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MULTIREGIONAL CLINICAL TRIALS: JAPANESE PERSPECTIVE ON DRUG DEVELOPMENT STRATEGY AND SAMPLE SIZE FOR JAPANESE SUBJECTS

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Multiregional clinical trials including Japanese subjects are playing a key role in new drug development in Japan. In addition to the consideration of differences in intrinsic and extrinsic ethnic factors, deciding the sample size of Japanese subjects is an important issue when a multiregional clinical trial is intended to be used for Japanese submission. Accumulated experience suggests that there are several points to consider, such as the basic principles described in the guidance document, drug development strategy, trial phase, and disease background. The difficulty of interpreting the results of Japanese trials should also be considered.

Key Words: Dose response; Ethnic factor; Multiregional clinical trial; Sample size.

1. INTRODUCTION

Clinical data packages for new drug applications in Japan have consisted essentially of data from clinical trials with Japanese subjects. However, since the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E5 guideline "Ethnic Factors in the Acceptance of Foreign Clinical Data" (ICH, 1998) was issued, foreign clinical trial data have been used for new drug applications in Japan based on the development strategy using a bridging study (Uyama et al., 2005). The strategy for using foreign clinical data shifted to global simultaneous drug development with multiregional clinical trials (MRCTs) since the issuing of the Q&A (questions-and-answers) No. 11 document for the E5 guideline (ICH, 2006) that clearly mentioned the use of MRCT for the purpose of bridging.

When MRCTs are conducted, the differences in intrinsic and extrinsic ethnic factors that can cause differences in drug efficacy and safety between the participating regions should be thoroughly considered through trial design, conduct,

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analysis, and results interpretation. Considering these factors and the cautious selection of the development strategy, the use of MRCTs in new drug development will be an efficient, rapid, and cost-effective way to provide evidence of drug efficacy and safety to many participating regions simultaneously. This feature of MRCTs potentially leads to simultaneous new drug registration and approval worldwide.

In Japan, we have had substantial experience discussing development strategies using foreign clinical data, such as bridging strategies and MRCT strategies, in Pharmaceuticals and Medical Devices Agency (PMDA) consultation meetings with sponsors held in the planning stage of the clinical trials in global drug development. Of particular interest, based on the accumulated experience of the consultations for MRCTs, "Basic Principles on Global Clinical Trials" was issued as a guidance document for MRCT planning (MHLW, 2007). Several topics frequently discussed in consultation meetings are covered in the guidance document, such as the necessity for pharmacokinetic and dose-response information in Japanese prior to the MRCT; management of potential differences in efficacy variables, controls, or concomitant drugs; and the appropriate sample size of Japanese subjects. Since we have many approved cases using MRCTs including Japanese patients as the pivotal trials in their clinical data packages, experience evaluating MRCT results is growing in Japan.

In this article, we first state the features of the global simultaneous drug development compared with bridging strategies in addition to the trend of using foreign data for Japanese new drug applications. The issues in deciding the sample size for Japanese subjects are discussed with the trends in clinical trial notifications. Finally, we discuss several points to consider when deciding the sample size of Japanese cohorts in the context of global simultaneous drug development. Although new drug safety is important when we review new drug application data, we focus on evaluating drug efficacy in this article.

2. MRCTs IN GLOBAL DRUG DEVELOPMENT AND RECENT TRENDS IN JAPAN

As previously mentioned, the use of foreign clinical trial data for Japanese new drug applications has shifted from the bridging strategy to MRCT development. In the bridging strategy, a bridging study, whose design is analogous to a dose-response study in most cases, is conducted in Japan. Then, if the results of the bridging study, such as the dose-response relationship of the drug efficacy, are similar to those of the corresponding foreign study, foreign clinical trial data can be extrapolated to Japan. Extrapolated trials are usually the trials conducted in the late stage of original clinical development, such as confirmatory trials, and those trials need not be conducted again in Japan. This strategy usually assumes that substantial clinical data already exist in the other regions; in other words, this strategy may imply that drug development in Japan is delayed compared to that in other regions. On the other hand, MRCTs can be implemented in every phase of clinical development, and duplication of the clinical trial data may be avoided in each stage. In addition, clinical data from several regions can be obtained simultaneously in one trial. Since participating in global drug development from the earlier stage is encouraged in Japan and globally simultaneous drug development is intended, the shift to MRCTs seems natural.

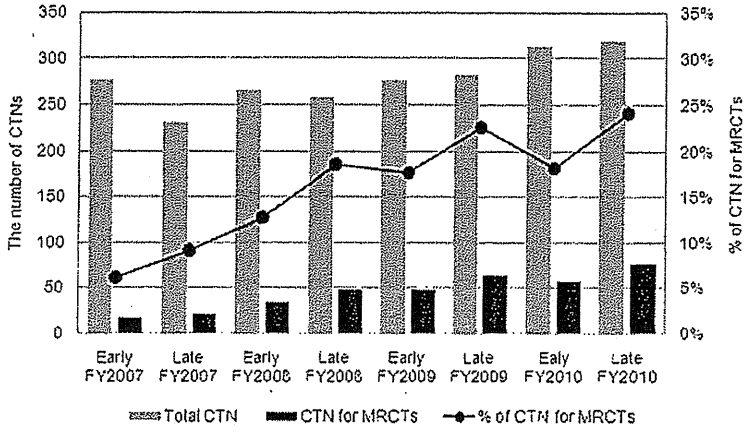

Figure 1 Half-yearly trends of clinical trial notifications (CTNs) for multiregional clinical trials (MRCTs) including Japanese subjects.

Figure 1 shows the half-yearly trends in the number of clinical trial notifications (CTNs) for MRCTs including Japanese subjects to the total number of CTNs from fiscal year 2007, the year the guidance document was issued, to 2010. The percentage of CTNs for MRCTs increased over these years, and more than 20% of CTNs were of MRCTs in 2010. This finding means that >20% of the clinical trials conducted for new drug registration in Japan are MRCTs.

Figure 2 shows the yearly trends of the percentages of the approved drugs with MRCTs and that with the bridging strategy of the total number of the approved

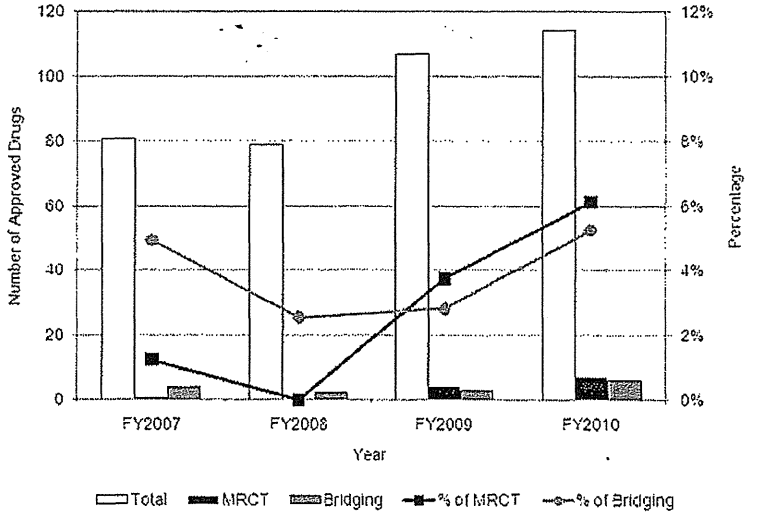

Figure 2 Yearly trends of the number of approved drugs with multiregional clinical trials (MRCTs) compared with those with the bridging strategy, along with percentages of the total number of approved drugs.

drugs. Although the percentage of approved cases with bridging was still larger than that with MRCTs in 2007 and 2008, the percentage of MRCTs following that was greatly increased. Since the number of approved drugs with MRCTs remains small compared to the total number of approved drugs and the numbers vary year to year, we should not yet draw a conclusion. However, the percentage of the approved drugs using MRCTs seems to be bypassing that using the bridging strategy.

