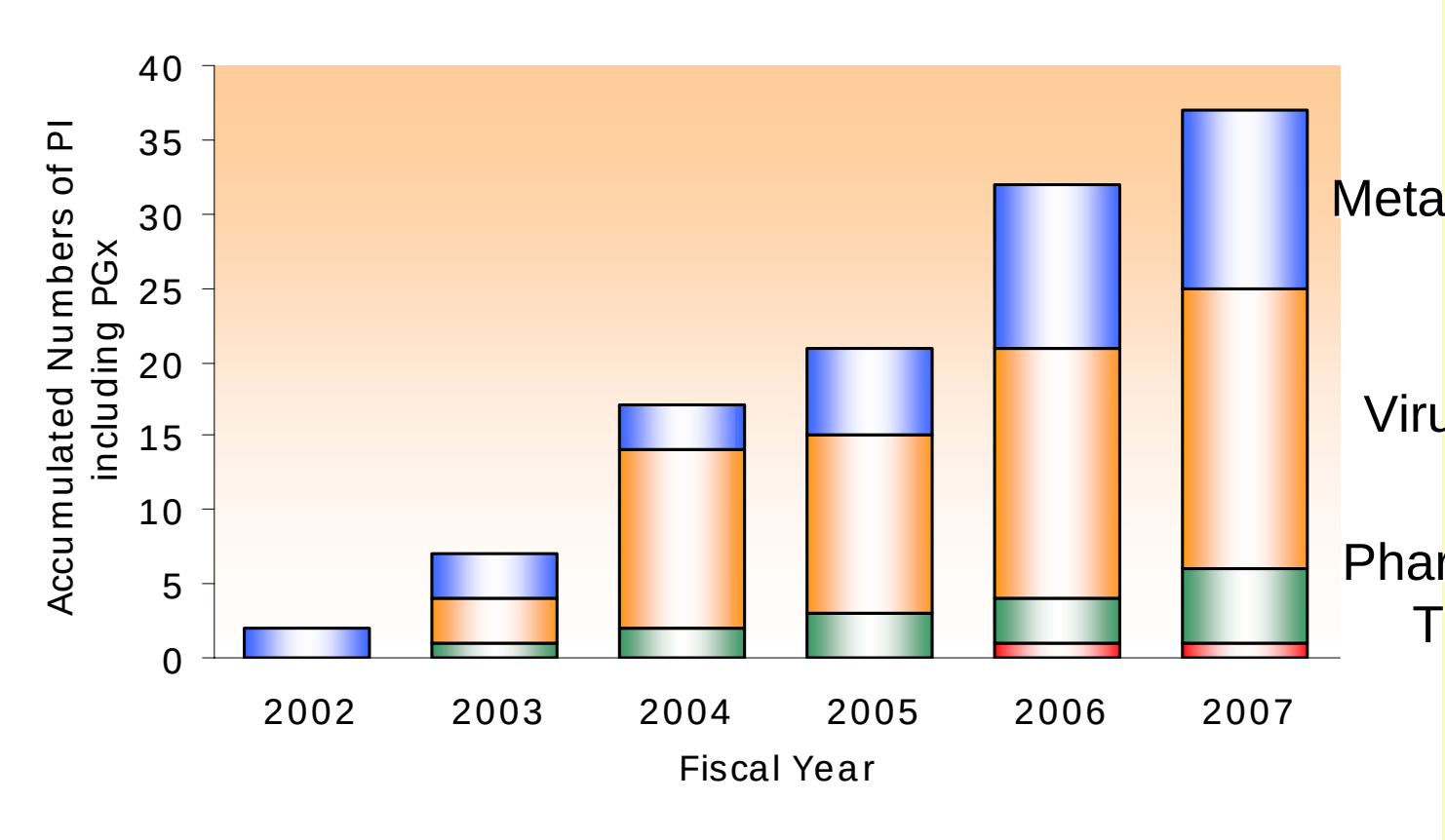
Trends of PI including PGx information



Trends of PI including PGx information



Guidances & Notifications related to PGx

Title	Date	Notifier
Points to consider on Clinical Trials using PGx	September 2008	PFSB/ELD
Points to consider for evaluating genotyping platforms based on DNA chips	April 2008	PFSB/ELD
Terminology in pharmacogenomics (ICH-E15)	January 2008	PFSB/ELD and PFSB/SD
Request to cooperate in research regarding severe cutaneous adverse reactions	June 2006	PFSB/SD **
Submission of information to regulatory authorities for preparation of guidance on the use of Pharmacogenomics in clinical studies.	March 2005	PFSB/ELD
Guidance on methods of drug interaction studies.	June 2001	PFSB/ELD
Guidance on clinical pharmacokinetics studies of Pharmaceuticals	June 2001	PFSB/ELD *

* PFSB/ELD: Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare (MHLW)

** PFSB/SD: Safety Division, Pharmaceutical and Food Safety Bureau, MHLW

Points to Consider on Clinical Trial using Pharmacogenomics

(Final Notification was published on Sep. 30th, 2008)

- This Q&A document describes basic principles on clinical trials using PGx.

Key Points

- Encourage to examine genetic effects in drug response
- Clarify a role of IRB on clinical study using PGx
- Clarify issues to be described in study protocol
- Clarify basic principles for information feed back to a subject
- Encourage to discuss with PMDA

