Investigation on how to effectively provide pharmacokinetic information to healthcare professionals in light of the current state of population pharmacokinetic research

Megumi Watanabe-Uchida

Graduate School of Pharmaceutical Sciences

Department of Clinical Medicine (Pharmaceutical Medicine)

Kitasato University

5-9-1 Shirokane, Minato-ku, Tokyo, 108-8641, Japan

Abstract

Population pharmacokinetics (PPK) is a useful approach to the evaluation of drug pharmacokinetics (PK) in patients and is a widely used method for the evaluation of PK in clinical trials. PPK uses a statistical model to calculate population parameters, their variance, and covariates from sparse and unbalanced data in a large target population. Population parameters, such as clearance (CL) and distribution of volume (Vd) can subsequently be used to establish individual prescribing regimens for specific patients. Following the publication of a guidance document on PPK by the United States (US) Food and Drug Administration (FDA) (1999), the use of PPK methods for the PK evaluation of new drugs for approval in Japan and abroad has increased. Furthermore, post-marketing clinical studies using PPK analysis have been reported by medical and academic institutions in order to complement the poor PK information, thus increasing the available PK information. However, because, in many cases, PPK information is not indicated in the package insert (PI), which is a document referred to by healthcare professionals, they point out that PK information such as PK parameters and associated variable factors is insufficient. Against this background, in this study, we aimed to investigate the ways of effectively providing PK information using PPK analysis in Japan.

We investigated the current status of utilization of the PPK approach in drug

development and the level of description of PPK analysis results in the Label and Clinical Pharmacology Biopharmaceutics Review report (CPBR) in the US, and PI, interview form (IF), review report of new drug application (NDA RR) and common technical document (CTD) in Japan, for new molecular entities (NMEs) approved in the US or Japan between 2012 and 2015. Also, we investigated what kind of new information was obtained in the post-marketing clinical studies using PPK analysis conducted in Japan and whether these PPK results were described in Japan PI and/or IF.

We showed that there is still insufficient provision of PPK information for setting appropriate dose regimen in medical practice in both countries. In addition, we showed that many post-marketing clinical studies were conducted as a single-center and observational study in order to supplement deficient PK data. Also, most PPK results obtained from post-marketing studies were not included in Japan PI and/or IF presumably due to lack of quality of PPK models.

PPK models constructed for NDA for approval are developed using data from subjects who satisfy certain inclusion criteria and therefore they can't be applied to real-world patients with various populations. If sufficient post-marketing clinical studies using high-quality PPK models are performed, PPK models based on patients with diverse backgrounds, which take inter-individual variability into consideration, can be

constructed. If data from PPK models that are applicable to patients in real-world settings are included in Japan PI and/or IF, by which useful PK information for the adjustment of dosage regimens would be provided, PPK information can contribute to the proper use of drugs and the promotion of individualized treatment strategies.

Table of Contents

List of Tables

List of Figures

Abbreviations

AIC	Akaike's information criterion
ATC classification	anatomical therapeutic chemical classification
A	alimentary tract and metabolism
B	blood and blood forming organs
C	cardiovascular system
D	dermatologicals
G	genitourinary system and sex hormones
H	systemic hormonal preparations, excl. sex hormones and insulins
J	anti-infectives for systemic use
L	antineoplastic and immunomodulating agents
M	musculoskeletal system
N	nervous system
P	anti-parasitic products, insecticides and repellents
R	respiratory system
S	sensory organs
V	various
AUC	area under the blood concentration-time curve
Cmax	maximum drug concentration
CPBR	Clinical Pharmacology Biopharmaceutics Reviews report
CL, CL/F	clearance
CTD	common technical document
DDD	defined daily dose
FDA	Food and Drug Administration
FPIA	fluorescence polarization immunoassay
HPLC	high performance liquid chromatography
IF	interview form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
JP	Japan
ke	elimination rate constant
KEGG	Kyoto Encyclopedia of Genes Genomes
MAE	mean absolute error
ME	mean prediction error
NDA	new drug applications

NME	new molecular entities
OBJ	objective function
PD	pharmacodynamics
PI	package insert
PK	pharmacokinetics
PMDA	pharmaceuticals and Medical Devices Agency
PPK	population pharmacokinetics
Q	inter-compartmental clearance
RMSE	root mean square error
RR	review report
SD	standard deviation
T1/2	elimination half-life
Tmax	time to reach the maximum drug plasma (serum/blood) concentration following drug administration
US	the United States
Vc	central volume of distribution
Vd, Vd/F	volume of distribution
Vp	peripheral volume of distribution
WHO	World Health Organization

Chapter 1: Introduction

Population pharmacokinetics (PPK), which was introduced in the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E7 guideline (1993) [1], and ICH-E11 guideline (2000) [2], is a useful method to evaluate drug pharmacokinetics (PK) in patients. Publications, including the United States (US) Food and Drug Administration (FDA) guidance document on PPK (1999) [3], guidelines on clinical PK studies (2001) [4] and drug interaction studies (2001) [5] in Japan, have helped make PPK widespread use as a means to analyze PK in clinical trials in patients. PPK uses a statistical model to calculate population parameters, their variance, and covariates from sparse and unbalanced data in a large target population [6]. Population parameters, such as clearance (CL) and distribution of volume (Vd) can subsequently be used to establish individual prescribing regimens for specific patients. PPK analysis identifies the measurable pathophysiologic factors that cause changes in the dose-concentration relationship and the extent of these changes so that the dose can be modified appropriately when such changes are associated with clinically significant shifts in the therapeutic index [7].