As shown in Table 1, as of October 2011, we have had 19 cases of approved drugs using MRCT(s) included as the clinical evaluation data in the clinical data packages, most of which were approved in 2010 and 2011. By therapeutic area, the number of oncology drugs stands out. Since a certain proportion of oncology drugs have been approved without the use of Phase 3 clinical trials in Japan, we seem to be having greater opportunities to obtain clinical data in target Japanese patients in later stages of clinical development by introducing MRCTs to oncologic drug development in Japan.

Table 1 Approved cases using multiregional clinical trials (MRCTs) including Japanese subjects as of October 2011

Name of drug	Indication	Approval
Tolterodine	Overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency	April 2006
Losartan	Diabetic nephropathy with proteinuria and hypertension in patients with type 2 diabetes	April 2006
Trastuzumab	Adjuvant therapy for metastatic *HER2*-overexpressing breast cancer	February 2008
Insulin glulisine	Diabetes mellitus	April 2009
Tadalafil	Pulmonary arterial hypertension	October 2009
Peramivir	Type A and Type B influenza virus infection	January 2010
Everolimus	Metastatic renal-cell carcinoma	January 2010
Panitumumab	Metastatic colorectal carcinoma with wild-type *KRAS* tumors	April 2010
Travoprost/timolol	Glaucoma	April 2010
Temsirolimus	Advanced renal-cell carcinoma	July 2010
Laninamivir	Type A and Type B influenza virus infection	September 2010
Nilotinib	Newly diagnosed chronic myeloid leukemia in chronic phase	November 2010
Dabigatran	Stroke and systemic embolism in patients with nonvalvular atrial fibrillation	January 2011
Trastuzumab	Metastatic *HER2*-overexpressing gastric cancer	March 2011
Pramipexole	Parkinson's disease	April 2011
Edoxaban	Prevention of venous thromboembolism after major orthopedic surgery	April 2011
Dasatinib	Chronic myeloid leukemia	June 2011
Indacaterol	Chronic obstructive pulmonary disease, including chronic bronchitis and/or emphysema	July 2011
Linagliptin	Type 2 diabetes mellitus (adjunctive to diet and exercise)	July 2011

Note. In these cases, MRCT was included in the submission package as the evaluation data.

3. DECIDING THE SAMPLE SIZE OF JAPANESE SUBJECTS IN MRCTs

3.1. Methods Referred to in the Japanese Guidance Document

A clinical trial is conducted with the aim of achieving the primary objective with all subjects included in the trial, and the same aim applies to MRCTs. The subjects in each region are treated as a subgroup of the entire population. The Q&A document for the E5 guideline says, "In general, a multi-regional study should be designed with sufficient numbers of subjects so that there is adequate power to have a reasonable likelihood of showing an effect in each region of interest" (ICH, 2006). However, the number of subjects investigated in each region affects the regional confidence of the efficacy and safety results. Therefore, issues regarding how to allocate the sample size of each region and how to show efficacy among the regions have been actively discussed.

According to the Japanese guidance document, it is generally not necessary to show statistically significant results within the Japanese population; however, consistency between results from the entire population and results from the Japanese population should be obtained. Based on this concept, two possible methods are referred to as examples of placebo-controlled studies using quantitative endpoints (MHLW, 2007), while the generally recommendable method has not been established and some factors including region number, trial scale, target disease, and the relevant ratio between the total and Japanese subject numbers should be considered.

In Method 1, the sample size of Japanese subjects is calculated to keep a high probability of showing the drug effect, the difference between the placebo and the study drug in this example, in the Japanese population to maintain a certain proportion of the drug effect in the entire population. In Method 2, the sample size for each region is decided to keep a high probability of showing the results in each region that have the same direction as the results in the entire population. This method expects that, for example, if the drug effect of the entire population is >0, the drug effect should be >0 for all of the participating regions. Method 1 focuses on the consistency between results of the entire population and the Japanese population. In contrast, Method 2 ensures the consistency of each region. Both methods are based on the probability of showing that the point estimate of the drug effect in one or each region achieves certain criteria, and the methods are based on the hypothesis of there being no difference in drug effect among participating regions.

3.2. Trends of the Proportion of Japanese Subjects to the Total Subjects

Many MRCTs including with Japanese subjects are already conducted in various types of drug development strategies, including globally simultaneous drug development. We investigated the proportions of the Japanese sample size to the total sample size based on the CTNs of MRCTs that were submitted between April 2008—the year when detailed description about MRCTs, such as participating regions and total sample size in the submitted CTN, was starting to be encouraged—and September 2011 (Uyama, 2011). This survey covered 392 CTNs of MRCTs in that period. For each CTN, both the expected sample size of Japanese subjects and

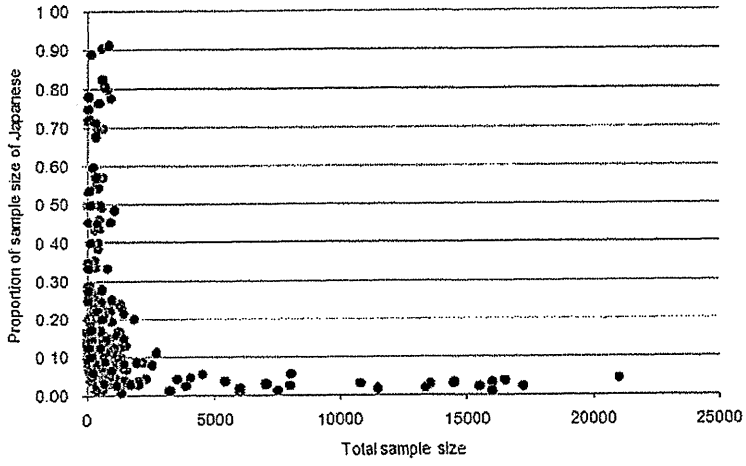

Figure 3 Relationship between the total sample size and the proportion of sample size of Japanese patients, excluding one case lacking a description of the total sample size in the clinical trial notification ($n = 391$).

the total sample size are read out. The proportion of Japanese sample size to total sample size is then calculated. These data are based on the first submitted CTN for each MRCT; therefore, changes in sample size in the middle of the trials are not reflected. In cases with clinical trials of the combination use of multiple test drugs, an identical trial may be counted more than once as the trial for each test drug. Therefore, we do not statistically summarize the proportions at this time.

Figure 3 shows the relationship between total sample size and the proportion of sample size of Japanese subjects. Although the examples of the proportion of sample size of Japanese subjects are mentioned as 20% and 15% based on Methods 1 and 2, respectively, in the reference of the guidance document, it seems that in many cases the proportion of the Japanese sample size is <0.2. For the MRCTs with large (>5000) total sample sizes, the proportions of the sample size of Japanese subjects are <0.1. There are some MRCTs with relatively higher proportions (>0.8) of Japanese sample size.

4. DISCUSSION

4.1. Trends of MRCTs in Japanese Drug Development

Compared to bridging strategies, MRCTs that can be used to collect clinical data from many regions at a time play a great role in the success of global simultaneous drug development and registration. MRCTs are expected to be conducted as Phase 3 confirmatory trials that tend to be on a large scale and over a long term for the convenience of subject enrollment. In fact, in Japan, most of the MRCTs have been planned as Phase 3 trials (Ando and Hamasaki, 2010). However, when an MRCT is planned to be conducted as a Phase 3 confirmatory trial, factors that affect the difference in drug efficacy and safety among regions and the validity of the common clinically recommended dose tested in the Phase 3 study should be

thoroughly investigated in advance. As a matter of course, regional dose-response studies can be used for this purpose; however, the Japanese guidance document recommends including Japanese subjects in a multiregional dose-response study to identify ethnic differences in the dose-response relationship among the regions early in clinical development. Figure 1 shows the rising proportion of MRCTs conducted in Japan to date; because of the increasing number of MRCTs including Japanese subjects in the early stage of clinical development, the proportion may increase in the near future.