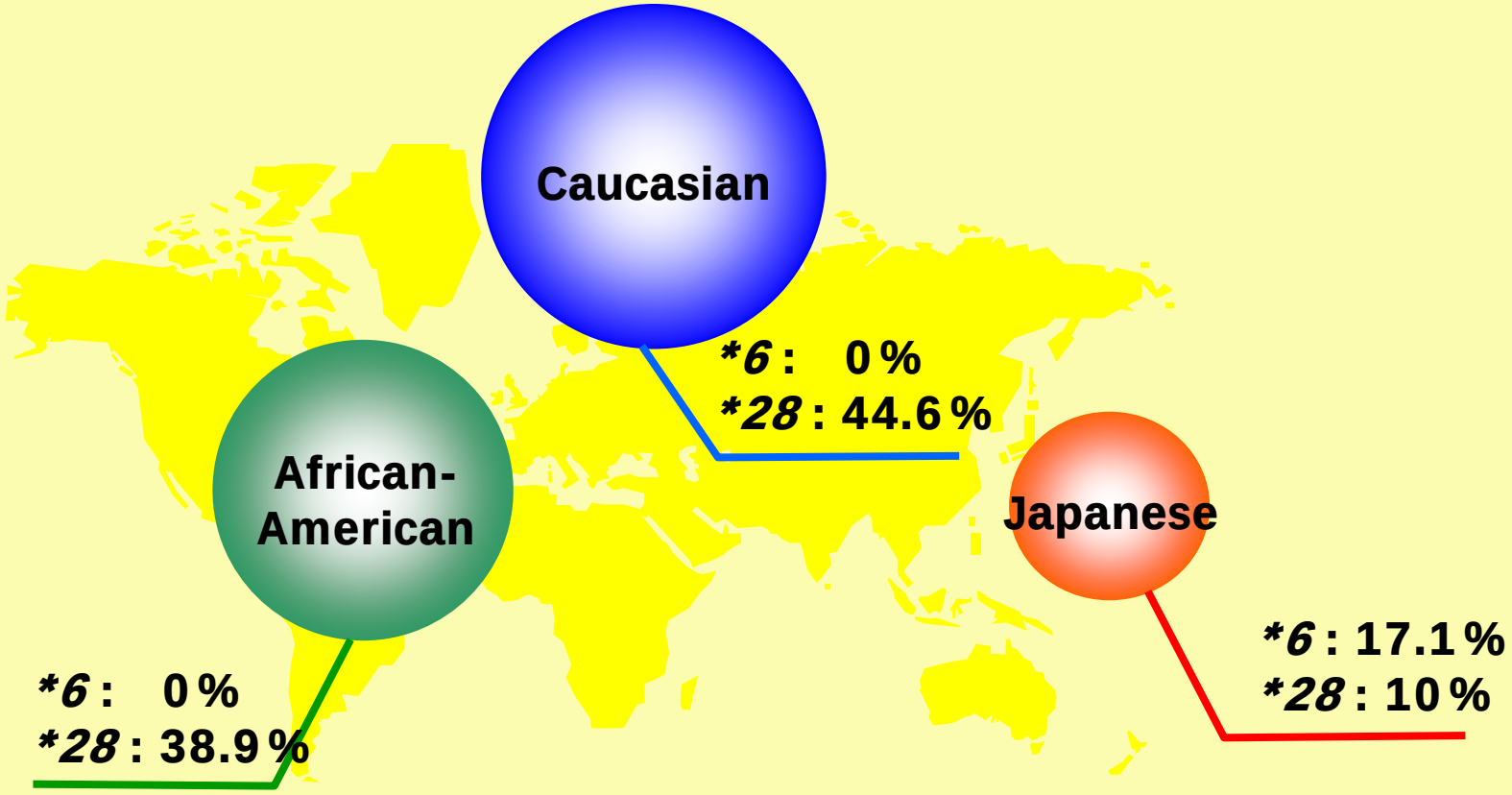
Major Reimbursable PGx tests in Japan

Genomic biomarker	Target	Date to be covered by NHI
UGT1A1	Irinotecan-induced Neutropenia	November 2008
Wilms tumor-1 mRNA	Acute Myelocytic Leukemia	November 2007
EGFR mutations	Lung Cancer	June 2007
KIT mutations	Gastrointestinal Stromal tumor	June 2007
Mutations in HIV	HIV	April 2006
Major bcr-abl mRNA (TMA)	Chronic Myelogenous Leukemia	November 2004
Mutations in HBV precore, Mutations in HBV core promoter (PCR)	HBV	July 2003
Her2/neu (*erbB2*) (FISH)	Breast Cancer	April 2003

Biomarker & Ethnic Differences (1)

Irinotecan & UGT1A1

Ethnic difference in allele frequencies of *UGT1A1 *6* and **28* mutant genes



Kaniwa N et al. Drug Metab Dispos (2005)

Examples of Package Insert including PGx information

