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EXPERT REVIEWS

Current Japanese regulatory situations of pharmacogenomics in drug administration

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Pharmacogenomics (PGx) has the potential impact to improve drug-development efficiencies and proper usages of drugs in clinical practice. However, in order to translate PGx into practical applications, multidisciplinary challenges, such as cost and time in development, processes of genomic biomarker qualification, PGx test availabilities and reimbursements, and education on PGx, still remain in clinical, pharmaceutical and regulatory settings. Japanese regulatory bodies for drug approval (i.e., Ministry of Health, Labour and Welfare and Pharmaceutical and Medical Devices Agency) have been taking proactive actions, both internally and internationally, toward translating PGx from bench to bedside. In this article, we summarize the current situations and projects in regulatory implementations of PGx in drug administrations in Japan, including activities to promote PGx-based drug/device developments and therapies. Moreover, we also discuss the future tasks for utilization of PGx in drug evaluations and clinical practices.

KEYWORDS: drug development • drug evaluation • genomic biomarker • Japan • Ministry of Health Labour and Welfare • Pharmaceutical and Medical Devices Agency • pharmacogenomics

The inter-individual variability in drug responses, such as bioavailabilities, efficacies and adverse effects of drugs, is a major issue to determine an optimal dose in drug developments and clinical practices [1–3]. Mainly, there are two potential factors, extrinsic ethnic factors and intrinsic ethnic factors, influencing drug responses [101]. Examples of former factors include the social and cultural aspects, such as medical practice, diet, use of tobacco, use of alcohol, exposure to pollution and socio–economic status, and latter factors include genetic polymorphism, age, gender, height, weight, lean body mass, body composition and organ dysfunction. Among these factors, inherited factors are one of the most important potential factors that affect the drug responses. Especially, genetic variations in genes relating to processes of drug actions, such as drug metabolizing enzymes, drug transporters, drug receptors and other pharmacological targets, are of even greater importance since accumulated knowledge of human genomic variation is being used for drug evaluations [4]. For example, it is reported that the genetic polymorphisms in the genes encoding β-adrenergic receptor and cytochrome P450 (CYP)2C9 are potential factors to explain the ethnic variability in drug response [5].

Pharmacogenomics (PGx) is defined as the study of variations of DNA and RNA characteristics related to drug responses by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidance: Topic E15 [102]. PGx has the potential to improve drug-development efficiencies and proper usages of drugs in clinical practices. In other words, promises of PGx lie in the possibility to reduce an attrition rate of drug development and to optimize a dose setting of a drug for individual patients [6–8]. Especially, maximizing effectiveness and minimizing the risks of drugs by introducing PGx into drug development will enable drug development to be more successful, since regulatory decisions of drug approvals have been made based on their benefit:risk ratio.

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In this article, we summarize the current situations and projects in regulatory implementations for PGx for drug evaluations in Japan, including activities to promote PGx-based drug/device developments and therapies. In addition, we also discuss future tasks for the utilization of PGx in drug evaluations and clinical practices.

Current activities to promote drug/device developments using PGx in Japan

Ministry of Health, Labour & Welfare activities

The Ministry of Health, Labour and Welfare (MHLW) has released notifications to promote drug/device developments using PGx. As shown in Table 1, the MHLW has taken proactive actions aiming to translate PGx from bench to bedside.

In June 2001, two notifications entitled *Guidance on Clinical Pharmacokinetics Studies of Pharmaceuticals* and *Guidance on Methods of Drug Interaction Studies* were published [9,10]. These two notifications show the basic concept related to a clinical pharmacokinetics study and drug-interaction study for new drug application. The former guidelines note that if a genetic polymorphism is likely to affect individual differences in pharmacokinetics, a sponsor is recommended to select subjects with or without specific genetic factors, based on objective criteria, such as genotyping tests [9]. In the 'Questions and Answers' section, it mentions that ethical issues should be taken into consideration to perform genetic examinations, and that genetic polymorphisms can be identified either by genotyping or phenotyping. However, in the case of genotyping, the genotype that clearly relates to metabolic activity should be used. It is also mentioned that, if a probable percentage of target genetic polymorphisms is very low in Japanese populations, data from foreign populations are expected to provide valuable information. The latter guidelines describe that, in case a polymorphically expressed enzyme significantly affects metabolism of the investigational drug, a sponsor is recommended to study drug interactions, considering phenotypes and/or genotypes of individual subject [10]. Thus, based on these notifications, the MHLW has encouraged sponsors to conduct studies using PGx, which can assess potential impacts of genetic polymorphisms of drug metabolizing enzymes on pharmacokinetics of individual subjects in clinical trials.

In March 2005, *Submission of Information to Regulatory Authorities for Preparation of Guidance on the Use of Pharmacogenomics in Clinical Studies* was published [11]. This notification encouraged sponsors to voluntarily submit a list of information to the MHLW on planned, ongoing, and past PGx clinical trials. The purpose of this notification is to collect all available information regarding PGx clinical trials to correctly understand situations of PGx activities in drug development.

Table 1. Notifications and reports related to pharmacogenomics issued by Ministry of Health, Labour and Welfare.

	Issued date	Notifier
Notification		
Guidance on Clinical Pharmacokinetics Studies of Pharmaceuticals	June 2001	PFSB/ELD
Guidance on Methods of Drug Interaction Studies	June 2001	PFSB/ELD
Submission of Information to Regulatory Authorities for Preparation of Guidance on the Use of Pharmacogenomics in Clinical Studies	March 2005	PFSB/ELD
Request to cooperate in research regarding severe cutaneous adverse reactions	June 2006	PFSB/SD
Terminology in Pharmacogenomics (ICH-E15 guideline)	January 2008	PFSB/ELD and PFSB/SD
Points to Consider for Evaluating Genotyping Platforms Based on DNA Chips	April 2008	PFSB/ELD
Reports		
Pharmaceuticals and Medical Devices Safety Information No. 219 – Future Prospect of Pharmacogenomics (1)	November 2005	PFSB/SD
Current Situations and Future Tasks for Utilization of Pharmacogenomics in Drug Evaluation	March 2007	The Japanese Society of Clinical Pharmacology and Therapeutics*
Pharmaceuticals and Medical Devices Safety Information No. 235 – Future Prospect of Pharmacogenomics (2)	April 2007	PFSB/SD

*The Japanese Society of Clinical Pharmacology and Therapeutics published the report by request from Ministry of Health, Labour and Welfare.
MHLW: Ministry of Health, Labour and Welfare; PFSB/ELD: Pharmaceutical and Food Safety Bureau/Evaluation and Licensing Division; PFSB/SD: Pharmaceutical and Food Safety Bureau/Safety Division.

Submitted lists include following information related to the trials, a purpose of the study, a phase of the study, the name of country where the study is performed, a target gene, a target disease, races of these individuals, subject numbers, methods for genetic tests and sample storage processes. In total, the information of 179 clinical trials from 22 industries were submitted based on the notification. Through this process, accumulated knowledge and experiences are intended to be used for taking appropriate regulatory measures, such as the establishment of guidelines.