4.2. Trends in the Sample Size of Japanese Subjects in Global Drug Development

Sample size for each region is one of the most controversial issues of MRCTs. In most of the clinical trial consultation meetings for MRCTs, this topic is included in inquiries from the sponsors. Based on the experience of the PMDA consultation meetings, the methods for determining the sample size of Japanese subjects can be categorized into three patterns. First, if there is a limited number of regions participating in an MRCT including Japan—for example, if there are two or three regions—they can decide the sample size for each region as being simply one-half or one-third of the total sample size. In the Japan–Korea studies among the approved cases, for tolterodine, for example, the number of Japanese subjects and the number of Korean subjects were nearly the same (PMDA, 2006). At times, one of the regions may be considered the main region, making its proportion higher. The second approach consists of calculating the sample size of Japanese subjects using Method 1 or Method 2 in the Japanese guidance document. The exact number calculated using the method is not always used. However, it is used at least as a reference for the discussion, and the actual sample size is decided by considering other study factors such as the number of regions, the trial scale, and the target disease as mentioned in the guidance document. Although the guidance document provides only example placebo-controlled studies using quantitative endpoints, the sponsors can use the methods with the modification along with the study design and endpoint type (Quan et al., 2009). Finally, in many cases of trials for orphan type diseases, oncology trials, and large-scale trials with many participating regions, the sample size of Japanese subjects is decided based on the feasibility of the trials, and the proportion of that to total sample size is usually very small compared with that in the two types just described.

As shown in Fig. 3, there are some cases with relatively high proportions of Japanese subjects, for example, > 0.8. One possible reason for this is that there are a few regions including Japan, and Japan is the region that plays a leading role in drug development. In such cases, the potential of using foreign data for Japanese submission or moving ahead of multiregional drug development may be investigated at this time of development. For example, in the situation when the drug has been developed mainly in Japan, investigating foreign clinical data and comparing them to clinical data of Japanese, especially in the early phase of development, may be a good foundation for global drug development in the future phases, even if the foreign data sets are not so large.

Figure 3 also shows that the proportions of the sample size of Japanese are relatively $< 20\%$ or $< 15\%$, as referenced in the guidance document, in many clinical

trials. However, in these cases, sample size calculated using Method 1, Method 2, or a modification of these may possibly be considered when the sample size is decided. In comparison, the proportion of Japanese subjects is very small in large-scale MRCTs with sample sizes > 5000. For such large-scale MRCTs, the number of participating regions may also be large, and the balance in sample size allocation among regions may be considered. In addition, the feasibility of patient enrollment may also be taken into account. For example, it will be difficult to enroll 20% of the total subjects of such large-scale trials only in Japan in many cases. Although there may be reasons for the small proportions of Japanese subjects, the difficulty interpreting results and the benefit-risk balance when there are small numbers of Japanese subjects compared to the entire populations should be considered. The generalizability of the Japanese results to actual Japanese patients and the possible coverage of special populations in Japan should also be carefully considered.

One approved case of a large-scale MRCT included a small proportion of Japanese subjects. Dabigatran, which is indicated for stroke and systemic embolism in patients with nonvalvular atrial fibrillation, was approved in January 2011 in Japan. The MRCT included in the submission data package was a global Phase 3 parallel group trial with the purpose of comparing the composite endpoint of stroke (including hemorrhagic) and systemic embolism in both the dabigatran 150 mg group and the 110 mg group to the warfarin group. Although 18,113 patients were randomized for this trial, the group contained only 326 Japanese patients. The sample size of Japanese patients was decided based on feasibility in this trial. Although it was concluded that there were no major discrepancies between the results of the Japanese population and those of the entire population, the difficulty in evaluating the similarities of both result sets and the limitation of interpreting the Japanese results were also mentioned in the review report (PMDA, 2010).

4.3. Sample Size of Japanese Subjects for MRCT for Investigating Dose Response

The Japanese guidance document currently mentions the two methods for deciding sample size for Japanese patients as examples under the assumption that the purpose of the trial is the comparison between the test drug and the placebo and the assumption that there is no difference in efficacy among the regions. In practice, the number of Japanese subjects needed in MRCTs may vary depending on the prior information of the possibility of ethnic difference in efficacy and/or safety. If there is sufficient information about the ethnic factors and clinically recommended dose among regions prior to the planning of the Phase 3 confirmatory trial and if there is a certain amount of evidence for denying the possibility of the ethnic difference regarding the drug efficacy and safety, the sample size of Japanese patients can possibly be reduced. On the contrary, if the sample size of Japanese patients seems to be relatively small in the Phase 3 trial because of the number of the regions and/or feasibility of participating in the trial, it is desirable that sufficient data about the ethnic difference be collected in advance. As previously mentioned, the Japanese guidance document recommends including Japanese subjects into a multiregional dose-response study to investigate the difference in dose-response relationship and/or recommended dose among the regions, and MRCTs in the early phase may be conducted actively in the context of global simultaneous

development in the future. Data from early-phase MRCTs that have sufficient numbers of patients from each region may be a good foundation for establishing region similarity for later phase trials. However, to date, there are no pronounced views on the sufficient sample size of Japanese subjects that should be included in early-phase MRCTs.

Most of the bridging studies conducted in Japan and the corresponding studies conducted in the other regions use a dose-response study design including multiple dose groups of the test drug and the placebo group. This means that both types of studies have sufficient power to detect the dose-response relationship and/or to determine the recommended dose for each region. Therefore, it is not difficult to compare them between Japan and other regions under the condition of similar study design. The recommended Japanese dose can be decided using the bridging study data. At times, despite the different recommended dose for Japanese patients, foreign clinical data could be extrapolated based on the comparison of the dose-response relationship and the recommended doses between the bridging study and the corresponding study (Uyama et al., 2005; Shimazawa et al., 2006). Regarding the recommended dose for each region, differences in approved doses among regions have been reported (Malinowski, 2008; Arnold et al., 2010). The possibility of adopting different recommended doses among regions should be taken into account in the early-phase development. MRCTs could be planned for all subjects to achieve the objective, and the subjects in each region are treated as a subgroup that does not have enough power to show clear achievement. In addition, since there generally is not substantial information about ethnic or other factors affecting the drug efficacy and safety in the early phase, there are many factors to be considered in the results interpretation. Even so, dose-response MRCTs may have great advantages, compared to bridging studies, as tools for efficient drug development with their simultaneity and the possibility of avoiding duplicate clinical data. To collect sufficient data for selecting the efficient development strategy in the later phase, the sample size for each region in dose-response MRCTs should be decided from the viewpoint of collecting a certain amount of information from each region. In some cases, total sample size may possibly be above that in an effort for all subjects to achieve the purpose of the trial, as a consequence of considering the amount of information in each region.

In early clinical development, the appropriateness of the endpoint for evaluating drug efficacy may be still unclear. To collect information on the dose-response relationship in each region, several endpoints should be used to strengthen the dose-response relationship in some cases, depending on the certainty of the primary endpoint or the sensitivity of the endpoints. Since pharmacological biomarkers may possibly be used to support the dose-response information, early investigations including pharmacokinetics/pharmacodynamics will also play a more important role when dose-response MRCT is the main database of the appropriate dose for each region.

5. CONCLUDING REMARKS

An MRCT is possibly the most efficient way to collect clinical data in the context of worldwide simultaneous drug development and registration. However, MRCT is one of many tools, and we should consider how to collect

sufficient efficacy and safety data in the drug development process using MRCTs in appropriate phases and situations. As a result of pursuing efficient clinical development and avoiding clinical data duplication, we will possibly evaluate rather limited data of the new drugs collected in MRCTs to evaluate efficacy, safety, and benefit-risk balance for each region before approval. Steady stepwise development with efficient data integration from each development phase will be the key in such development programs (Ichimaru et al., 2010). In addition, we should make sure to share the clinical data before approval and plan to share the data after approval among the regions where the drug is approved for the subsequent postapproval phase of actual use of the drug worldwide.

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REFERENCES

Ando, Y., Hamasaki, T. (2010). Practical issues and lessons learned from multi-regional clinical trials via case examples: A Japanese perspective. *Pharmaceutical Statistics* 9:190–200.

Arnold, F. L., Kusama, M., Ono, S. (2010). Exploring differences in drug doses between Japan and Western countries. *Clinical Pharmacology & Therapeutics* 87:714–720.