※※2008年６月改訂(第11版)
※2007年７月改訂

貯　　法	室温保存
使用期限	容器および外装に記載

抗悪性腫瘍剤

劇薬・指定医薬品・処方せん医薬品*

※※カンプト®点滴静注40mg
※※カンプト®点滴静注100mg

※※イリノテカン塩酸塩水和物点滴静注

※※CAMPTO® 40mg for I.V. infusion
※※CAMPTO® 100mg for I.V. infusion

日本標準商品分類番号
87424

		カンプト点滴静注40mg	カンプト点滴静注100mg
※※	承認番号	22000AMX01082	22000AMX01084
※※	薬価収載	2008年６月	
	販売開始	1994年４月	
	再審査結果	2007年６月	
	効能追加	1995年９月	
	国際誕生	1994年１月	

＊注意－医師等の処方せんにより使用すること

- **Important Precautions**

※※(10)　本剤の活性代謝物(SN-38)の主な代謝酵素であるUDP-グルクロン酸転移酵素(UDP-glucuronosyltransferase、UGT)の２つの遺伝子多型(*UGT1A1*6*、*UGT1A1*28*)について、いずれかをホモ接合体(*UGT1A1*6/*6*、*UGT1A1*28/*28*)またはいずれもヘテロ接合体(*UGT1A1*6/*28*)としてもつ患者では、UGT1A1のグルクロン酸抱合能が低下し、SN-38の代謝が遅延することにより、重篤な副作用(特に好中球減少)発現の可能性が高くなることが報告されているため、十分注意すること(「薬物動態」、「臨床成績」の項参照)[1)~3)]。

Biomarker & Ethnic Differences (2)