In March 2007, the Japanese Society of Clinical Pharmacology and Therapeutics published the report entitled *Current Situations and Future Tasks for Utilization of PGx in Drug Evaluation* by the request of the MHLW [12]. The report summarized the current knowledge and usefulness of PGx and identified future tasks that should be taken into consideration in regulatory sciences to promote PGx utilization in drug development and clinical practices in Japan. In order to further introduce PGx in drug development in Japan, five issues were identified:

- Establishment of general guidelines regarding PGx applications in clinical trials
- Clarification of PGx data handling in a common technical document (CTD) for a new drug application
- Considering potential strategies for promoting drug/device codevelopments for utilizing PGx
- Establishment of general guidelines regarding genomic biomarkers in drug development
- Establishment of general guidelines regarding clinical trial designs using PGx

A guideline entitled *Points to Consider for Evaluating Genetic Tests Based on DNA Chips* was also released in April 2008 [13]. The purpose for the preparation of this guideline was to facilitate considerations by industries and accelerate regulatory reviews regarding issues in *in vitro* diagnostics (IVD) devices. It summarizes important points to obtain reliable data genotyped by DNA chips and its dedicated devices, including software. This guideline is expected to will mutually promote the development of genetic tests and PGx-based drug developments in Japan.

Regulatory approaches relating to PGx are expanding globally and many regulatory authorities have published guidelines or concept papers [9,10,13–15,103,104]. In this new field, international regulatory collaborations are important to avoid unnecessary works for regulatory measures, such as establishment of guidelines related to PGx. ICH will be an appropriate forum for the purpose of harmonizing regulatory approaches in PGx, since more than 50 regulatory guidelines of drugs in the quality, safety, efficacy and multidisciplinary fields have already been harmonized among the regions. The MHLW is currently working on harmonizing regulatory approaches relating to PGx in the ICH, in addition to the domestic activities described previously. In November 2007, the ICH established the E15 guideline entitled *Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories* [102]. This is the first guideline for the ICH to adopt in this emerging science area and it will be a basis for future ICH guidelines relating to PGx. In January 2008, the ICH-E15 guideline was officially notified and implemented in Japan [15]. The guideline will help to make common understanding of PGx issues, not only in ICH regions, but also in non-ICH regions, by avoiding either conflicting use of terms in regulatory documentation and guidelines, or inconsistent interpretation among regions and any bodies relating to PGx, such as regulatory authorities, sponsor companies and ethical committees.

Pharmaceutical & Medical Devices Agency activities

The Pharmaceutical and Medical Devices Agency (PMDA) is an independent regulatory agency from the MHLW and is responsible for scientific reviews for the approval of drugs and medical devices and for safety monitoring after approval.

In September 2005, the Pharmacogenomics Discussion Group (PDG) was established in the PMDA to manage PGx issues from regulatory stand points with cooperation of the MHLW. Missions of the PDG are described as follows: share PGx data, information and knowledge, discuss regulatory issues relating to PGx, keep consistency of PMDA decisions among offices/reviewers and promote appropriate drug development using PGx. The PDG currently consists of 21 members from various offices in PMDA, such as the Office of New Drugs, Office of Biologics, Office of Medical Devices, Office of Review Administration, Office of Safety and Office of Compliance and Standards. The PDG has not only had internal meetings on a regular basis, but also more than 15 informal meetings with pharmaceutical companies and academia over the last 2.5 years to understand updated scientific knowledge relating to PGx and to identify practical issues for PGx utilization in drug/device developments in Japan. Major topics in the informal PDG meetings were drug/device development strategies using PGx and interpretation of PGx data, including genomic biomarkers. For example, issues regarding processes of sample storages in PGx studies, including sample coding and sample withdrawal, codevelopment strategies of devices with drugs and interpretations of preliminary PGx data, were discussed. Increased interactions between pharmaceutical companies/academia and the PMDA at the informal PDG meetings will help and promote PGx applications in drug development and clinical practices. Recently, the PDG joined the US FDA and European Medicines Agency (EMEA) joint Voluntary Genomic Data Submission briefing meeting as an observer [105]. Strengthening collaborations with other international regulatory agencies, such as the FDA and EMEA are important to promote appropriate PGx use in drug development and clinical practices and harmonization of regulatory approaches in PGx.

Current PGx implementations for drugs approved in Japan

Availabilities of PGx information in package inserts on approved drugs in Japan

Package inserts are the most fundamental tools to provide information on approved drugs to healthcare professionals and promote the proper use of drugs. Package inserts of drugs approved in Japan are posted on the information page on the PMDA website [106]. We searched this publicly available PMDA website to investigate how much information on genomic biomarkers is included in package inserts of new drugs that were reviewed by the Drug Committees of the Pharmaceutical Affairs and Food Sanitation Council of the MHLW and were approved from fiscal year 2002 to fiscal year 2006 in Japan. The criteria for a selection were to include at least one of 12 items (i.e., single nucleotide polymorphism, genome, genomics, metabolic pathway, genotype, polymorphism, poor metabolizer, extensive metabolizer, metabolizer, pharmaco-, genetic and variation). Numbers of accumulated package inserts including PGx information have been increasing year by year during the period (Figure 1). Approximately 16% of the package inserts (32 out of 199 package inserts) included the information related to PGx in the 2006 fiscal year.

The PGx information in the package inserts was classified into four groups according to the type of genomic biomarker as follows; metabolizing enzyme, virus and bacterium, pharmacological target and others (Table 2). Within the 32 package inserts including PGx information, the most common type was 'virus and bacterium', which consists of 17 products, such as hepatitis B virus (HBV), hepatitis C virus (HCV) and HIV. For example, efficacy results based on genotypes of HCV in clinical trials were included in the package inserts of ribavirin and pegylated (peg)-IFN-α_{2a}. Similarly, the resistance of drugs to certain HIV genotypes was described in the package inserts for anti-HIV drugs, such as emtricitabine and lamivudine–abacavir sulfate. The second most popular type after 'virus and bacterium' was 'metabolizing enzyme' such as CYP. For example, information on the differences of pharmacokinetic parameters, such as AUC, C_{max} and elimination half-life ($t_{1/2}$) between extensive metabolizers and poor metabolizers were described in the package inserts of letrozole for *CYP2A6*, tolterodine tartrate for *CYP2D6* and proton-pump inhibitors, such as omeprazole, sodium rabeprazole and lansoprazole for *CYP2C19*. 'Pharmacological target' information was the third most popular group, but was limited in the field of anticancer drugs, such as imatinib mesylate, for patients with KIT (CD117)-positive metastatic malignant gastrointestinal stromal tumors and tamibarotene for patients with *PML-RAR-α* gene positive acute promyelocytic leukemia. A recent study showed similar tendency to our finding (i.e., the genes coding for drug metabolizing enzymes and viral genes was the major PGx information included in the package inserts of drugs approved in the USA) [16].