Ichimaru, K., Toyoshima, S., Uyama, Y. (2010). Effective global drug development strategy for obtaining regulatory approval in Japan in the context of ethnicity-related drug response factors. *Clinical Pharmacology & Therapeutics* 87:362–366.

International Conference on Harmonization. (1998). E5 Guideline: Ethnic Factors in the Acceptability of Foreign Clinical Data (R1). Accessed October 30, 2011. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E5_R1/Step4/E5_R1__Guideline.pdf

International Conference on Harmonization. (2006). E5 Guideline: Ethnic Factors in the Acceptability of Foreign Clinical Data Questions & Answers (R1). Accessed October 30, 2011. http://www.ich.org/fileadmin/Public _Web_Site/ICH_ Products/Guidelines/Efficacy/E5_R1/Q_As/E5_Q_As__R5_.pdf

Malinowski, H. J., Westelinck, A., Sato, J., Ong, T. (2008). Same drug, different dosing: Differences in dosing for drugs approved in the United States, Europe, and Japan. *Journal of Clinical Pharmacology* 48:900–908.

Ministry of Health, Labour and Welfare. (2007). Basic Principles on Global Clinical Trials. Notification No. 0928010, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, Tokyo, Japan.

Pharmaceuticals and Medical Devices Agency. (2006). Review Report of Tolterodine Tartrate (in Japanese). Pharmaceuticals and Medical Devices Agency, Tokyo, Japan. Accessed October 30, 2011. http://www.info.pmda.go.jp/shinyaku/P200600014/40007900_21800AMY10088_ Q100_1.pdf

Pharmaceuticals and Medical Devices Agency. (2010). Review Report of Dabigatran (in Japanese). Pharmaceuticals and Medical Devices Agency, Tokyo, Japan. Accessed October 30, 2011. http://www.info.pmda.go.jp/shinyaku/P201100019/530353000_22300AMX00433000_ A100_1.pdf

Quan, H., Zhao, P. L., Zhang, J., Roessner, M., Akizawa, K. (2009). Sample size considerations for Japanese patients in a multi-regional trial based on MHLW guidance. *Pharmaceutical Statistics* 9:100–112.

Shimazawa, R., Ando, Y., Hidaka, S., Saito, K., Toyoshima, S., Kobayashi, F. (2006). Development of triptans in Japan: Bridging strategy based on the ICH-E5 guideline. *Journal of Health Science* 52:443–449.

Uyama, Y, Shibata, T, Nagai, N, Hanaoka, H, Toyoshima, S, Mori, K. (2005). Successful bridging strategy based on ICH E5 guideline for drugs approved in Japan. *Clinical Pharmacology & Therapeutics* 78:102–113.

Uyama, Y. (2011). East-Asian Contributions to Global Drug Developments for Providing a Better Drug to Patients. Presentation at 2011 APEC Multi-Regional Clinical Trials Tokyo Workshop highlighting Korea, China, and Japan tripartite symposium. Accessed November 9, 2011. http://www.pmda.go.jp/english/past/2011apec_workshop/file/3-2Yoshiaki_Uyama.pdf

Regulatory perspective on remaining challenges for utilization of pharmacogenomics-guided drug developments

Pharmacogenomics-guided drug development has been implemented in practice in the last decade, resulting in increased labeling of drugs with pharmacogenomic information. However, there are still many challenges remaining in utilizing this process. Here, we describe such remaining challenges from the regulatory perspective, specifically focusing on sample collection, biomarker qualification, ethnic factors, codevelopment of companion diagnostics and means to provide drugs for off-target patients. To improve the situation, it is important to strengthen international harmonization and collaboration among academia, industries and regulatory agencies, followed by the establishment of an international guideline on this topic. Communication with a regulatory agency from an early stage of drug development is also a key to success.

KEYWORDS: biomarker drug development international harmonization personalized medicine pharmacogenomics regulatory science

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Pharmacogenomics (PGx) has been implemented in the practice of drug development over the last decade. As a result, the number of approved drugs with PGx information listed on their labels under the section 'dosage/administration' or 'indication/usage' has increased [1,2]. For example, in Japan, the number of drugs with PGx information (e.g., HER2, EGFR, *KRAS* or ALK in the case of anticancer drugs) listed on their labels (known as prescribing information [PI]) has increased during the last 4 years (Figure 1).

In this article, we describe the remaining challenges in the utilization of PGx-guided drug development (PGxDD) from a regulatory perspective.

Sample collection for future genetic analysis in clinical trials

The first challenge is the collection and storage of samples for future genetic analysis in clinical trials. During the early stages of drug development, it usually remains unknown which genetic factors contributed to drug response (efficacy/safety), especially with respect to drug safety. It is important that samples for performing a genetic test/analysis are readily available when a genetic factor is found or expected to influence the response of a drug based on new research findings. Even in a retrospective analysis, genetic tests, particularly targeting areas of DNA thought to be stable, may provide useful scientific information for examining the possibility of the involvement of a genetic factor in drug response, although appropriate steps, including the stabilization process of the collected sample, should be employed [3]. In fact, retrospective analysis of samples collected in clinical trials has led to the identification of biomarkers (e.g., *KRAS* and EGFR) that are currently used for anticancer drugs [4]. Therefore, the regulatory agencies of Japan (Pharmaceuticals and Medical Devices Agency; PMDA), the USA (the US FDA) and the EU (EMA) have encouraged sample collection in clinical trials [Maliepaard M *et al.* Pharmacogenetics in the evaluation of new drugs; a multiregional regulatory perspective (2012), Submitted]. To appropriately evaluate the results of genetic tests, based on samples collected in a clinical trial without any bias, samples should be collected as often as possible, from all subjects enrolled in the trial. A convenience sample acquired without statistical consideration may lead to a misinterpretation of the PGx data [5]. It has been reported that the current rate of sample collection in clinical trials is relatively low (50–69%) for most therapeutic areas [6]. In the case of a multiregional clinical trial (MRCT), sample collection is more challenging because the policy and principle for a process for storing, shipping and maintaining samples with integrity may differ among different countries where the MRCT is conducted. The main reason for sample attrition is the rejection by the Institutional Review Board/Ethics Committee, health authority and/or an investigator choosing not to participate in the trial [6,7].

To improve the situation, a workshop was held by the Drug Information Association to discuss this topic and subsequently several tasks, including promotion of a common understanding

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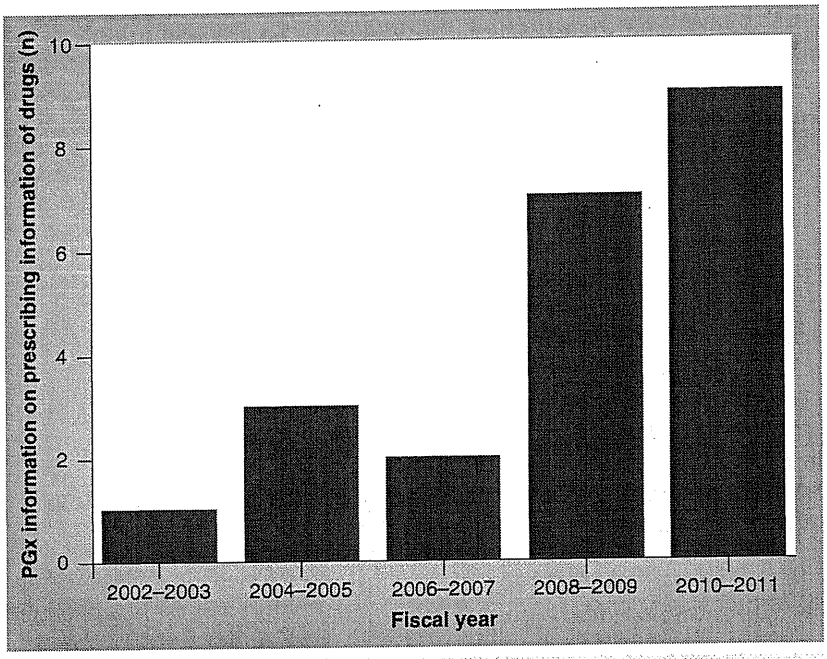