HLA-B*1502 & SJS/TEN

Han-Chinese-SJS/TEN and HLA*B1502

Study Site	Total CBZ-SJS/TEN patients	Patient with HLA-B*1502 positive	Ethnic background of the subjects and the place of birth	Reference
Taiwan	60	59	Han Chinese (53 were born in Taiwan, and 1 in US, 1 in Hong Kong, 4 in Mainland China)	• *Nature*, 2004 Apr 1; 428 , (6982) :486. • Pharmacogenetics and Genomics, 2006, 16, p297-306
Taiwan	44	44	Han Chinese (41 were born in Taiwan, and 3 in Mainland China)	• Unpublished data (By Chen et al.)
Hong Kong	4	4	Han Chinese (All 4 were born in Hong Kong)	• Epilepsia. 2007 , may;48(5):1015-8
France	12	4	4 subjects were born in China, Vietnam, Cambodia, and Reunion island	• The Pharmacogenomics J. (2006),1-4
UK	58	1	Descendant from Thailand	• Pharmacogenomics, 2006, 7, p813-818 (by Alfirevic A Et al.)
Australia	-	1	Descendant from Thailand	• 2nd international drug hypersensitivity conference

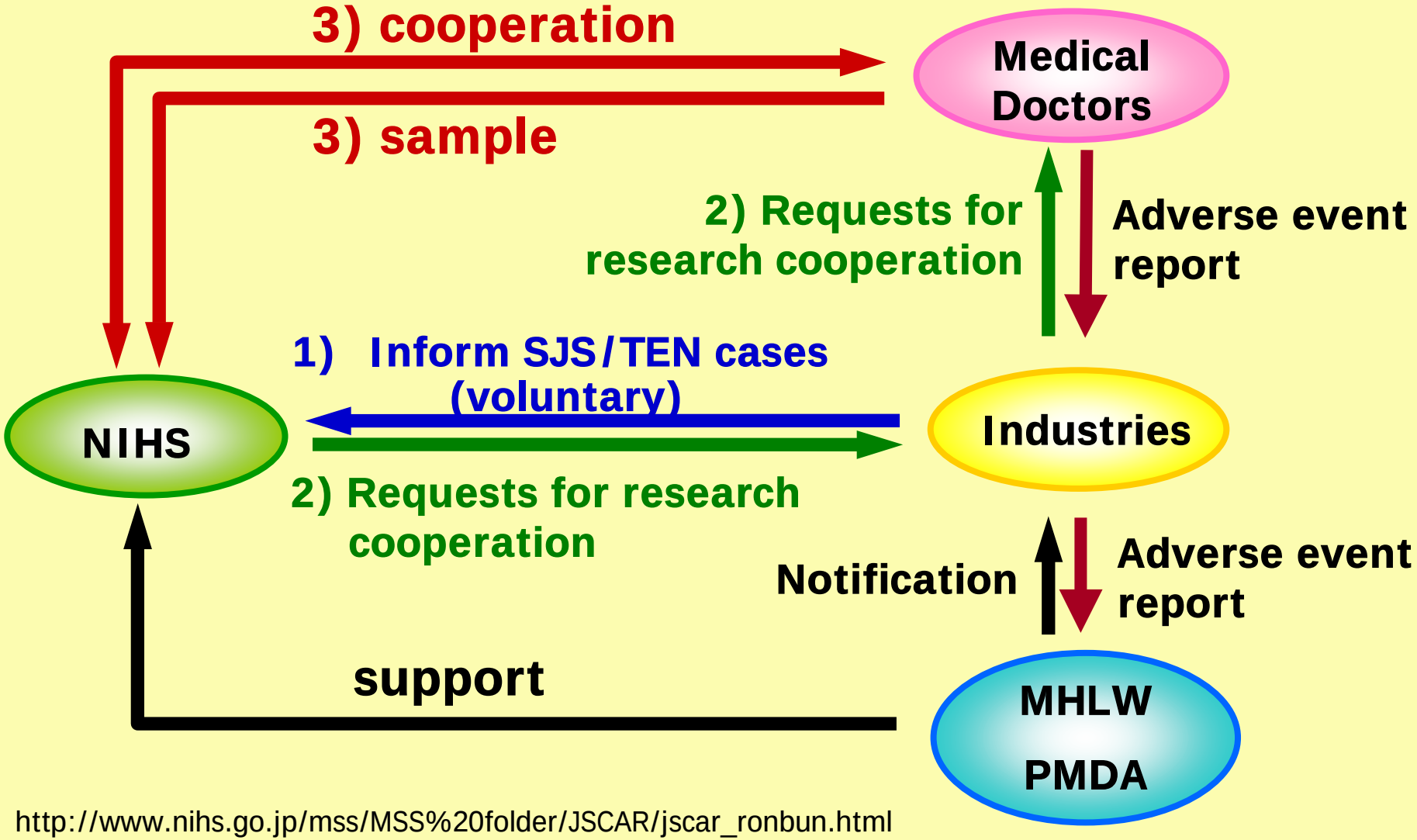
Dr Chang CF, APEC PRS, 2007

Ethnic differences in HLA-B*1502

Ethnic group	prevalence
Han-Chinese	1.9-7.1 %
Thai	8.5 %
Singaporean	5.7 %
Korean	0.2 %
Japanese	0.1 %
Caucasian	0-1 %