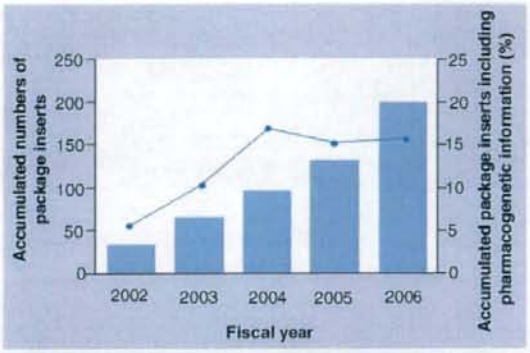

Figure 1. Trends in information relating to pharmacogenomics in package inserts of drugs approved in Japan. Bars represent the accumulated numbers of package inserts of new drugs that were reviewed by the Drug Committees of the Pharmaceutical Affairs and Food Sanitation Council of the Ministry of Health, Labour and Welfare and were approved in Japan from fiscal year 2002 to fiscal year 2006. Generic and over-the-counter drugs are not included. Circles and line are the accumulated percentages of package inserts of the drugs including information related to pharmacogenomics.

According to the degree of requirement for testing of the genomic biomarker, PGx information was classified into three types: 'test required', 'test recommended' and 'information only' (Table 2). Each type of information relating to the requirement of testing was calculated as one case, thus, 50 cases of information were identified in the 32 package inserts because two or three cases were included in a package insert. Types of genomic biomarkers and relationships with PGx test requirement status are shown in Figure 2. PGx-related information of metabolizing enzyme only showed 'information only', which provides the allele frequency of *CYP* mutant gene (i.e., *CYP2A6*, *CYP2C9*, *CYP2C19* and *CYP2D6*) and the relationship between genotypes and pharmacokinetics parameters. Within the PGx-related information of 'virus and bacterium', 9% of the information was 'test required', asking genotyping of the virus to be performed before starting drug administrations in order to achieve a desired antiretroviral therapeutic effect. For example, one of the indications of peg-IFN-α_{2a} was limited to patients infected with HCV genotype I and/or II. The percentages of 'test recommended' and 'information only' regarding 'virus and bacterium' were 39 and 52%, respectively. Within the PGx-related information of 'pharmacological targets', 60% of the cases were categorized as 'test required', asking for diagnostic genetic tests to confirm the existence of genomic biomarker before starting administrations of anticancer drugs (i.e., imatinib mesylate, arsenic trioxide and tamibarotene). Although relationships between clinical outcome and PGx-based prescribing information in package inserts of drugs have not been studied extensively , the PGx-based information relating to 'test required' and 'test recommended' in package inserts can be contributed for promoting to conduct proactive PGx studies.

Table 2. Drugs including PGx information in package inserts in Japan.

Genomic biomarker	Drug name (nonproprietary name)	Requirement status of testing for the genomic biomarker
Metabolizing enzyme		
CYP2A6	Letrozole	Information only
CYP2C9	Candesartan Cilexetil	Information only
	Celecoxib	Information only
CYP2C19	Omeprazole–clarithromycin–amoxicillin	Information only
	Clarithromycin	Information only[*]
	Sodium rabeprazole[‡]	Information only
	Voriconazole	Information only
	Lansoprazole	Information only
CYP2D6	Gefitinib	Information only
	Tolterodine tartrate	Information only
Virus/bacterium		
Cytomegalovirus	Valganciclovir hydrochloride	Information only
Enterococcus faecium *Enterococcus faecalis* *Staphylococcus aureus* *Staphylococcus epidermidis*	Linezolid	Information only
Hepatitis B virus	Adefovir dipivixil	Recommended
	Lamivudine	Recommended
	Entecavir hydrate	Recommended
Hepatitis C virus	Peg-IFN-α_{2a}[‡]	Required
	IFN-α_{2b}	Recommended
	Peg-IFN-α_{2b}	Recommended
	IFN-β	Recommended
	Ribavirin	Required
HIV	Atazanavir sulfate	Recommended
	Tenofovir disoproxil fumarate	Information only
	Fosamprenavir calcium hydrate	Recommended
	Lamivudine–abacavir sulfate	Recommended
	Emtricitabine	Recommended
	Emtricitabine-tenofovir disoproxil fumarate	Recommended
Pharmacological target		
KIT expression, Philadelphia chromosome presence	Imatinib mesylate	Required
PML/RAR-α fusion gene presence	Arsenic trioxide	Required
	Tamibarotene	Required
Others		
Protein C deficiency	Human-activated protein C[§]	Required

[*]Information on coadministration with clarithromycin and sodium labeprazole.
[‡]Counted twice because approved indications, dosage and administration were partially changed during the period.
[§]Indications of human-activated protein C are deep venous thrombosis, acute pulmonary thromboembolism and fulminant purpura due to congenital protein C deficiency. Protein C deficiency is classified into 'others' because this genomic biomarker is directly concerned with the hereditary disorder.

Moreover, as use of PGx test and qualification of genomic biomarkers are actively studied in drug development, the availability of PGx-based prescribing information in package inserts could be expanded in the near future.

Current situations of PGx tests covered by National Health Insurance

Reimbursement of the medical fee is one of the important factors to translate validated genomic biomarker from the research environment to clinical use [17–19].

Fortunately, Japan has the National Health Insurance (NHI) system, which applies to all Japanese citizens. In this system, parts of medical costs, including medication and the use of medical devices, are reimbursed. As described in the previous section, some package inserts of approved drugs include information on PGx tests as a requirement or a recommendation before starting drug administrations, specifically in the field of antivirus and anticancer drugs. In these fields, several PGx tests are already available that can be covered by the NHI. Major PGx tests related to leukemia, malignant tumor and infectious disease, which are covered by the NHI over the past 5 years in Japan, are summarized in Table 3. [20].

For example, PGx testd for EGF receptor (*EGFR*) gene mutation in lung cancer patients was covered by the NHI in June 2007. It has been reported that efficacy of gefitinib for the treatment of non-small-cell lung cancer depends on genetic variants of *EGFR*, and *EFGR* mutation rate is higher in Japanese than that in Caucasian individuals [21,22]. Consequently, many commercial clinical laboratories are currently available in Japan for providing the service of analysis of *EGFR* gene mutations, such as exon 19 deletions (e.g., *E746-A750* deletion), *T790M* substitution in exon 20, and *L858R* substitution in exon 21. In the near future, as implementation of PGx test for *EGFR* gene mutation widely spreads in clinical practices, data of *EGFR* gene mutation as a genomic biomarker relating to drug responses will be further accumulated.

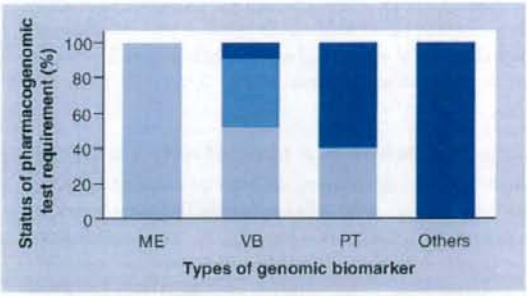

Figure 2. Relationships between types of genomic biomarker and status of pharmacogenomics (PGx) test requirements in the package inserts of drugs approved in Japan. Percentages of PGx test-requirement status are shown in each type of genomic biomarker included in the package inserts of new drugs that were reviewed by the Drug Committees of the Pharmaceutical Affairs and Food Sanitation Council of the Ministry of Health, Labour and Welfare, and were approved in Japan from fiscal year 2002 to fiscal year 2006. Dark, mid and light blue bars are 'test requirement', 'test recommended ' and 'information only', respectively. Total numbers of information cases relating to PGx tests in ME, VB, PT and others are 11, 33, five and one, respectively.
ME: Metabolizing enzyme; PT: Pharmacological target; VB: Virus and bacterium.