Searching PubMed up to 2015 for papers on PPK revealed 4,024 papers, including reviews, with papers published since the FDA guideline of 1999 accounting for 86.4% of the overall (3,477/4,024), with numbers of papers gradually increasing each year. And the use of PPK methods for the PK evaluation of new drugs for approval in Japan and abroad

has increased [8-10]. In addition, post-marketing clinical studies using PPK analysis have been published in academic journals and presented in conferences by medical and academic institutions in Japan in order to complement the poor PK information because it is difficult to apply the PK findings from clinical trials to real-world patients with complex and multiple backgrounds. These indicate the increasing availability of PK information. On the other hand, healthcare professionals pointed out that provision of PK information such as PK parameters and associated variable factors in package insert (PI) is insufficient [11, 12] under existing conditions.

PPK analysis results are useful to supplement deficient PK parameters and associated variable factors. However, no research has been conducted to compare the description of PPK analysis results in published documents in Japan and the US and to evaluate the value of population pharmacokinetic research in post-marketing clinical studies in Japan.

In this study, we aimed to investigate the ways of effectively providing PK information using PPK analysis in Japan. In study 1, we investigated the current status of utilization of the PPK approach and the level of description of PPK analysis results in US-Label, US-Clinical Pharmacology Biopharmaceutics Review report (CPBR), Japan PI, interview form (IF), review report of new drug applications (NDA RR) and common technical document (CTD) of new molecular entities (NMEs) approved between 2012 and 2015. In study 2, we investigated what kind of new information was obtained in the

post-marketing clinical studies using PPK analysis conducted in Japan and whether these results are described in Japan PI and/or IF.

Based on the above studies, we discuss how we should effectively provide PK information using PPK analysis in Japan.

Chapter 2:

Utilization of population pharmacokinetics in drug development and provision of the results to healthcare professionals

2.1. Introduction

The FDA guideline on PPK indicates that PPK analysis identifies the measurable pathophysiologic factors that cause changes in the dose-concentration relationship and the extent of these changes, so that, if such changes are associated with clinically-significant shifts in the therapeutic index, dosage can be appropriately modified [3, 7]. It also discusses when to perform a PPK study and/or analysis, how to design and execute a PPK study, how to handle and analyze PPK data, what model validation methods are available, and how to provide appropriate documentation for PPK reports intended for submission to the FDA. There are no guidelines in Japan for implementing PPK methods, and no stipulations as to how PPK analysis results should be described Japan PI.

US Label and Japan PI are legal documents in which the items to be described are set by law. They serve to provide information for the proper use of drugs to the healthcare professionals and are posted on the website of the regulatory health authority in each country. In Japan, drug information on Japan PI and IF is highly valued and used extensively in the routine work of pharmacists at some medical institutions and pharmacies. In these environments, it is hoped that the information provided in many sections can be improved [11, 12]. In particular, in the PK section, items highlighted for

improvement include pharmacokinetic parameters and the causes of their variances [11, 12]. In contrast, other pharmacists do not take PPK analysis results into consideration in their work, and it has been reported that there are little comprehension and interest in PPK analysis results [13]. Therefore, even if PPK analysis results were listed in Japan PI, it may not be applied in all medical practices.

Nakade et al. reported that the number of PPK studies among CTD and NDA RR was larger in the US than in Japan – 14.9% (10/67) in 2001 in the US vs. 5.1% (7/137) between 1999 and 2003 in Japan [8]. Patric et al. [9] reported in 2002 that no pharmaceutical companies listed the results of PPK analysis on their US-Label. In contrast, Joo et al. [10] reported that PPK analysis results were included in ~ 57% of 198 documents submitted by pharmaceutical companies between 2000 and 2008 to FDA pharmacometricians. These reports suggest that PPK analysis results are being listed more frequently. However, little has been published regarding the listing of PPK results in FDA-approved drug reviews and US-Label or in Japan NDA RR, PI and IF, nor are there any published comparisons.

In the present study, we investigated the current status of utilization of the PPK approach and the level of description of PPK analysis results in US-Label, US-CPBR, Japan PI, IF, NDA RR and CTD of NMEs. The aim of this study was to understand the state of utilization of the PPK approach in drug development and to discuss what kind of PPK information should be provided to healthcare professionals.

2.2 Method

2.2.1 Data sources and extraction

A list of approved products from the FDA and the Pharmaceuticals and Medical Devices Agency (PMDA) website was obtained, and, from this, NME products registered between January 2012 and December 2015 were identified. An NDA RR is released by the PMDA shortly after the approval of a new drug in Japan. US-Label and US-CPBR and Japan PI, IF, NDA RR and CTD were studied for each new drug. All documents were the latest editions available in June 2016. To identify products that utilized PPK, the active ingredient name, use of PPK, and description of PPK analyses were extracted from the product documents.

2.2.2 Data analyses

2.2.2.1 Utilization of PPK

Products using PPK were identified and counted. The proportion of products using PPK was calculated for each year and for each document. These results were presented in a graph.