Figure 1. Trends of pharmacogenomics information in prescribing information of approved drugs in Japan. The number represents approved PGx information on drug label under the section 'dosage/administration' or 'indication/usage' in each fiscal year. If different PGx information is included for a drug, those are counted separately. The names of approved drugs are imatinib mesilate for 2002–2003; tamibarotene, arsenic trioxide and leuprorelin acetate for 2004–2005; ibritumomab tiuxetan and imatinib mesilate for 2006–2007; atomoxetine hydrochloride, cetuximab (for two PGx informations), dasatinib hydrate, lapatinib tosilate hydrate, maraviroc and nilotinib hydrochloride hydrate for 2008–2009; and bevacizumab, crizotinib, escitalopram oxalate, fulvestrant, gefitinib, imatinib mesilate, lenalidomide hydrate, mogamulizumab and panitumumab for 2010–2011.
PGx: Pharmacogenomics.

of drug regulation in each country, proper distribution of information regarding PGx and harmonization of the sample collection process by the participating industries, among others, were proposed [8]. To conduct sample collection in a MRCT smoothly and appropriately, its feasibility in each country should be checked before starting. International harmonization of the regulatory guidelines, describing the standards for collection and storage of samples in clinical trials, will be necessary to further promote the use of PGx in drug developments.

Biomarker qualification for regulatory use

The second challenge is 'biomarker qualification'. A PGx biomarker to be used in drug developments should be qualified and accepted by a regulatory agency [9] because use of an unqualified and unacceptable biomarker may result in misinterpretation of the acquired data due to false signals (false-positive or -negative signal) and, therefore, may not be used in regulatory decision-making. Biomarker qualification by a regulatory agency is an important process to qualify the objective and context of use of the biomarker before it can be widely used in drug development. To confirm the acceptability of the biomarker, each agency – PMDA, the FDA and the EMA – has established a biomarker qualification process. Seven biomarkers, including KIM-1, cystatin-C and β-2 microglobulin, have been qualified by these three regulatory agencies for nonclinical use to detect nephrotoxicity in rats [10]. To qualify a biomarker by the regulatory agency, an important point to consider is to clearly define the 'context use of biomarker' according to the E16 guideline of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) [9,10]. The process of accumulating evidence for the biomarker qualification is both lengthy and a costly affair. The final goal would be to establish a qualified biomarker for accurately estimating the drug responses in patients, resulting in maximizing benefit and minimizing risk of the drug. In the situation where the biomarker was not qualified until enough evidence was accumulated, it would be unrealistic to use the biomarker in drug development. Therefore, a biomarker should be qualified as early as possible for promoting its use in drug development when reasonable evidence for a particular context of use is available. As depicted in Figure 2A, a repeatable biomarker qualification process would be important for this purpose. More specifically, the first biomarker qualification may be conducted for a narrow context of use (e.g., nonclinical investigation only). Through this first round of qualification process, tasks requiring further studies could then be identified by a regulatory agency. When more information and data are available from the studies performed based on the qualification advice, a second biomarker qualification process may be conducted to expand the original context (context A) to a broader context of use (Figure 2B; addition of context B to context A). Following this stepwise approach of a repeatable qualification process, the context of use of a biomarker would become an ideal one (e.g., clinical predictability in humans). In this approach, it is important to discuss a study design with a regulatory agency before starting the study for biomarker qualification, particularly for a study translating the context between species (e.g., expanding the context from animal to human). If a biomarker is expected to be useful only for clinical use, a reason why nonclinical qualification cannot be carried out for

the biomarker should adequately be presented and methods to accumulate data for the qualification should also be discussed with a regulatory agency. To promote the stepwise approach, roles of scientific consortiums, such as the Predictive Safety Testing Consortium in the USA for the biomarker qualification of nephrotoxicity in rats, are important [10] because it may be difficult in terms of resources for an individual organization (i.e., an academic institute or industry) to accumulate enough evidence for the biomarker qualification and to repeat the qualification process as well. To promote this concept of biomarker qualification and to provide more opportunities for discussion with a regulatory agency, PMDA expanded the biomarker qualification program in April 2012 by formally establishing new scientific consultation categories focusing on PGx/biomarkers. Specifically, these new consultation categories include the planning-stage studies, as well as follow-ups on previous consultations for qualifying a new context of use of a biomarker.

Another important point to consider is that a biomarker should be qualified internationally rather than by a single regulatory agency because most drugs are currently developed globally, and conducting a MRCT has become a standard strategy for drug development [11]. For global drug developments, an internationally qualified biomarker is necessary so that the data can be submitted to multiple regulatory agencies for a regulatory review and decision-making. For example, the seven biomarkers for nonclinical nephrotoxicity described above are now qualified and accepted for the specific context of use by all ICH regulatory agencies (PMDA, the FDA and the EMA) for the regulatory purpose. Thus, the use of these seven nonclinical biomarkers could be promoted in drug development for regulatory submission to these three agencies. In the case of a clinical biomarker, which is only useful in a specific population due to ethnic difference, international qualification would be still useful, because the recognition of such scientific facts by multiple regulatory agencies will enable better scientific advice and review for global drug development (e.g., discussion about a design of a MRCT and acceptance of MRCT data). In the near future, more qualified biomarkers, especially clinical biomarkers, would be necessary to promote use of PGx in clinical trials. Recently, the EMA's opinion regarding the clinical biomarkers for Alzheimer's disease – namely, tau and Aβ42 in the cerebrospinal fluid – has been published [12]. To promote the use of such clinical biomarkers in MRCTs, the biomarker should be confirmed as internationally acceptable. For this purpose, reinforcement of international regulatory cooperation is a key for facilitating the

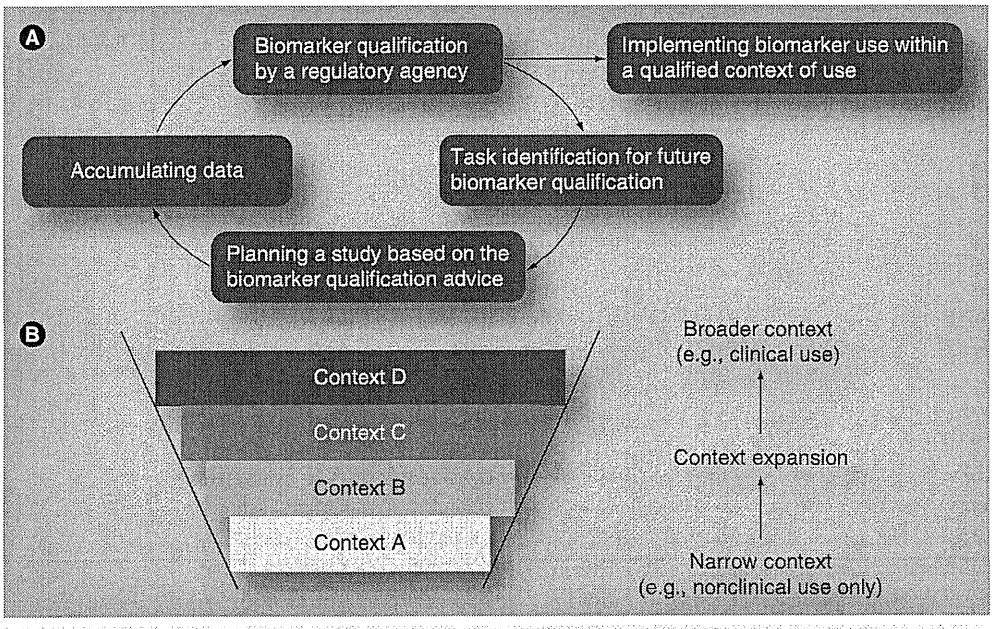

Figure 2. Stepwise approach of a repeatable process for biomarker qualification in expanding the 'context of use'. (A) Steps for biomarker qualification and implementation. **(B)** Stepwise approach to expand the context of use. A biomarker may firstly be qualified in the narrow context (e.g., nonclinical use only). It may be expanded to the broader context (e.g., adding the clinical use) when new data are available. In case of a biomarker that is only useful in nonclinical use, the context may be expanded to other purposes or use in other species.

biomarker qualification process. In recent years, PMDA has worked closely with the FDA and EMA to promote the use of biomarkers in drug developments. Active collaborations among the regulatory agencies will increase the interests of pharmaceutical/medical device industries and other stakeholders involved in the biomarker qualification process.