Furthermore, to allow drug selections and reselections of antiretroviral drugs in order to avoid drug inefficacy and drug resistance, a genotyping test for HIV drug resistances was covered by the NHI in April 2006. It is reported that drug resistance is closely related to virological failure and poorer prognosis in drug-experienced patients [23]. The prevalence of drug resistant HIV-1 strains is also related to global availability of antiretroviral drugs [23,24]. Therefore, a PGx test would be of growing importance in maintaining optimal efficacy of the anti-HIV drugs for the long-term periods.

As described previously, the several NHI-covered PGx tests are widely available in the fields of cancer therapy and antiretroviral therapy in Japan.

MHLW activities to identify potential factors associated with drug-related severe adverse reactions

The notification entitled *Request to Cooperate in Research Regarding Severe Cutaneous Adverse Reactions* was issued by the MHLW in June 2006 (Table 1) [14]. This notification encourages pharmaceutical companies to cooperate to the exploratory research of genomic biomarkers in order to predict drug-related severe cutaneous adverse reactions, such as Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), in the National Institute of Health Science (NIHS). In case a serious cutaneous adverse event, such as SJS and TEN, occurs and is recognized, the pharmaceutical companies will voluntary inform the event to the NIHS based on the notification and, additionally, report adverse drug reactions to the PMDA based on the Pharmaceutical Affairs Law where necessary (Figure 3). The incidence frequencies of SJS and TEN are extremely low (approximately one or two patients per 1 million people per year) [25]. The pathological mechanisms underlying the onset of SJS and TEN are not fully

Table 3. Major reimbursable PGx tests in Japan.

Genomic biomarker	Requirements for reimbursement	Date to be covered by NHI
PGx tests related to leukemia and malignant tumor		
Her2/neu (erbB2)	FISH assay for selection of HER2 overexpressing breast cancer patients appropriate for HER2 monoclonal antibody therapy	April 2003
Major bcr-abl mRNA	TMA assay to quantify major bcr-abl mRNA in hematocyte	November 2004
EGFR mutations	Test to detect *EGFR* mutations in patient with lung cancer	June 2007
KIT mutations	Test to detect *KIT* mutations in patient with gastrointestinal stromal tumor	June 2007
Wilms tumor-1 mRNA	Real time RT-PCR assay to quantify wilms tumor-1 mRNA for diagnostic aid and follow-up in patients with acute myelocytic leukemia	November 2007
PGx tests related to infectious disease		
Mutations in HBV precore, mutations in HBV core promoter	PCR assay to detect mutations in HBV precore and core promoter in plasma	July 2003
Mutations in HIV	Test to detect mutations in HIV for anti-HIV drugs selection and reselection	April 2006

EGFR: Epidermal growth factor receptor; FISH: Fluorescence *in situ* hybridization; HBV: Hepatitis B virus; HER2: Human epidermal growth factor receptor 2; NHI: National Health Insurance; PGx: Pharmacogenomics; RT-PCR: Reverse transcription polymerase chain reaction; TMA: Transcription-mediated amplification

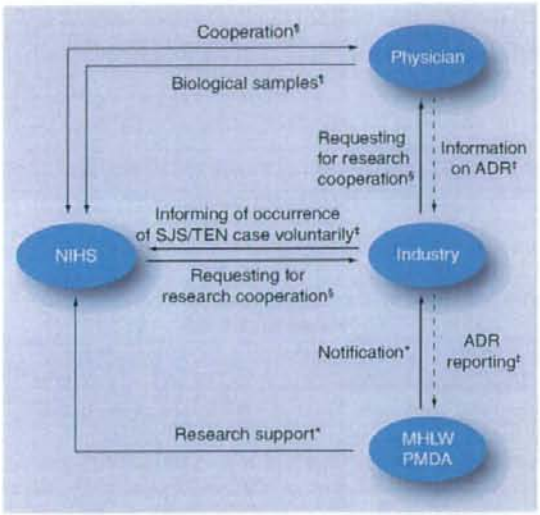

Figure 3. Framework of research regarding severe cutaneous adverse reactions in NIHS. Dotted arrows represent the flow of information on report of ADR to the PMDA based on the Pharmaceutical Affairs Law. Solid arrows represents the scheme related to the research regarding severe cutaneous adverse reaction, including SJS and TEN, in the NIHS.
*Request to cooperate in research regarding severe cutaneous adverse reactions: Safety Division, Pharmaceutical and Food Safety Bureau, MHLW, Notification No. 0615001 [14].
†In case a serious cutaneous adverse event, such as SJS and TEN, occurs and is recognized, the industry will voluntarily inform the NIHS based on the notification, and additionally report on ADR to PMDA based on the Pharmaceutical Affairs Law where necessary.
‡Then, to the physicians who diagnosed the case, the NIHS requests for cooperation to the research via industries.
¶The NIHS will conduct genetic analysis only after the physician agrees to the request.
ADR: Adverse drug reaction; MHLW: Ministry of Health, Labour and Welfare; NIHS: National Institute of Health Sciences; PMDA: Pharmaceuticals and Medical Devices Agency; SJS: Stevens–Johnson syndrome; TEN: Toxic epidermal necrolysis.

established, although the involvement of immune mechanisms has been suggested. A recent study suggested the strong genetic association between HLA and drug-induced SJS/TEN [26,27]. For example, 100% association of carbamazepine-induced SJS and TEN with *HLA-B*1502* has been reported in 44 Han Chinese patients [28]. Meanwhile, such association is not obtained in patients of European ancestry [29]. It is suggested that although the HLA region may contain important genes for SJS and TEN, the *HLA-B*1502* allele may not be a universal marker for this adverse reaction. Roles of *HLA-B*1502* for predicting SJS/TEN risks in Japanese populations are not currently clear, but allele frequency of *HLA-B*1502* was 0.1% in unrelated healthy Japanese individuals [30], which is lower than that in Han Chinese populations (10–15%) [107]. In drug development, it is difficult to study about an extremely rare adverse event, such as a drug-induced SJS or TEN. Therefore, a cooperate research to explore genomic biomarkers related to severe adverse drug reactions will be useful to accumulate basic information in order to establish proper actions based on PGx in Japan.

Pharmaceuticals & Medical Devices Safety Information

With the objective of providing the latest information and safety topics for the safer use of drugs and medical devices to healthcare professionals, the MHLW has compiled commentaries and notices when major revisions based on important case reports on severe adverse reactions were made in package inserts. A digested form, *Pharmaceuticals and Medical Devices Safety Information*, was also published bimonthly from June 1973 and then monthly from June 2001 [108]. As of February 2008, 244 digests have been published and disseminated to healthcare professionals in Japan. In two digests published in November 2005 (no. 219) and April 2007 (no. 235), the MHLW has featured on the future prospects of PGx (Table 1). The digests summarized the domestic and international situations of updated practical usage of PGx. In the no. 219 digest, it was described that the MHLW encourages industries to develop IVD devices for genotyping *UGT1A1* mutant genes, which have been reported to have a potential role in irinotecan-induced neutropenia [31]. In irinotecan therapy, some alleles of *UGT1A1*, such as *UGT1A1*6* and **28*, have been suggested to have clinical impacts in Japanese populations [32–34]. It is expected that PGx-based dose adjustments of irinotecan in clinical practices will be popularized when the IVD device for the genotyping of these *UGT1A1* mutant alleles is approved in Japan.