2.2.2.2 Utilization of PPK by therapeutic area

For analysis, NMEs were used for which a US-CPBR or a Japan NDA RR was available. These products were categorized according to the Anatomical Therapeutic Chemical (ATC) classification system, which was defined as the WHO ATC/DDD index (http://www.whocc.no/atc_ddd_index/) and KEGG DRUG

(http://www.genome.jp/kegg/drug/). The presence or absence of PPK analysis was determined in these documents. The number of products with or without PPK analysis by country (US or Japan) and ATC classification (primary level, anatomical main group) were presented in a graph.

2.2.2.3 Descriptive content of PPK analysis

Products that had PPK analysis results in US-Label, Japan PI and IF were used for this analysis. The descriptive contents of the PPK analysis in these documents were investigated and classified into six categories based on the presence of pharmacokinetic parameters (maximum drug concentration (Cmax), area under the blood concentration-time curve (AUC), CL and Vd) and covariance. The proportion of each category contained within each document was calculated.

The six categories are as follows: (1) individual patient PK parameters can be calculated from the model equation, (2) PK parameters are listed according to a patient background (such as weight or creatinine clearance), (3) PK parameters are listed, but not according to a patient background, (4) covariate is identified, and the necessity of dose adjustment by its covariate is stated, (5) covariate is identified, but whether it is necessary to adjust the dosage cannot be determined and (6) only information that does not apply to categories (1) – (5) is shown, or only the fact that PPK analysis was performed is shown, without further information.

2.2.2.4 Investigation into reasons why PPK results were not reflected in US-Label

There are some products that do not include PPK information in US-Label despite US-CPBR containing statements about the PPK analysis results. The reasons for this discrepancy were investigated.

2.3 Results

Between January 2012 and December 2015, 152 NMEs were approved in the US and 176 in Japan (Table 2-1). Three NDA RRs, 10 Ifs, and 2 PIs, were not available, and these products were excluded from the denominator of each analysis.

2.3.1 Utilization of PPK

The percentage using PPK per number of NMEs was calculated (Figure 2-1). The percentage using PPK in US-Label and in US-CPBR increased each year from 43.6 to 68.9% and 61.5 to 88.9%, respectively, with higher usage in US-CPBR than in US-Label in any year. In Japan, the percentage plateaued at 15 – 25% PPK data inclusion for Japan PI, and at ~ 50% for Japan IF and NDA RR. The differences between Japan PI and IF, and Japan PI and NDA RR for any given year was around 30 percentage points, respectively. Overall, the percentage of PPK reporting was higher in the US documents than in Japanese documents.

2.3.2 Utilization of PPK by therapeutic area

Since the number of approved drugs for each therapeutic area varies from year to year, the ratio of drugs using the PPK approach was calculated by ATC classification for

each country (Figure 2-2). Between January 2012 and December 2015, the number of approved products and the percentage using PPK were high for codes A (alimentary tract and metabolism), J (anti-infectives for systemic use), L (antineoplastic and immunomodulating agents), and N (nervous system).

2.3.3 Descriptive content of PPK analysis

The descriptive contents of the PPK analysis in US-Label and Japan PI and IF were classified into six categories as shown in Table 2-2. 52.3% (45/86) of US-Label were classified into category 4 whereas Japan PI most commonly fell into category 5 (48.4%; 15/31), followed by category 3 (35.5%, 11/31). Regarding Japan IF, about 30% were classified into categories 3, 4 and 5, respectively. The percentage at which the PPK parameter was mentioned (classified as categories 1 to 3) in US-Label was 37.2% (32/86), 37.8% (34/90) in Japan IF and 41.9% (13/31) in Japan PI.

2.3.4 Investigation into why PPK results were not reflected in US-Label

There were 31 products with no PPK results in US-Label despite having PPK results in US-CPBR. Review by the FDA pharmacometrics team confirmed that PPK analysis was performed in 29 products. Reasons why the PPK analyses were not in US-Label were classified: 32.3% (10/31) was because of “inappropriate PPK model/construction process”, 54.8% (17/31) was because “dose adjustment was unnecessary”, and 3.2% (1/31) was because “more information than that provided by the PPK analysis was obtained from other analysis results” and “there was inconsistency between PPK and the

results of standard PK study", and 6.5% (2/31) were "unknown".