Ethnic factors in evaluating PGx data

In our experience, ethnic factors should also be taken into consideration when evaluating PGx data. The first example is the case of UGT1A1 activity in cancer patients following irinotecan administration. SN-38, an active metabolite of irinotecan, is mainly generated by carboxylesterases and then detoxicated by UGT1A1 to SN-38G. Thus, UGT1A1 plays an important role in determining the blood concentration of SN-38 and its toxicity [13]. In this regard, racial variability in haplotype frequencies of UGT1A1 and glucuronidation activity has been reported [14]. The *UGT1A1*28* allele is commonly found in the Japanese, Caucasian and African–American populations, but the *UGT1A1*6* allele is frequently found only in the Japanese population but not in the other populations. A prospective clinical trial has confirmed that the area under the the curve ratio of SN-38 glucuronide to SN-38 is decreased (i.e., area under the curve of SN-38 is increased) and the risk of neutropenia is higher in Japanese patients carrying haplotypes of the homozygotes and double heterozygotes of *UGT1A1*6* and **28* (**6/*6, *28/*28* and **6/*28*) [13]. Therefore, the irinotecan label includes information on both *UGT1A1*6* and *UGT1A1*28* alleles in Japan but not in the USA.

Another example is the case of EGFR mutation, which is an important factor in predicting the efficacy of gefitinib, the tyrosine kinase inhibitor, for the non-small-cell lung cancer; it should be noted that the EGFR mutation rate is higher in the Japanese population than in the Caucasian population [15,16]. Recent randomized prospective studies have confirmed the higher efficacy of gefitinib in Japanese non-small-cell lung cancer patients with an EGFR mutation [17–19], resulting in the revision of the Japanese PI of this drug focusing on the patients with EGFR mutation.

The final example is the case of *HLA-B*1502*, which is associated with carbamazepine (CBZ)-induced Stevens–Johnson syndrome (SJS). Strong association of *HLA-B*1502* with CBZ-induced SJS has been reported in the Han Chinese population [20,21], while such association has not been observed in the Japanese population [22,23]. Recently, it has been suggested that *HLA-A*3101* has an important role in predicting the CBZ-induced cutaneous adverse drug reaction, including SJS, in the Japanese population [23], although the clinical importance of *HLA-A*3101* on patient selection should be further investigated. Currently, the Japanese PI for CBZ includes information on *HLA-B*1502* and *HLA-A*3101* as reference information without any specific recommendation. Interestingly, the *HLA-A*3101* has also been reported to play a similar role in the European population [24]. This may be related to a difference in the background prevalence of the HLA allele in each population, because the *HLA-B*1502* allele is rare in Japanese and European populations (China: 7.4; Japan: 0.4; Europe: 0.5–0.8%) [25], but a substantial percentage of the *HLA-A*3101* allele exists in those populations (China: 2.2;Japan: 8.7; Europe: 2–5%) [24,25]. This example also illustrates differences in the impact of a genetic factor on drug responses even among the east-Asian population.

Based on the above discussion, it is important to carefully evaluate whether the role of a biomarker in one population could be extrapolated to other populations in terms of ethnic factors. Our recent study demonstrated that many differences are found in the warning or recommendation level of biomarker contexts on the drug labels of the USA and Japan, and one important factor that contributed to the difference in the label is the availability of clinical evidence in the Japanese population [26]. From a regulatory perspective, data acquired from studies in own national subjects are very useful and important to guide regulatory action. In the era of globalization of drug development, utilization of PGx in MRCTs is strongly encouraged for accumulating PGx data on various populations, followed by examining the effects of genetic factors in drug responses (efficacy and safety) in a subset population based on ethnic factors, although background prevalence ratio of the target genetic marker among populations should be taken into consideration when evaluating the data.

Codevelopment of companion diagnostics with a drug

Recently, the number of drugs whose companion diagnostics (CDx) were simultaneously approved has increased. As shown in Table 1, CDx for anticancer drugs are currently most popular in Japan. Following the approval of a drug, the availability of CDx significantly affects the applicability and utilization of PGx in clinical

Table 1. Recent examples of drugs for which companion diagnostics were simultaneously approved in Japan.

Nonproprietary name	Indication	Biomarker	Relevant companion diagnostics (type of analysis)	Fiscal year approved
Cetuximab	EGFR-expressing, unresectable and advanced/recurrent colorectal carcinoma	EGFR	EGFR pharmDx Kit (IHC)	2008
		KRAS	TheraScreen: K-RAS Mutation Kit (PCR)	2010
Lapatinib	Inoperable or recurrent breast cancer with HER2 overexpression	Her2/neu	Ventana I VIEW PATHWAY HER2(4B5) (IHC)	2009
Panitumumab	Unresectable, advanced or recurrent colorectal cancer with wild-type *KRAS*	*KRAS*	TheraScreen: K-RAS Mutation Kit (PCR)	2010
Gefitinib	Unresectable advanced or recurrent non-small-cell lung cancer in patients with *EGFR* gene mutation	EGFR	Therascreen EGFR Mutation Detection Kit RGQ (PCR)	2011
Mogamulizumab	Relapsed and refractory CCR4-positive adult T-cell leukemia/lymphoma	CCR4	Poteligeo test (IHC and FCM)	2011
Crizotinib	Unresectable advanced/relapsed *ALK* fusion gene-positive non-small-cell lung cancer	ALK	Vysis ALK Break Apart FISH Probe Kit (FISH)	2011

FCM: Flow cytometry; IHC: Immunohistochemistry.

practices because the genetic tests used as a guide for drug administration should be reliable, easily handled and achievable even in a small clinic or hospital without a specialized laboratory. The feasibility of the genetic test would depend on the availability of its CDx that is approved by a regulatory agency. Another factor that could affect the applicability and utilization of PGx would be whether the cost for the genetic test is covered by health insurance. In Japan, the test fees for all CDx listed in Table 1 are covered by the national health insurance, although test fees for some of other genetic tests may be not covered. Thus, such CDx would become increasingly accessible to the physicians in clinical practices and to patients requiring drug administration. However, there is only a limited number of drugs, especially for the noncancer diseases, for which approved CDx are currently available. Thus, a strategy for developing a CDx simultaneously with a drug for approval should be established and implemented, not only for treating cancer patients but also for treating patients with other diseases.

There are many challenges in CDx development. One of the challenges is how to synchronize the development of a CDx with that of a drug. The first possible scenario is that a target biomarker affecting the drug response was initially discovered during the process of a new drug being developed. In this scenario, the time to begin the CDx development for the target biomarker will be always run behind the drug development. Thus, there may not be enough time for the analytical and clinical validation of the CDx before the corresponding drug gets approval. The second possible scenario is that a biomarker has already been identified independently of the development of a particular drug. In this scenario, an assay for the biomarker may already be available as a laboratory test for research purposes but not approved as a CDx by a regulatory agency. When a drug targeting the identified biomarker is developed, it may lead to less incentive for a device company, as well as the physicians, to conduct clinical trials for clinical validation of the CDx, because the assay might be already in use in clinical practice [27]. In both scenarios, an early-stage close collaboration between the pharmaceutical and CDx development teams/companies is important in achieving the final goal. An example of one such collaboration that has led to success is the development of the anticancer drug vemurafenib (a BRAF kinase inhibitor) [28]. In the second scenario, use of the assay without clinical validation as a guide for drug administration might be problematic because a medical decision based on the assay result could be inaccurate and incorrect. Thus, before widely using an assay for a biomarker, its reliability (i.e., analytical and clinical validity) should be confirmed by a regulatory agency. Recently, the FDA and EMA published a draft guideline for codevelopment of CDx with a drug, wherein the importance of simultaneous approval of a CDx along with a drug has been described [29,30]. PMDA has also been working on this issue and our consideration regarding CDx will be published in the near future [102]. Pharmaceutical companies are thus encouraged to take the initiative to develop CDx in collaboration with the CDx development

teams/companies so that a CDx is available at the time of drug approval. Early communication with a regulatory agency is also a key to achieve success for the codevelopment. In the near future, it will be necessary to establish an international guideline on this topic to appropriately promote the codevelopment at the global level.