Although PGx information for intended dose adjustments based on genetic profiles is currently limited in package inserts in Japan, the more information that is included, the more IVD devices for validated genomic biomarkers are approved.

To promote the appropriate use of PGx in clinical practices, the PGx information in package inserts should be properly interpreted and understood. However, in Western countries and Japan, the lack of knowledge regarding PGx among healthcare professionals has been reported [35–37]. Therefore, adequate education and supply of proper information to people who prescribe, dispense and use drug products are indispensable. From this viewpoint, PGx information in the digest will contribute greatly to establish the basis of PGx-based medicine in clinical practices in Japan.

Expert commentary

Looking at current PGx implementation for approved drugs, utilization of PGx has been expanding recently in Japan. To achieve the goal of PGx utilizations, strengthening cooperation/collaboration among regulatory agencies and other stakeholders, such as industries, academia and healthcare professionals, and further international harmonization of PGx regulatory approaches, are critical and essential.

Five-year view

As described previously, some genomic biomarkers that are useful in a certain population may not be useful in other populations (e.g., the association between carbamazepine-induced SJS/TEN and *HLA-B*1502*). Therefore, in order to apply PGx to drug development and usage of drugs in clinical settings appropriately, it should be taken into consideration that allele frequencies of the genomic biomarkers may be different among populations. During the drug development period especially, it will be very important to examine from an early stage whether ethnic differences in a genomic biomarker have any impact on drug efficacy and safety.

In the future, drug developments will be more globalized and PGx in drug developments will be more practically applied and implemented. In such situations, PGx data obtained in global clinical trials including various populations who may have various ethnicities are very important in order to properly evaluate PGx utilities in drug administration. To promote simultaneous global drug developments including Japan, the MHLW published the final notification of points to consider document entitled *Basic Principles on Global Clinical Trials* last September [38]. This notification will also have impacts in PGx applications in global clinical trials. If ethnic differences in drug efficacy and safety have been examined from an early stage of clinical developments, drug efficacy and safety profiles can be more properly identified, resulting in an increase in success rates drug developments and a decrease of possibility to discover unexpected serious adverse events in a postmarket stage after approval.

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Key issues

- Over the past 5 years (from fiscal year 2002 to fiscal year 2006), of the approved drugs in Japan, approximately 16% of the package inserts (32 out of 199 package inserts) included the information related to pharmacogenomics (PGx).
- Several PGx tests for genomic biomarkers (e.g., *EGFR* mutation, *KIT* mutation and mutations in HIV) are covered by National Health Insurance, and widely available in the field of cancer therapy and antiretroviral therapy in Japan.
- PGx implementations, in terms of information in package inserts and reimbursable PGx tests, could rapidly expand in Japan.
- The Pharmacogenomics Discussion Group of the Pharmaceuticals and Medical Devices Agency has played an important role in promoting PGx utilization in Japan, as well as international harmonization of PGx regulatory approaches.
- The Ministry of Health, Labour and Welfare has taken action to promote PGx utilization in Japan, such as publishing guidelines, disseminating PGx information and supporting PGx researches.
- Establishing more guidelines relating to PGx based on the report from the Japanese Society of Clinical Pharmacology and Therapeutics will be necessary in order to further introduce PGx in drug developments in Japan.
- To achieve the goal of PGx utilizations, strengthening cooperation/collaboration among regulatory agencies and other stakeholders, such as industries, academia and healthcare professionals, and international harmonization of PGx regulatory approaches, are critical and essential.
- PGx applications in global drug development will also be important to properly evaluate PGx utilities in drug administration and can contribute to increased efficiency of drug development.

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国際共同治験の基本的考え方について***

森　和彦*,**，宇山　佳明*

1. 医薬品開発の現状

1.1 臨床開発の失敗

世界の医薬品開発の中心はアメリカです．したがって，アメリカでは多くの治験が行われていますが，様々な理由で失敗するものも多くあります[1,2]．どの領域でも程度の差こそあれ，臨床試験の少なくとも1割は失敗しているとの分析もありますが，実際にはもっと失敗している可能性があります．

臨床開発が失敗している原因についても，様々な理由がありますが，時間の経過に伴って失敗の原因が変わってきています．例えば，新手法であるマイクロドージングの説明をする際に良く用いられる表現として，以前はPKの問題によって開発を失敗していたので，この部分をきちんと評価するためにマイクロドージングを用いると，早い段階でPKの特性の優れたものを選べるため，PKの問題による失敗は減らせるといった例があります．

マイクロドージングに限った話ではありませんが，科学の進歩によって吸収性が良くないものや生体内の安定性が悪いものは早いうちに予測できるようになり，そういった化合物は早いうちに排除できます．例えば，1991年と2000年で比べますと，PKなどの問題で失敗する例はかなり減少しました[2]．

一方で，有効性について差が出ず，開発を中止してしまうものや，あるいは後で毒性の問題が現れて失敗してしまうもの，毒性といっても恐らく臨床的な副作用が背景にあると思われるもので，それをきっかけに様々な動物実験を行ってみると思わぬ毒性があることが判明してしまうものや，あるいは臨床試験と並行して追加で行っている長期の動物実験で予測できない毒性が現れることもあります．

こうした様々な原因によって開発効率が落ちています．実際に臨床開発に入ったものが徐々に脱落し，申請してから承認される間に更に脱落します．化合物を探索する段階から考えますと，5000分の1，1万分の1の割合でしか残らないともいわれており，開発効率の悪いことが非常に問題となっています．

ただし，化合物を選ぶ部分に関しては，ベーシックサイエンスの進歩に期待するものですので，我々が現在関心を持っているのは，臨床開発での脱落を何とか減らすことで，開発を進める間に，日本が乗り遅れないようにどうやって開発の中に入っていくか，場合によっては日本がリードすることもあっても良いと考えています．

1.2 国内企業の医薬品開発の動向

国内企業の医薬品開発の動向を見た場合，最近10年間では海外先行で開発するものが着実に増え，相対的に国内先行の割合が減少しています[3]．

これはある意味，日本の製薬企業が海外にも拠点を持ち，海外での開発展開を開発のオプションの中にきちんと入れるようになり，真の意味でグローバル化が日本の製薬企業においても進んできたことを表しているといえます．

しかし一方で，日本国内の臨床開発環境が劣悪であることが明らかとなるにしたがって，条件の整った海外での開発を先行させるようになっているとの指摘も確かにあります．この問題は日本での臨床開発の今後の行方を予測する上で非常に深刻な，懸念