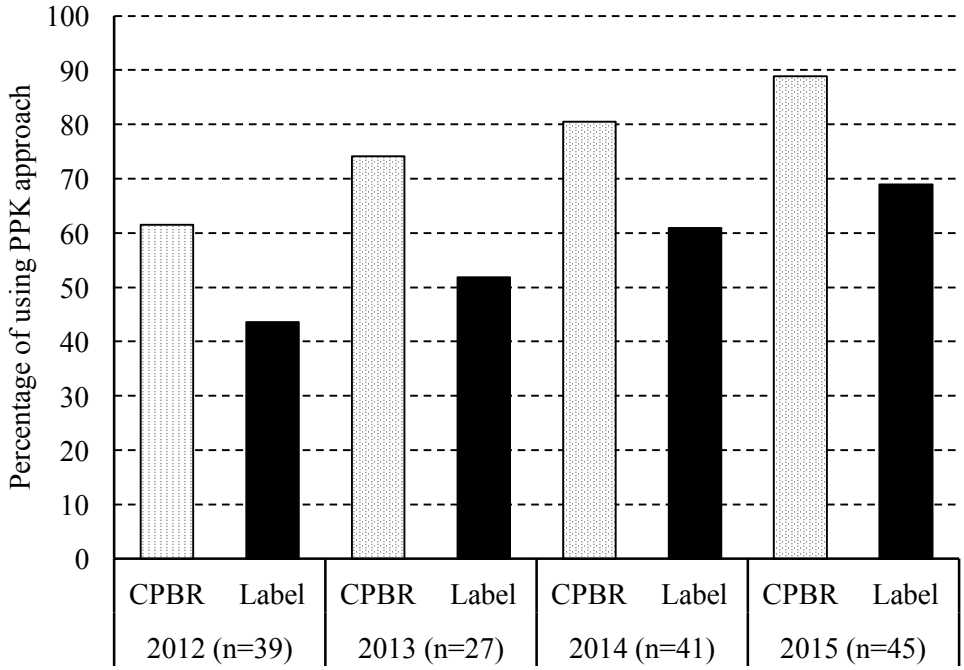
Table 2-1

Number of new molecular entities approved each year between 2012 and 2015 in the United States and Japan

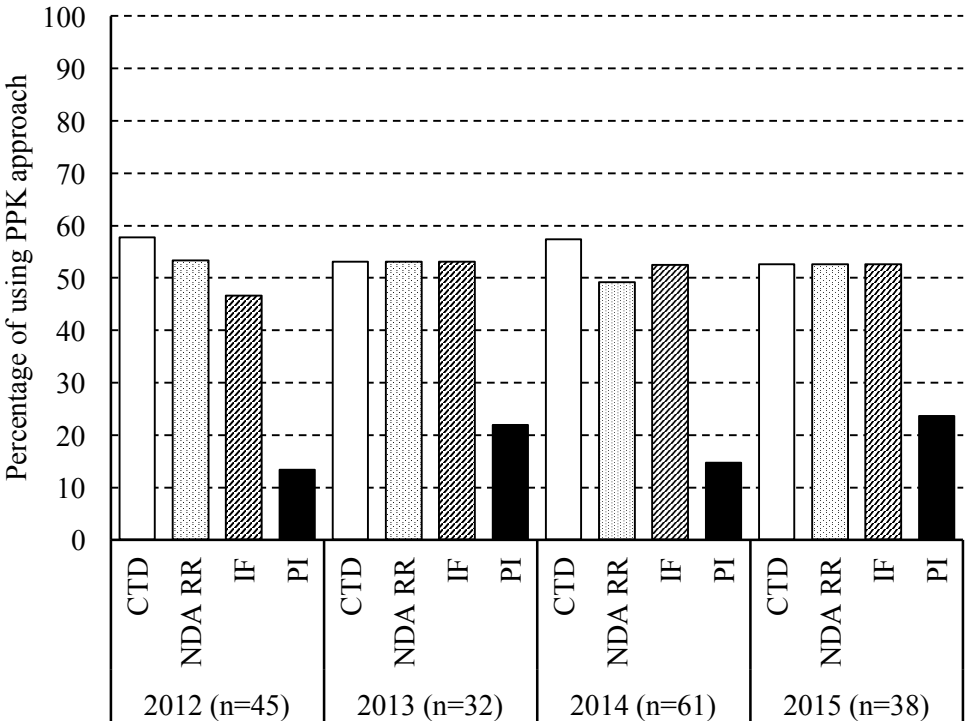
Country	Approval year				Total
	2012	2013	2014	2015	
the United States	39	27	41	45	152
Japan	45	32	61	38	176