Providing drugs to off-target patients

It should be mentioned here that even during the process of implementation of PGxDD we should not forget to consider a way to provide drugs to off-target patients. If a biomarker is considered to have an important role in drug response during the exploratory stage of drug development, the biomarker(+) patients may be selected as a target population in clinical trials. This enrichment approach may be an effective way to clearly identify a target population for a drug. If clear and sufficient data, showing positive benefit:risk balance of a drug on the target population are obtained during the confirmatory stage, then such a drug will likely be approved. One important point to consider in applying such an enrichment strategy is how data were accumulated at the exploratory stage for selecting biomarker(+) patients. In other words, it is also important to consider the scientific evidence that was available at that stage to exclude the biomarker(-) patients. A patient selection process without sufficient supporting data may lead to an inappropriate drug development strategy, as a result of which the biomarker(-) patients would likely miss a chance to be treated with the drug. Table 2 summarizes the differences in the available evidence from strategies used in drug development. If no PGx were implemented in the drug development and data were only available for the overall population, as a result it would be difficult to conclude in which population (the biomarker[+] and [-]) drug administration would be appropriate. In the case of the enrichment strategy that included only the biomarker(+) patients, data are available for the biomarker(+) population, but not for the biomarker(-) population and the overall population. Without the available data, we cannot conclude whether or not a drug could be administered to the biomarker(-) population. Therefore, the standard strategy using PGx in the exploratory stage of drug development should include both the biomarker(+) and (-) populations in clinical trials, and should examine which population is suitable as the target population of a drug. Whether the drug really has no effect on the biomarker(-) population should be carefully evaluated before conducting a confirmatory trial focusing on the biomarker(+) population. In the case of a safety biomarker, conducting a prospective clinical study on both biomarker(+) and biomarker(-) populations may be difficult owing to ethical concerns, even at the exploratory stage. In such cases, all available evidence including related trial data, literature and other published works should be thoroughly reviewed, and appropriateness to exclude the biomarker(-) population due to suggested high risks should be clearly explained. Furthermore, evaluating biomarker data together with pharmacokinetics/pharmacodynamics data in the exploratory stage may be helpful to identify an appropriate target population and to design a confirmatory trial. A discussion with a regulatory agency on these points is also very important. In addition, if a drug has been developed and approved only for the biomarker(+) population without clear evidence to exclude the biomarker(-) population, continuous efforts should be made to provide a drug for the biomarker(-) population.

Future challenges in implementing PGxDD

Patient satisfaction in drug therapy is still low in many therapeutic areas, such as pulmonary cancer and Alzheimer's disease [31]. More new drugs are clearly needed to improve public health, and PGxDD should be utilized as one of the standard

Table 2. Different scientific data available from various pharmacogenomics strategies used in drug development.

PGx strategy used	Population used for gathering scientific evidence		
	Overall population	*Biomarker(+) population*	*Biomarker(-) population*
No PGx	o	x	x
Enroll biomarker(+) patients only	x	o	x
Enroll both biomarker(+) and (-) patients	o	o	o

o: Data available; PGx: Pharmacogenomics; x: Data not available.

drug development strategies in broader disease areas than is currently practised. In particular, implementation of PGxDD in neurological and psychiatric diseases is expected in the near future because the attrition rate of drug developments is higher [32] and objective surrogate end points have been less established [33]. PGxDD focusing on pediatric and geriatric populations will also be one of the high priority areas where utilization of PGx may contribute to providing a better drug because high interindividual differences in drug responses are expected owing to various factors such as age/growth, differences in physiological and pharmacological functions, including the PGx of drug metabolizing enzymes, drug transporters and target markers of a drug [34,35]. Similarly, more efforts should be advocated for the utilization of PGx in orphan and rare diseases because PGx research may contribute to understanding a mechanism of the disease and may increase an efficiency of clinical trial by providing clear evidence on the efficacy/safety, even in a stratified small population. For the above purpose, a standard strategy for PGxDD, including the development of CDx, which is acceptable to the regulatory agencies, should be established in the next few years. Establishment of qualified biomarkers, arising from increased collaborative efforts among academia, industries and regulatory agencies, will contribute to reduce the attrition rate of drug developments [32] and will provide more new drugs to patients. If clinical data were already available on the qualified biomarkers, they could be incorporated in the drug label (the Japanese PI) with a specific recommendation for promoting the use of PGx in clinical practices.

The strategies described above should be internationally harmonized and they should be acceptable to multiple regulatory agencies in the era of globalization of drug developments. Thus, a practical platform to strengthen collaborations

Executive summary

Background

- Pharmacogenomics (PGx)-guided drug developments have been implemented in practice in the last decade, resulting in an increase in the number of approved drugs whose labels clearly state the PGx information under the section 'dosage/administration' or 'indication/usage' as important information.
- As remaining challenges, several topics are discussed, focusing on sample collection for future genetic analysis in clinical trials, biomarker qualification for regulatory use, ethnic factors in evaluating PGx data, codevelopment of companion diagnostics (CDx) with a drug and means to provide drugs for off-target patients.

Sample collection for future genetic analysis in clinical trials

- Samples for genetic tests/analyses should be collected in clinical trials so that genetic tests/analyses could be conducted when involvement of genetic factors in drug responses are found or expected based on new research findings.

Biomarker qualification for regulatory use

- Biomarkers should be qualified as early as possible to promote their use in drug developments. For this purpose, a stepwise approach with a repeatable qualification process by a regulatory agency is important.
- In the era of globalization of drug developments, acceptability of biomarkers should be confirmed internationally and reinforcement of international regulatory cooperation is a key to facilitate biomarker qualification.

Ethnic factors in evaluating PGx data

- Ethnic factors should be considered in PGx data evaluation. Utilization of PGx in multiregional clinical trials is strongly encouraged for accumulating PGx data on various populations, followed by examination of the effects of genetic factors on drug responses (efficacy and safety) in an ethnic factor-based subset population.

Codevelopment of CDx with a drug

- CDx should be available at the time of approval of the relevant drug, because availability of CDx significantly affects the applicability and utilization of PGx in clinical practices. To promote the codevelopment, close collaboration is important between the pharmaceutical and CDx development teams/companies from an early stage of the development process.

Providing drugs to off-target patients

- The standard strategy of using PGx in the exploratory stage of drug development should include both the biomarker(+) and biomarker(-) populations in clinical trials and should examine which population is suitable as the target population of a drug. Whether the drug has really no effect on the biomarker(-) population should be carefully evaluated before conducting a confirmatory trial focusing on the biomarker(+) population.

Future challenges in implementing PGx-guided drug developments

- To utilize PGx-guided drug developments and approval, it is important to reinforce international harmonization and collaboration among academia, industries and regulatory agencies, followed by establishment of an international guideline on this topic.
- Communication with a regulatory agency from an early stage of drug development, including CDx development, is the key to success.

not only between regulatory agencies, but also among industries, academia and regulatory agencies, is necessary to discuss the appropriate strategy and its applicability on the global level. Based on the outcome of the discussion, an international guideline should be developed. The challenges mentioned in this article may serve as an agenda for such a guideline.

Disclaimer

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References

Papers of special note have been highlighted as:
* of interest
** of considerable interest

1 Uyama Y, Ishiguro A, Nakamura H, Toyoshima S. Use of biomarkers in drug development: Japanese perspectives. In: *Predictive Approaches in Drug Discovery and Development: Biomarkers and In Vitro/In Vivo Correlations*. Williams JA, Koup J, Lalonde R, Christ DD (Eds). John Wiley & Sons Inc., NJ, USA, 269–287 (2012).