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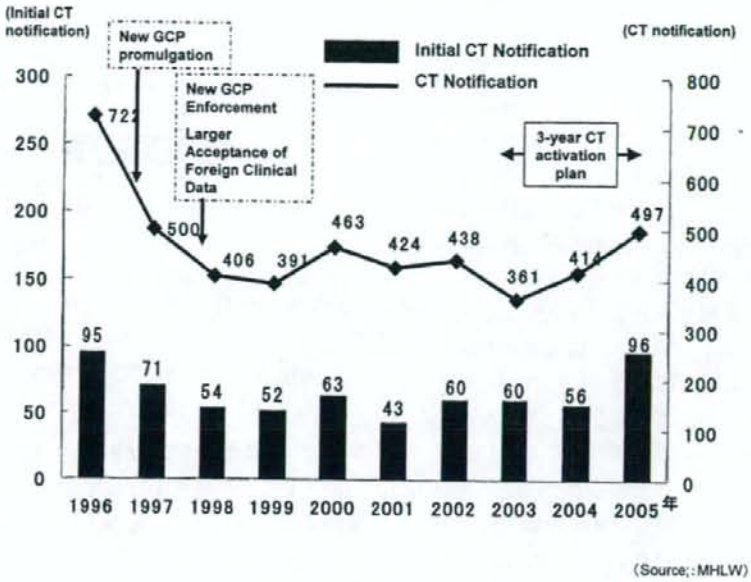


Fig. 1　日本での治験届出数

すべき現象でもあります．

1.3　日本での治験届出数

日本の治験届出数は，Fig. 1に示すように最近10年で減少してきています．

その原因は，新GCPの導入に歩調を合わせたこと以外にも治験に関する費用の問題，更に効能効果の似た新薬，すなわちゾロ新薬と呼ばれるものの開発に対し，医療保険での薬価算定ルールの見直しが行われたことなど様々な要因がからんでいます．日本での開発品目，あるいは治験本数を絞っていくといった動きが急激に進んだ時期があり，その後しばらくは低調な状態が続き，新規成分の治験届出は一時，年間40～50件と低調でした．しかしまた盛り返し，最近3～4年は件数的にも非常に伸びて，2006年は100件程の開発が日本で開始されています．これは全国治験活性化計画の成果との見方もありますし，医薬品開発全般が活発になってきたこと，あるいは海外での開発の時期が少しずれて日本に入ってきたことなど様々なファクターが背景にあると思います．

日本における治験本数が増加していることは，新たな希望が持てる現象でもあります．したがって，前述した海外先行の開発があるとしても，我々のこれからの舵の取り方，あるいは歩み方をよく考える必要があると思います．

2.　現在の医薬品開発の問題点

Fig. 2はドラッグラグの発生を象徴的に示している図です．つまり，日本より先に海外での開発が始まり，先に申請されて承認となるのに対し，日本は海外より遅れて開発がスタートし，更に申請も遅れて承認も遅れて，ドラッグラグが生じます．この問題は今に始まった話ではありませんが，以前からこの状態であったわけではなく，むしろ日本がFDAより審査が早く，先に承認された例もあります．

しかし，多くは海外で開発されたものを日本に導

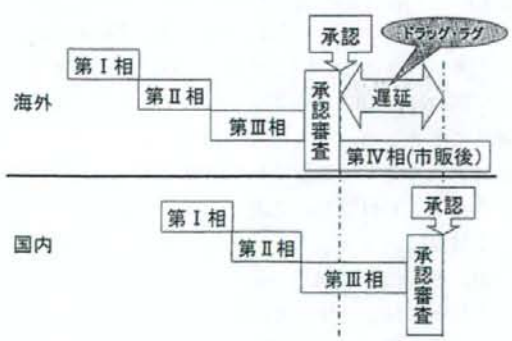


Fig. 2　現在の医薬品開発の問題点

入して，日本でも使えるようにするといった医薬品開発が一般的です．したがって，ドラッグラグは以前からあったと思われます．ただ，それが現状では許されなくなってきています．患者さんにとってみれば，インターネットを見ればアメリカの患者さんが使用している事が分かり，なぜ日本では使えないのかといった疑問があります．実際は個人輸入で買うことができますので，使おうと思えば使うことができますが，それは正規なルートではありません．患者さんは正式な方法で入手し，保険も適用されるようにして欲しいと希望しています．したがってこのドラッグラグが許せず，審査をしている我々が批判されますし，開発している企業の皆さんに対しても，早く開発して，早く承認を取るようにプレッシャーがかかると思います．我々は常に患者さんたちから要求される側の立場にいることを忘れてはいけないのです．

3．ドラッグラグの現状

ドラッグラグが実際どれぐらいの格差なのかをいろいろな角度で分析してみます．まず，世界で最初に上市された日から自分の国の市場に登場するまでの差を比較しますと，日本はアメリカと比較して約2.5年遅れていると解析されています[4]．したがって，この2.5年を何とか縮めたいと考えるのは妥当な考えです．

4．国際共同治験

4.1 国際共同開発（主要国同時開発）

ドラッグラグを出さないための方策としては，国際共同開発の話に一気に進んでしまいます．これは，Fig. 3に示すように開発のタイムラインを海外と国内でずらさないようにし，Phaseを追って進めていくところもできるだけ同じスパンで進め，同時に申請して同時に承認されるようになればドラッグラグが解消できると考えました．

海外と同じ時期に承認されて医療現場で使えることを目指すことは当然のことであり，以前からそのような提案はありました．しかし近年その要望が多く，特に差し迫った病状にある患者さんにとっては本当に切実な問題ですので，何とかしなければいけないという課題が我々にずっと課されています．

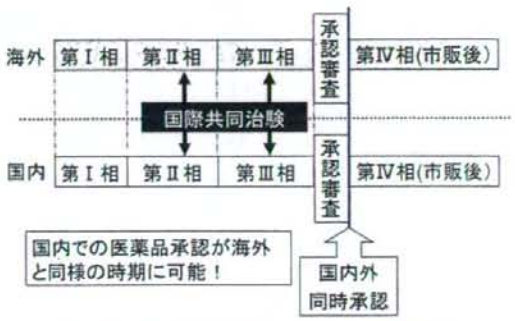


Fig. 3　国際共同開発（主要国同時開発）

4.2 国際共同治験に関する対面助言

Fig. 4は総合機構が行っている治験相談のうち，国際共同治験の相談，治験を行っている件数を示しています．PMDA設立以来4年目になりますが，国際共同治験に関する相談は着実に増え続けています．

平成18年度末までの集計で合計70件以上行っていますので，相談全体の中の国際共同治験に関する相談の割合は，14～15%に届くようになってきています．かつてブリッジング試験が流行した際の数の変化に比べるとまだ少ないところがありますが，急激に数が増えていますので，国際共同治験による開発に対して非常に高い関心があることが表れています．

4.3 対面助言で検討された国際共同治験の対象疾患

Fig. 5に示すように，様々な領域で国際共同治験の可能性が議論され，チャレンジしようといった動きが出てきています．

現在，最も多いのはがんの領域です．次に循環器，内分泌，精神神経系，抗菌薬などの領域が続きます．このように，かなりバラエティに富んだ領域で国際共同治験の可能性が議論されています．したがって実施の難易に差があるかもしれませんが，どの領域でも可能性を検討し，実施できるものはしようと議論していることが読み取れると思います．

がんの領域が多いのは，患者さんにとって切実で，何とか早く承認して欲しいと最も差し迫った要望があるためで，それを実現するために国際共同治験を議論していることが背景にあります．