Figure 2-1 Utilization of population pharmacokinetic approach from 2012 to 2015

A. US NMEs (N=152)



B. Japan NMEs (N=176)

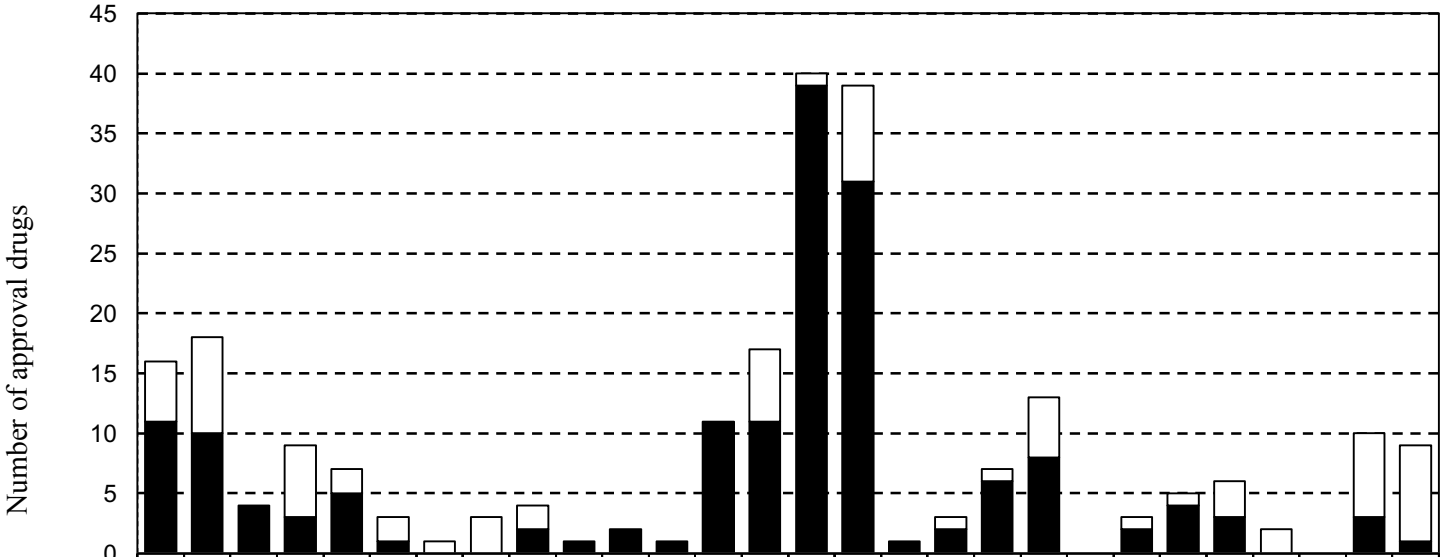


US: the United States, PPK: population pharmacokinetics, CPBR: Clinical Pharmacology Biopharmaceutics Reviews report, CTD: common technical document, NDA RR: review report of new drug application, IF: interview form, PI: package insert

Figure 2-2

Number of new molecular entities approved in Japan and the United States by Anatomical Therapeutic Chemical Classification code

<NMEs US (N=152), Japan (N=176)>



	US	JP	US	JP	US	JP	US	JP	US	JP	US	JP	US	JP	US	JP	US	JP	US	JP	US	JP	US	JP	US	JP	US	JP
	A		B		C		D		G		H		J		L		M		N		P		R		S		V	
□PPK (−)	5	8	0	6	2	2	1	3	2	0	0	0	0	6	1	8	0	1	1	5	0	1	1	3	2	0	7	8
■PPK (+)	11	10	4	3	5	1	0	0	2	1	2	1	11	11	39	31	1	2	6	8	0	2	4	3	0	0	3	1

US: the United States, JP: Japan, PPK: population pharmacokinetics

A: alimentary tract and metabolism, B: blood and blood forming organs, C: cardiovascular system, D: dermatologicals, G: genitourinary system and sex hormones, H: systemic hormonal preparations, excl. sex hormones and insulins, J: anti-infectives for systemic use, L: antineoplastic and immunomodulating agents, M: musculoskeletal system, N: nervous system, P: anti-parasitic products, insecticides and repellents, R: respiratory system, S: sensory organs, V: various.

Table 2-2

Percentage of US-Label and Japan package insert listing population pharmacokinetic analysis details

<NMEs US (N=152), Japan (N=176) >

Document		N	Categories [a)]					
			1	2	3	4	5	6
US	Label	86	0 (0%)	2 (2.3%)	30 (34.9%)	45 (52.3%)	4 (4.7%)	5 (5.8%)
Japan	Package insert	31	0 (0%)	2 (6.5%)	11 (35.5%)	3 (9.7%)	15 (48.4%)	0 (0%)
	Interview form	90	1 (1.1%)	6 (6.7%)	27 (30.0%)	28 (31.1%)	27 (30.0%)	1 (1.1%)

US: the Unites States

a) Categories

1: Individual patient pharmacokinetic parameters can be calculated from the model equation;

2: pharmacokinetic parameters are listed according to a patient background (such as weight or creatinine clearance);

3: pharmacokinetic parameters are listed, but not according to a patient background;

4: covariate is identified, and the necessity of dose adjustment by its covariate is stated;

5: covariate is identified, but the whether it is necessary to adjust the dosage cannot be determined;

6: only information that does not apply to categories 1–5 is shown, or only the fact that population pharmacokinetic analysis was performed is shown, without further information

2.4 Discussion

The present study demonstrated that while PPK use in drug development in the US is increasing each year, there is no similar increase occurring in Japan. Moreover, there were fewer products for which PPK results in Japan PI and IF were considered useful at a medical practice level in Japan. There is still insufficient provision of information about PPK to the medical practice.

The US FDA guideline specifies which PPK analysis results should be on the product label, but such regulatory documents do not yet exist in Japan. This is considered to be one of the reasons why PPK analyses are not included in Japan PIs. In December 2015, the Ministry of Health, Labor and Welfare of Japan released a draft guideline on PPK/Pharmacodynamics (PD) analysis [14]. This draft guideline specifies which PPK results should be included in Japan PI. In the wake of this guideline, we do believe that the situation of PPK in Japan will be improved. It requires future follow-up.