2 Frueh FW, Amur S, Mummaneni P *et al.* Pharmacogenomic biomarker information in drug labels approved by the United States food and drug administration: prevalence of related drug use. *Pharmacotherapy* 28(8), 992–998 (2008).

3 Poste G, Carbone DP, Parkinson DR, Verweij J, Hewitt SM, Jessup JM. Leveling the playing field: bringing development of biomarkers and molecular diagnostics up to the standards for drug development. *Clin. Cancer Res.* 18(6), 1515–1523 (2012).

4 La Thangue NB, Kerr DJ. Predictive biomarkers: a paradigm shift towards personalized cancer medicine. *Nat. Rev. Clin. Oncol.* 8(10), 587–596 (2011).

5 Wang S-J, O'Neill RT, Hung HJ. Statistical considerations in evaluating pharmacogenomics-based clinical effect for confirmatory trials. *Clin. Trials* 7(5), 525–536 (2010).

6 Warner AW, Bhathena A, Gilardi S *et al.* Challenges in obtaining adequate genetic sample sets in clinical trials: the perspective of the industry pharmacogenomics working group. *Clin. Pharmacol. Ther.* 89(4), 529–536 (2011).

* **Describes the current situation of a sample collection and reasons for its failure.**

7 Ricci DS, Broderick ED, Tchelet A *et al.* Global requirements for DNA sample collections: results of a survey of 204 ethics committees in 40 countries. *Clin. Pharmacol. Ther.* 89(4), 554–561 (2011).

8 Warner A, Nelsen A, Bhathena A *et al.* Enabling pharmacogenomic clinical trials through sampling. *Pharmacogenomics* 11(12), 1649–1654 (2010).

** **Describes the outcome of the workshop focusing on genomic sample collection for future use.**

9 Goodsaid F. Challenges of biomarkers in drug discovery and development. *Expert Opin. Drug Discov.* 7(6), 457–461 (2012).

10 Dieterle F, Sistare F, Goodsaid F *et al.* Renal biomarker qualification submission: a dialog between the FDA-EMEA and predictive safety testing consortium. *Nat. Biotech.* 28(5), 455–462 (2010).

*** **First biomarkers that were qualified internationally by more than two regulatory agencies.**

11 Thiers FA, Sinskey AJ, Berndt ER. Trends in the globalization of clinical trials. *Nat. Rev. Drug Discov.* 7(1), 13–14 (2008).

12 Isaac M, Vamvakas S, Abadie E, Jonsson B, Gispen C, Pani L. Qualification opinion of novel methodologies in the predementia stage of Alzheimer's disease: cerebro-spinal-fluid related biomarkers for drugs affecting amyloid burden: regulatory considerations by European Medicines Agency focusing in improving benefit/risk in regulatory trials. *Eur. Neuropsychopharmacol.* 21(11), 781–788 (2011).

13 Minami H, Sai K, Saeki M *et al.* Irinotecan pharmacokinetics/pharmacodynamics and *UGT1A* genetic polymorphisms in Japanese: roles of *UGT1A1*6* and **28*. *Pharmacogenet. Genomics* 17, 497–504 (2007).

14 Kaniwa N, Kurose K, Jinno H *et al.* Racial variability in haplotype frequencies of *UGT1A1* and glucuronidation activity of a novel single nucleotide polymorphism 686c> t (p229l) found in an African–American. *Drug Metab. Dispos.* 33(3), 458–465 (2005).

15 Paez JG, Jänne PA, Lee JC *et al.* *EGFR* mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* 304(5676), 1497–1500 (2004).

16 Lynch TJ, Bell DW, Sordella R *et al.* Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N. Engl. J. Med.* 350(21), 2129–2139 (2004).

17 Fukuoka M, Wu Y-L, Thongprasert S *et al.* Biomarker analyses and final overall survival results from a Phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). *J. Clin. Oncol.* 29(21), 2866–2874 (2011).

18 Maemondo M, Inoue A, Kobayashi K *et al.* Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N. Engl. J. Med.* 362(25), 2380–2388 (2010).

19 Mitsudomi T, Morita S, Yatabe Y *et al.* Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised Phase III trial. *Lancet Oncol.* 11(2), 121–128 (2010).

20 Chung WH, Hung SI, Hong HS *et al.* Medical genetics: a marker for Stevens–Johnson syndrome. *Nature* 428(6982), 486 (2004).

21 Chen P, Lin JJ, Lu CS *et al.* Carbamazepine-induced toxic effects and *HLA-B*1502* screening in Taiwan. *N. Engl. J. Med.* 364(12), 1126–1133 (2011).

22 Kaniwa N, Saito Y, Aihara M *et al.* HLA-B locus in Japanese patients with antiepileptics and allopurinol-related Stevens–Johnson syndrome and toxic epidermal necrolysis. *Pharmacogenomics* 9(11), 1617–1622 (2008).

23 Ozeki T, Mushiroda T, Yowang A *et al.* Genome-wide association study identifies *HLA-A*3101* allele as a genetic risk factor for

carbamazepine-induced cutaneous adverse drug reactions in Japanese population. *Hum. Mol. Genet.* 20(5), 1034–1041 (2011).

24 McCormack M, Alfirevic A, Bourgeois S *et al.* *HLA-A*3101* and carbamazepine-induced hypersensitivity reactions in Europeans. *N. Engl. J. Med.* 364(12), 1134–1143 (2011).

25 Kurose K, Sugiyama E, Saito Y. Population differences in major functional polymorphisms of pharmacokinetics/pharmacodynamics-related genes in eastern asians and europeans: implications in the clinical trials for novel drug development. *Drug Metab. Pharmacokinet.* 27(1), 9–54 (2012).

26 Otsubo Y, Asahina Y, Noguchi A, Sato Y, Ando Y, Uyama Y. Similarities and differences between US and Japan as to pharmacogenomic biomarker information in drug labels. *Drug Metab. Pharmacokinet.* 27(1), 142–149 (2012).

* **Comparison of pharmacogenomic information on drug labels between the USA and Japan.**

27 Kelley RK, Atreya C, Venook AP, Febbo PG. Predictive biomarkers in advance of a companion drug: ahead of their time? *J. Natl. Compr. Canc. Netw.* 10(3), 303–309 (2012).

28 Cheng S, Koch WH, Wu L. Co-development of a companion diagnostic for targeted cancer therapy. *N. Biotechnol.* 29(6), 682–688 (2012).

29 Committee for Medicinal Products for Human Use. *Reflection Paper on Co-Development of Pharmacogenomic Biomarkers and Assays in the Context of Drug Development: Draft.* EMA, London, UK (2010).

30 US FDA. *Draft Guidance for Industry and Food and Drug Administration Staff: In Vitro Companion Diagnostic Devices.* US FDA, MD, USA (2011).

31 Japan Health Science Foundation. *Report on Basic Technology: Medical Needs in 2015.* Japan Health Science Foundation, Tokyo, Japan (2005).

32 Kola I, Landis J. Can the pharmaceutical industry reduce attrition rates? *Nat. Rev. Drug Discov.* 3(8), 711–716 (2004).

33 Narasimhan S, Lohoff FW. Pharmacogenetics of antidepressant drugs: current clinical practice and future directions. *Pharmacogenomics* 13(4), 441–464 (2012).

34 Pilotto A, Panza F, Seripa D. Pharmacogenetics in geriatric medicine: challenges and opportunities for clinical practice. *Curr. Drug Metab.* 12(7), 621–634 (2011).

35 Goldman J, Becker ML, Jones B, Clements M, Leeder JS. Development of biomarkers to optimize pediatric patient management: what makes children different? *Biomarker Med.* 5(6), 781–794 (2011).

Websites

101 Biomarkers related to drug or biotechnology product development: context, structure and format of qualification submissions. International Conference on Harmonisation, Geneva Switzerland (2010). www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E16/Step4/E16_Step_4.pdf

* **International guideline describing the context, structure and format of qualification submissions.**

102 PMDA Companion Diagnostics Project. www.pmda.go.jp/kijunsakusei/companion.html