更にがん患者と一括りにすると，日本人の3人に

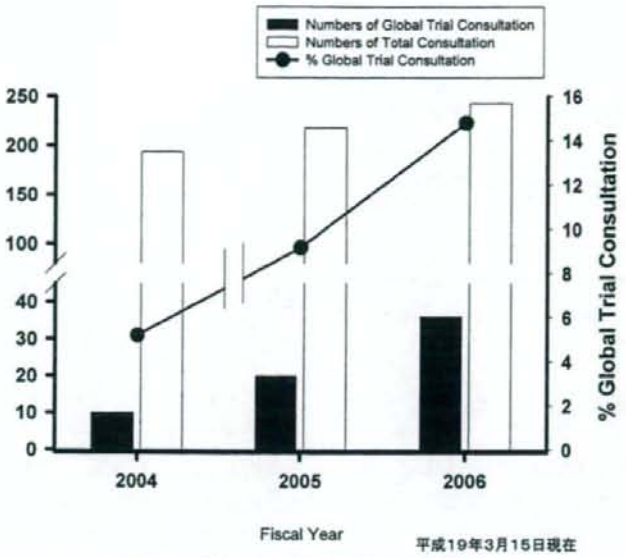


Fig. 4 国際共同治験に関する対面助言

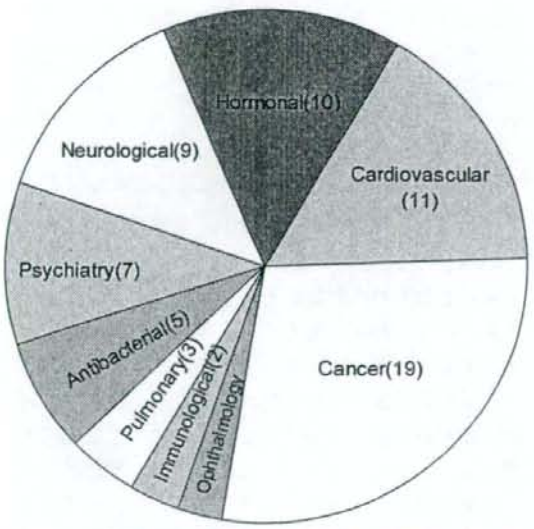


Fig. 5 対面助言で検討された国際共同治験の対象疾患（平成19年3月15日現在）

1人がいずれはがんで亡くなるメジャーな病気ですが，実際は細かく分類されます．例えば，肺がんであっても非小細胞肺がんと小細胞肺がんは全く異なりますし，大腸がんは結腸がんと直腸がんに分かれます．また，がんのステージによって治療方法が全く異なりますので実際は一括りにできません．しかし，そのように分類すると，ほとんどがオーファンドラッグとなるくらい患者数は限られてしまいます．ところが世界中に患者さんはいます．したがって，一つの国より複数の国で患者を集積し，トータルで十分な症例を確保することは，早い開発を望んでいればいるほどその手段を使うべきではないかといった議論となり，がんの領域における国際共同治験の計画件数の多さに表れていると思います．

4.4 国際共同治験の結果を踏まえて承認した事例（Table 1）

国際共同治験を行って承認されたロサルタンの事例を紹介します．

4.4.1 臨床データパッケージ

データパッケージについては，最初の時点で同時に治験を実施できないかと考え，日本と海外と両方で実施しました（Fig. 6）．これは非常に優れた開発戦略であったと思います．

Table 1 ロサルタン：ニューロタン錠25/50（萬有製薬）

- 2006年4月20日承認
- アンジオテンシンII受容体（type AT1）拮抗薬
- 効能・効果：2型糖尿病における糖尿病性腎症
- 日本を含む国際共同試験を第3相試験として実施

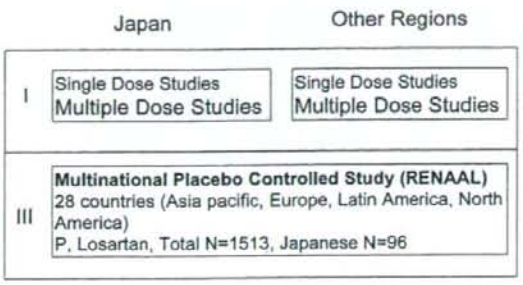


Fig. 6　臨床データパッケージ（ロサルタン）

4.4.2 RENAAL 試験（Table 2）

単回投与試験及び反復投与試験の検討をアメリカをはじめとする欧米と日本がそれぞれ実施し，その上でRENAAL 試験という，検証的で非常に規模の大きい難しい試験を開始しました．

ここに至るまでには用量設定やエンドポイントなどについて，非常にたくさんの議論がありました．なかなか難しい調整もありましたし，得られた結果についてもかなり複雑な結果となっています．

プラセボ対照の二重盲検群間比較試験は有名な試験です．しかし，日本においてはプラセボ対照の比較試験を長期間実施することは，プラセボ投与群に割り付けられる患者さんが試験薬投与群に割り付けられる患者さんより不利益を受けるのではないかという懸念がつきまとうので，同意を得るための説明が困難で手間がかかりますが，実施されました．

対象患者はII型糖尿病性腎症の患者さんで，内訳は，白人の割合が5割，残りはアジア人や黒人，あるいはラテン系のスペイン人の割合が高くなっています．

Table 2　第III相試験：RENAAL試験

The Reduction of Endpoints in NIDDM with the Angiotensin II Receptor Antagonist Losartan (RENAAL) study

- 無作為化多施設共同プラセボ対照二重盲検群間比較試験
- 対象患者：1513人の2型糖尿病性腎症患者
- 患者内訳：アジア人 16.7%, 黒人 15.2%, スペイン人 18.3%, 白人 48.6%
- 主要評価項目：血清クレアチン値倍増，end stage renal disease（ESRD：透析又は移植の必要性）又は死亡からなる複合指標

またエンドポイントの設定も困難でした．用量を検討する際は尿タンパクの減少を目安として選んでいるようですが，最終的な決め手となるのは，進行した腎症の進展を抑制するという観点からしますと，複合のエンドポイントで評価すべきとしています．したがって，血清クレアチン値倍増，ESRD，すなわち透析又は移植の必要性，死亡の場合を合わせる複合指標で，科学的に難しい様々な議論があります．しかし，現在では他の薬剤の適用についての評価をする際にも用いられていることから，臨床的に重要と思われるものをきちんと組み込んでいることも事実ですので，デファクト・スタンダードとなっているのも納得いくと思います．

Fig. 7に示す結果では，二つの治療群の差は少ないですが，差が認められた初めてのデータであり，非常にインパクトがありました．リスクリダクションは16%です．また，この試験を行うために，4年近くも多くの患者さんが薬を服用し続けました．これだけの効果を今までの薬では得られませんでしたので，この結果だけでも価値があるといわれています．

4.4.3　各地域/国ごとのハザード比

FDA でも Fig. 8 に示すような分析を行っています．プラセボとのハザード比1を境界線としますと，1を越えている国や地域があります．ただし，米国を除くと国別の症例数がそんなに多いわけではありませんので，効果の出ていると考えられるハザード比が1よりも低い国や地域でも値はかなり異なります．最も症例数の多い米国はほとんど1に近く，非常に際どい結果となっています．このような差の原因について様々な分析がされています．統計的には，この試験結果では薬効が安定して常に一定しているわけではないので，差は明確ではありません．一方，臨床的には薬効が全体に現れているのだから充分効いているといっているため，FDA の審査報告では珍しく意見が分かれているものがそのまま掲載されています．