Results of the contents of PPK analysis in US-Label, Japan PI and IF showed that there was only one product for which the individual PPK parameters could be calculated from the PPK model equation (classified as category 1) described in Japan IF, although many products listed data on covariance related to individual variance (classified as categories 4 and 5). The responses regarding the efficacy and safety after administration of medicine vary according to different patient conditions. This difference between individuals is primarily caused by PK and PD factors. To plan individualized

administration based on the differences in patient response, Japanese pharmacists want to obtain PK parameters, variable factors, and the range of variation from Japan PI and IF [10, 11]. The use of a model including PPK is useful for planning individualized drug administration. US-Label and Japan PI are documents designed for reporting to medical practitioners and should list information that helps determine individual PK characteristics. The information needed is not just the PK parameter population mean but also information on variable factors, the range of variation in such parameters, and if possible, the PPK model that can calculate each patient's PK parameters so that individualized drug administration could be planned, if necessary. PPK analysis is a methodology that is used for individual administration planning; therefore, many reports show PPK modeling using concentration data obtained from clinical practice. If more information on the PPK model can be obtained from clinical trials, the administration plan for patients, considering individual background factors, will be available from the early stage of treatment. Furthermore, we believe it is important for healthcare professionals to understand what PPK is, what information can be obtained from PPK analyses, and how the procedure differs from the standard PK method. Healthcare professionals should collect as much information as possible from US-Label, Japan PI and IF, and if necessary, Japan NDA RR and CTD.

For products that did not cite the use of PPK within US-Label but were recorded in US-CPBR, we primarily referenced the section of pharmacometric reviews. The

pharmacometrics review is a valuable resource used to identify problems in drug development and includes quantitative analysis results of drug exposure levels, efficacy, safety, and pathology. In general, pharmacometrics reviewers at the FDA start their review by evaluating the pharmaceutical company's approach to supporting the regulatory decision. If the pharmaceutical company's approach is found to be unsatisfactory, the reviewers conduct independent analyses [10]. In the present study, there were 31 products that did not cite PPK analysis on their US-Label, despite the analysis having been conducted. The reason for this non-inclusion of data was "PPK model or construction process is inappropriate" for 10 of the 31 products. There are various approaches to and interpretations of PPK model construction and PPK analysis results, which may also differ between FDA and pharmaceutical company. However, the pharmacometrics reviewers assess the PPK analysis of the pharmaceutical company with a view to ensuring that erroneous interpretations of the proper use of a drug should not be passed on to medical practice. The pharmaceutical companies should understand the FDA's approach and interpretation from the publicly-available pharmacometrics reviews, and should actively provide information of the PPK analysis on US-Label, Japan PI and IF to promote the proper use of drugs in medical practice.

In the present study, the therapeutic areas in which PPK approaches were frequently used were for anticancer agents and anti-infective agents. One reason for this is that anticancer agents and anti-infective agents generally have a narrow therapeutic range, and

a change in PK can have a big effect on both efficacy and safety. For anticancer agents, especially drugs with a molecular target, the target protein is clear. For anti-infective agents, especially antibacterial agents, the PK parameters are correlated according to the mechanism of action. In a therapeutic area with a clear PD index, it is possible to plan the dosage and administration for an individual.

As a limitation of this research, we referred to US-Label and US-CPBR, Japan PI, IF, NDA RR and CTD – all publicly-available documents, but we did not refer to other documents. Furthermore, because “use of PPK” was defined as the use of PPK clearly written in the wording of the surveyed documents, the products that implied PPK data in the “dosage and administration” and/or “precautions” sections rather than directly mentioning it, might be missed. Moreover, although the usefulness of PPK to medical practice is discussed, the results of standard PK method and PPK analysis should ideally be combined to produce comprehensive PK for evaluation. In this study, we conducted a literature search for the situation in other countries, but we could not find any material. We would like to investigate it in future.

In future, we expect the utilization of pharmacometrics, including PPK and PPK/PD, to become more common in drug development, and that by sharing the PPK model obtained from clinical trials promptly in medical practice, these data will be effectively used in individualized drug administration plans.

Chapter 3:

The value of population pharmacokinetic research in post-marketing clinical studies in Japan

3.1 Introduction

Following the publication of the guidance on PPK by the FDA (1999), the use of PPK methods for the PK evaluation of new drugs for approval in Japan and abroad has increased [8-10]. Furthermore, post-marketing clinical studies using PPK analysis have been reported by medical and academic institutions in order to complement the poor PK information, thus increasing the available PK information. In the US, the PPK data are frequently listed in drug label, although this is less often the case in Japan [15]. Healthcare professionals pointed out that PK information such as parameters and associated variable factors described in Japan PI is insufficient [11, 12] under the existing conditions.

A general limitation of PK data from clinical trials [16] is that it is difficult to apply the findings to all the patient populations with complex and multiple backgrounds. Therefore, PPK data obtained in post-marketing clinical studies can complement the existing information on PK parameters and their variable factors for the following reasons: (1) PK information, including that from studies conducted for NDA for drug approval, is often not fully disclosed by pharmaceutical companies [15], (2) PK information is rarely collected in post-marketing studies, though post-marketing surveillance and clinical trials on efficacy and safety may be required as a condition for

approval [17]. To date, the value of PPK research in post-marketing clinical studies in Japan has not been evaluated.

In this study, we aimed to examine the value of PPK research in post-marketing clinical studies in Japan and investigated what kind of new information was obtained in the post-marketing clinical studies using PPK analysis and whether these PPK results are described in Japan PI and/or IF.

3.2 Methods

3.2.1 Selection of analysis object

Clinical research papers using PPK analysis were extracted from the Ichushi-Web (Search formula; (“母集団薬物動態解析” or “母集団薬物動態” or “PPK 解析” or “population pharmacokinetic”) and “原著論文”). We excluded studies conducted by pharmaceutical companies, studies conducted outside of Japan, studies on methodology, and studies with a different definition of PPK (e.g., palmoplantar keratoderma). As a result, studies on post-marketing clinical studies using PPK analysis in Japan conducted by medical and academic institution were extracted.