- Differences exist even among Asian populations

Framework of NIHS research regarding SCAR



http://www.nihs.go.jp/mss/MSS%20folder/JSCAR/jscar_ronbun.html

Japanese-SJS/TEN and HLA*B

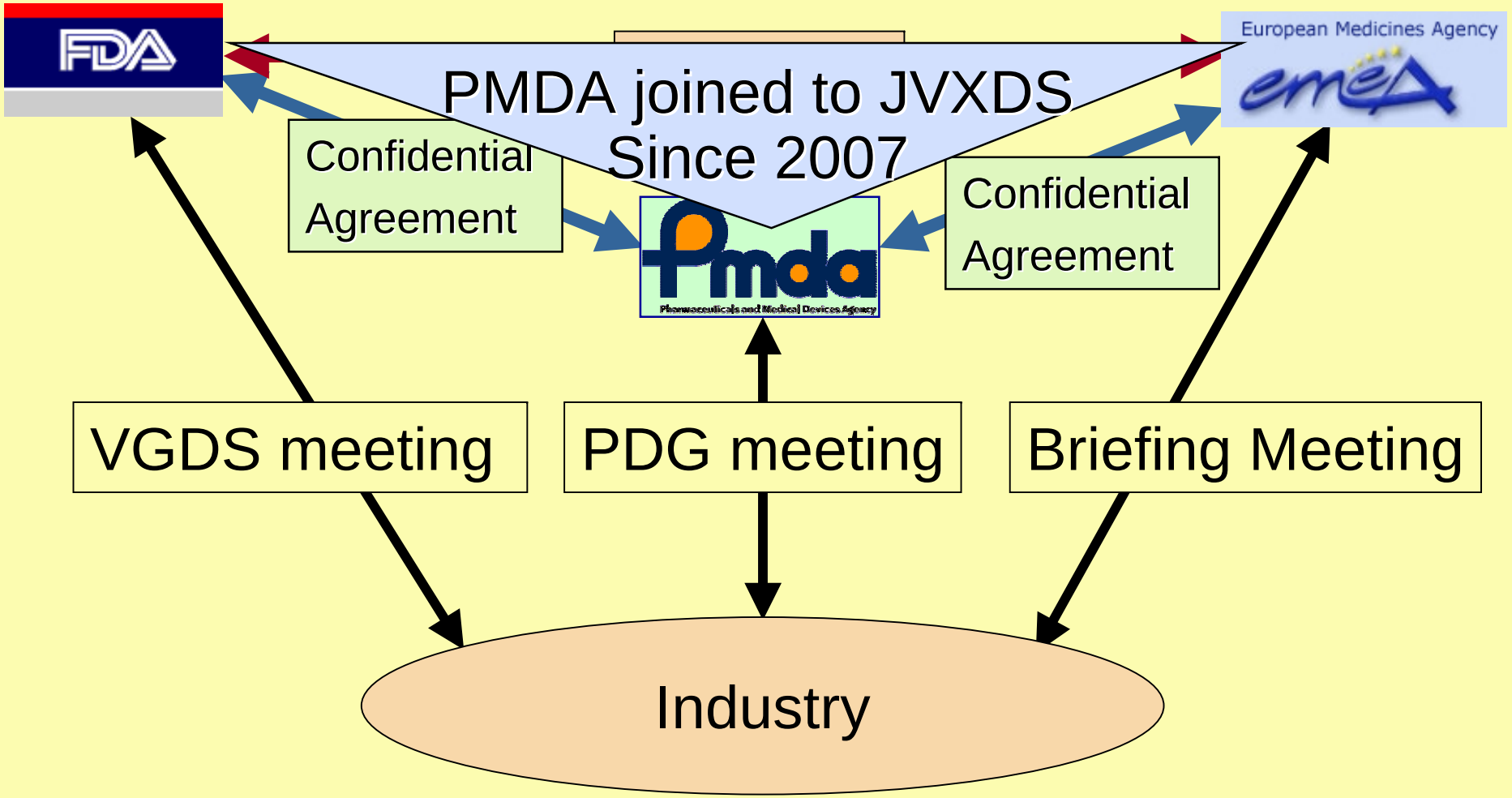
ID number	Sex	Age (years)	Disease	Aromatic anti-epileptic drugs prescribed	Severity score in ophthalmic disorders	*HLA-B* diplotype
1	M	73	SJS	Carbamazepine	1	*1511/*4801
2	F	42	SJS	Carbamazepine	3	*4001/*5201
3	M	45	SJS	Carbamazepine	3	*4801/*5601
4	M	54	SJS	Carbamazepine	0	*1501/*3501
5*	F	6	SJS	Carbamazepine	Severity unknown	*4006/*5101
6*	F	52	SJS	Carbamazepine/zonisamide	Severity unknown	*4601/*5901
7	M	17	TEN	Carbamazepine/zonisamide	3	*4601/*5601
8	M	67	SJS	Phenytoin	Ocular involvement unknown	*4001/*4601
9	F	5	SJS	Phenytoin	0	*5504/*6701
10	F	64	TEN	Phenytoin	3	*1501/*5101
11	F	56	TEN	Phenytoin	0	*1501/*5401
12	M	6	SJS	Phenobarbital	Severity unknown	*1501/*5101
13	M	69	SJS	Phenobarbital	1	*1501/*5101
14	F	42	TEN	Phenobarbital	0	*5101/*5401
15	M	25	SJS	Zonisamide	2	*1301/*4601
16	F	71	SJS	Zonisamide	1	*4002/*5101
17	M	52	TEN	Zonisamide	Severity unknown	*3501/*4601
18	M	78	TEN	Zonisamide	Severity unknown	*3901/*6701

These patients were reported in the previous report [10]. F: Female; M: Male; SJS: Stevens–Johnson syndrome; TEN: Toxic epidermal necrolysis.

Kaniwa N et al, Pharmacogenomics, 9: 1617-1622, 2008

Biomarker Qualification

International Biomarker Qualification
-Regulatory Collaborations-



Future Tasks in PGx

- General principles on PGx clinical trials

  Q&A was published in Sep 2008

- Genomic biomarker qualification

  ICH E16 is drafting

  draft will be available by next summer

- Clinical trial designs using PGx
- PGx test availability (co-development)
- PGx data handling in approval process

Near Future

Healthcare Insurance Card:
001279541235
2015/01/01
Name: ???????
Address: XXXXXXXX
Sex: Male
Race: Japanese
Birthl: 1950/01/01

Electric Medical Record (History, Genetic Inf. etc)

Diagnosis

A selection of Drugs and Doses

Administer a right drug at a right dose in a right timing

Information

- **PMDA HOMEPAGE**
  http://www.pmda.go.jp/english/index.html

- **PMDA DRUG Information Search**
  http://www.info.pmda.go.jp/info/search.html

- **E-mail:**
  uyama-yoshiaki@pmda.go.jp

Thank you for your attention