日本において議論する場合は，日本人のデータではどうかを見ますが，全体のトレンドに対し，日本人と似たアジアでも，全体から見て良さそうな感じとなっているため，この範囲であれば良いと考えました．

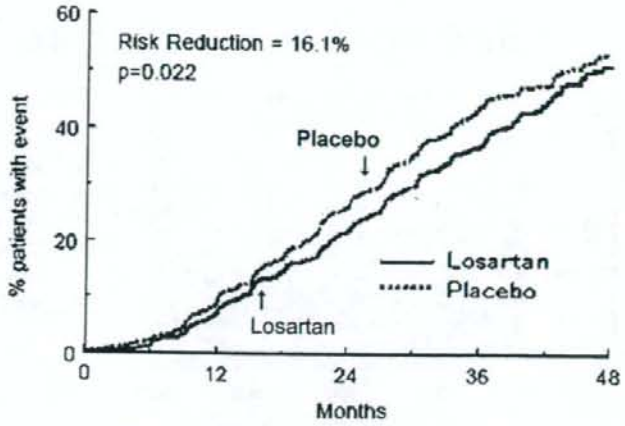
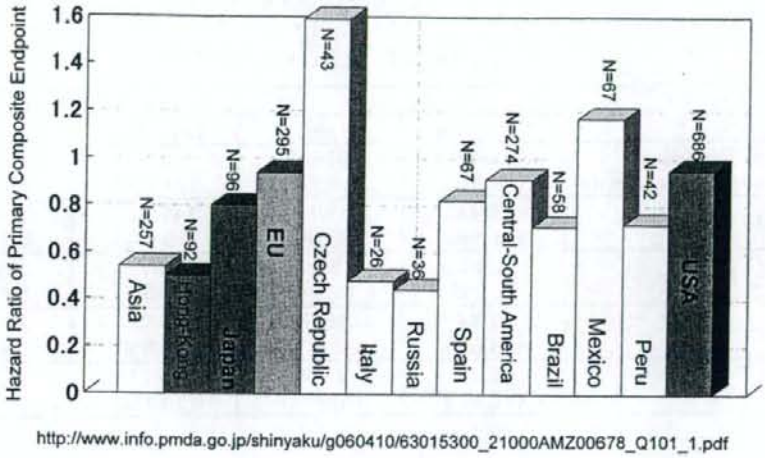


Fig. 7 Primary Composite End-point



http://www.info.pmda.go.jp/shinyaku/g060410/63015300_21000AMZ00678_Q101_1.pdf

Fig. 8 各地域/国ごとのハザード比

Fig. 9 でも，やはり日本や香港で良い結果が示されています．症例数も割と多く集まっています．アメリカが何となく足を引っ張っているようになっていますが，全体のハザード比は 1 よりも下にあります．

4.4.4 主要評価項目の内訳

プライマリー・エンドポイントが複合エンドポイントになっているところが難しいことについて述べました．これについては，項目ごとに分けてみますと，Table 3 に示すようにはっきりと違いが分かります．例えば，c）の死亡の欄を見ますと，全体では約 2 割の方がこの試験期間中に亡くなっています．それに対し日本人の患者さんの死亡の割合は，それほど高くありません．その理由について良く考える必要があると思いますが，日本では透析医療を含め，患者さんの管理がしっかりしていることなどが考えられます．また，日本では血清クレアチニン値倍増のエンドポイントに到達した人たちが多くいます．更にプラセボグループも全体と比べて全く異なります．このことは日本の患者さんが，全体とは違う病状の進み方をしていると考えられなくもありません．そのことが何を意味しているか，あるいはそれによって薬を使用する際にどのようなことに気をつけたら良いかよく考えておく必要がありますし，その中には有益な知識，情報が含まれている可能性があります．非常にありふれていますが説得力がある解釈

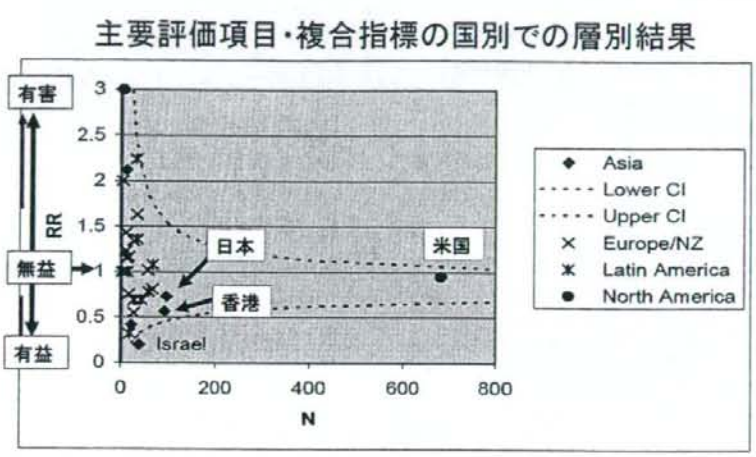


Fig. 9　ロサルタンの成績（FDA 審査報告より）

Table 3　主要評価項目の内訳

	Japan		All regions	
	Losartan	Placebo	Losartan	Placebo
a) Doubling serum creatinine	17/44 (38.6%)	25/52 (48.1%)	162/751 (21.6%)	198/762 (26.0%)
b) ESRD	14/44 (31.8%)	19/52 (36.5%)	147/751 (19.6%)	194/762 (25.5%)
c) Death	4/44 (9.1%)	3/52 (5.8%)	158/751 (21.0%)	155/762 (20.3%)
d) or c)	17/44 (38.6%)	22/52 (42.3%)	255/751 (34.0%)	300/762 (39.4%)
a) or b)	19/44 (43.2%)	31/52 (59.6%)	226/751 (30.1%)	263/762 (34.5%)

として，アメリカ以外の他の国々に関していいますと，透析に移行すると医療費がかかりすぎるため，患者さんは支払うことができません．そのため，治療の選択肢として透析を選べず，移植ができなければ死を迎えるばかりとなります．透析が容易に行える医療体制が整っている国でなければ，死亡の割合が大きくなり，どうしてもエンドポイントが死亡の方に集中してしまいます．このように経済的な要因が背景にあるとの説明もそれなりに納得できるところがあります．

こうした点は，多国籍で実施するとそれぞれの国の経済や医療体制の違いが明らかに現れてきます．逆にそこで集めた患者さんたちが，その国の状況をきちんと反映している患者さんかどうかを考えるために，このような分析は有益と思います．あらかじめ多くの方々を入れていたので，副次的な話ですが，このような評価も議論もできます．

4.4.5　RENNAL Study の結果（Table 4）

RENNAL 試験の結果は全体的に良く，アジア人，日本人の結果でも良好でした．念のため，香港で日本による GCP の実地調査を行いましたが大きな問題はありませんでした．各地域間で一貫した結果に

Table 4　RENNAL Studyの結果

- 全集団では複合指標でプラセボに対する優越性が検証
- 相対的にアジア人で有効性が高い（特に香港）
- 日本人集団での結果は，ロサルタンの有効性を支持
- 香港で実施された日本による GCP 調査で，大きな問題はなかった
- しかしながら，各地域で，一貫した結果は得られていない