3.2.2 Extraction and summarization of data

3.2.2.1 Extraction of data

We extracted data on the drug name, research purpose, number of centers, subjects and total samples, type of study and newly found information in the study from the published research papers. In addition, PK information was extracted from Japan PI, IF,

NDA RR and CTD (hereafter “Japan application data”) of the target drugs.

3.2.2.2 Study classification

The identified studies were classified by the number of centers (single, multiple, or unknown), therapeutic category, and research design (interventional, observational, or unknown), as well as by research purpose.

3.2.2.3 Number of subjects and total samples

From each study, data on the number of subjects and total samples were extracted. Next, the average number of subjects and total samples were calculated and statistically compared between single-center and multiple-center using a *t*-test (5% significance level).

3.2.2.4 Newly found information from post-marketing clinical studies using PPK analysis

Newly found information in each study was extracted and categorized as follows: (1) development of a new PPK model in patients in clinical practice, (2) identification of factors requiring dose adjustment, (3) modification of PPK model, and (4) Others. Also, PK information, presence or absence of PPK information and covariate information were extracted from Japan application data. Furthermore, we investigated whether newly found information from the post-marketing clinical studies using PPK analysis had been incorporated into Japan PI and IF.

3.2.2.5 Quality of PPK research in post-marketing clinical studies

We determined whether the studies in the present research met the following criteria:

(1) it was conducted as a multi-center study with more than 30 subjects, (2) unified measurement of blood (serum, plasma) concentration of drug was applied among different centers and throughout the investigation period, (3) blood samples were collected at around time to reach the maximum drug blood concentration following drug administration (Tmax) and elimination half-life (T1/2), (4) information on the construction of the PPK model and on the accuracy from the base model to the final model were provided, and (5) formula of the final PPK model was included.

3.3 Results

Of the 244 papers identified on the Ichushi-Web as of March 2, 2017, we excluded 46 studies conducted by pharmaceutical companies, 10 studies conducted outside of Japan, 85 studies which were studies on methodology or studies with a different PPK definition. The remaining 103 studies were selected for the analysis.

3.3.1 Study breakdown

Table 3-1 shows the breakdown of the studies. Of a total of 47 identified drugs, 17 drugs were subject to the therapeutic drug monitoring (TDM). Thirty four were classified as antibiotics (therapeutic category number: 8761) and 17 were classified as circulatory drugs (8721). Regarding the number of centers, 63 studies were single-center studies and 23 were multi-center studies. For research design, there were 32 interventional studies and 64 observational studies. For the research purpose, 38 studies were conducted for "PK in a special population is not examined or insufficient", 22 studies for "no or

insufficient reports, studies on PPK and PPK/PD" and 16 studies for "overestimation or underestimation by the current PPK model (including software)".

3.3.2 Number of subjects and total samples

The number of centers was reported for 87 of the identified studies. The mean number of subjects and total samples for single-center and multi-center studies were compared using a *t*-test, and the results are shown in Table 3-2. No significant difference was observed in the number of subjects between single-center and multi-center studies. The mean number of total samples was significantly larger in multi-center studies than in single-center studies ($p = 0.0028$).

3.3.3 Newly found information from post-marketing clinical studies using PPK analysis

Newly found information reported in the selected post-marketing studies using PPK analysis are shown in Table 3-3A and Table 3-3B.

The newly found information on the drugs for which information on PPK analysis had not been available in Japan application data (29 drugs, 66 reports) was mainly (1) development of a new PPK model based on patients in clinical practice (26 drugs, 54 reports), and (2) identification of factors requiring dose adjustment (20 drugs, 34 reports). When we looked into the detailed breakdown of the information falling into these 2 categories, "information on the patients' PK" was the largest with 40 reports. Also, development of PPK models based on patients in post-marketing clinical studies in

addition to the patient standard PK information or to the PK information from healthy subjects in Japan application data were included in these categories. There were some cases where PK data was obtained for the first time using PPK modeling from post-marketing studies.

The most common newly found information on the drugs for which information on PPK analysis had been available in Japan application data (17 drugs, 36 reports) was (3) development of a modified PPK model (16 drugs, 24 reports), with many reports suggesting different covariates from those specified in Japan application data. Reports pointing out “different age group” include studies in which PPK models in pediatric patients were developed in addition to the existing PPK data for adult patients; those pointing out “different diseases” include studies in which PPK models for different diseases from the existing ones were developed.

3.3.4 PPK related information from post-marketing clinical studies reflectable to Japan PI

Among the studies subject to the present research, there was only one study whose PPK analysis data was shown in Japan IF. No PPK analysis data from post-marketing clinical studies were reflected in Japan PI.

To investigate the feasibility of including PPK data in Japan PI and/or IF, each study was assessed according to the criteria defined in section 3.2.2.5. Six studies were found to meet all the criteria for the inclusion of PPK data in Japan PI and/or IF (Table 3-4A

and Table 3-4B).

Table 3-1 Study breakdown

<All studies (N=103)>

Classification		Number of studies
Number of drugs		47
Therapeutic Category of Drugs in Japan 87	1 Agents affecting nervous system and sensory organs	12
	11 Agents affecting central nervous system	12
	2 Agents affecting individual organs	26
	21 Cardiovascular agents	17[a)]
	22 Respiratory organ agents	8
	24 Hormones	1
	3 Agents affecting metabolism	15
	39 Other agents affecting metabolism	15[b)]
	4 Agents affecting cellular function	8
	42 Antineoplastics	7
	44 Allergic agents	1
	6 Agents against pathologic organisms and parasites	39
	61 Antibiotics	34
	62 Chemotherapeutics	5
	7 Agents not mainly for therapeutic purpose	2
	72 Intracorporeal diagnostic agents	2
	8 Narcotics	1
	81 Alkaloidal narcotics	1
Number of centers	Single-center	63
	Multi-center	23

Classification		Number of studies
	Unknown	17
Research design	Interventional	32
	Observational	64
	Unknown	7
Research purpose [c)]	No or insufficient reports/studies on PPK and PPK/PD	22
	It is necessary to search for suitable dosage	16
	Overestimation or underestimation by the current model (including software)	18
	Insufficient consideration of influence factors	19
	PK in the special population is not examined or insufficient	38
	Pediatric	13
	Geriatric	2
	Hepatic/renal impairment	4
	Patient (including under special circumstances)	13
	Japanese	9
	Others	9

PPK: population pharmacokinetics, PD: pharmacodynamics, PK: pharmacokinetics

a) A paper of an ingredient that therapeutic category of drugs in Japan corresponds to 21 and 22 was classified as 21.

b) The 4 papers of ingredients that therapeutic category of drugs in Japan corresponds to 39 and 42 were classified as 39.

c) When there are two or more items corresponding to one paper, it is counted in plural categories.

Table 3-2 Number of subjects and number of total samples

<All studies (N=103)>

	Number of subjects			Number of total samples		
	Number of data	Mean ± SD	*p* value	Number of data	Mean ± SD	*p* value
Single-center (n=63)	60	56.93 ± 77.23	*p*=0.1187	39	154.18 ± 127.77	*p*=0.0028
Multi-center (n=24)	24	84.17 ± 54.16		19	312.16 ± 259.13	

SD: standard deviation

Table 3-3 Newly found information from post-marketing clinical studies using PPK analysis

<All studies (N=103)>

A. Drugs for which information on PPK analysis had NOT been available in Japan application data (29 drugs, 66 reports)

Classification	Number of data	Breakdown	
(1) Development of a new PPK model based on patients in clinical practice	26 drugs, 54 reports	Patient	40 reports
(2) Identification of factors requiring dose adjustment	20 drugs, 34 reports	Pediatric	9 reports
		Geriatric	2 reports
		Renal impairment	1 report
		Japanese	1 report
		First PK information	1 report
(3) Development of a modification of PPK model	—	—	
(4) Others	9 drugs, 13 reports	—	

B. Drugs for which information on PPK analysis had been available in Japan application data (17drugs, 36 reports)

Classification	Number of data	Breakdown	
(1) Development of a new PPK model based on patients in clinical practice	—	—	
(2) Identification of factors requiring dose adjustment	11 drugs, 15 reports	Different covariates	13 reports
		Different age groups	3 reports
(3) Development of a modification of PPK model	16 drugs, 24 reports	Different diseases	3 reports
		Patient	2 reports
		Japanese	2 reports
(4) Others	9 drugs, 12 reports	—	

PPK: population pharmacokinetics, PK: pharmacokinetics

Table 3-4 PPK related information from post-marketing clinical studies reflectable to package insert

<All studies (N=103)>

A. Interventional studies

Evaluation criteria		The Japanese Journal of Therapeutic Drug Monitoring (2012) 29; 77-82 [18]	Japanese journal of clinical pharmacology (1995) 26; 697-706 [19]	Journal of Infection Chemotherapy (2008) 14; 130-136 [20]
(1)	Number of centers	2	≥ 2	2
	Number of subjects (total samples)	95 (101)	33 (108)	32 (145)
(2)	Measuring method	HPLC	HPLC	HPLC
(3)	Validity of sampling points [a)]	Yes	Yes	Yes
(4)	Method of confirmation of model accuracy	- Residual of measured value and calculated value - Judgement by bootstrap method and OBJ function	- Superposition of measured value and calculated value - Judgement by OBJ function	- Judgement by AIC and OBJ function
	Model construction information [b)]	Yes	Yes	Yes
(5)	Final model formula	Yes (CL/F, Vd/F)	Yes (ke, Vd/F)	Yes (CL, Vc, Q, Vp)

HPLC: high performance liquid chromatography, OBJ: objective function, CL/F: clearance, Vd/F: distribution of volume, AIC: Akaike's information criterion, ke: elimination rate constant, Vc: central volume of distribution, Q: inter-compartmental clearance, Vp: peripheral volume of distribution

a) Whether or not sampling points were obtained around Tmax and/or T1/2

b) Information of software, construction and selection of PPK model, and background for covariate evaluation

B. Observational studies

Evaluation criteria		The Japanese Journal of Therapeutic Drug Monitoring (2015) 32; 188-197 [21]	Clinical and Experimental Nephrology (2012) 16; 799-804 [22]	Annual report of the research on nervous and mental disorders (1990) 288-292 [23]
(1)	Number of facilities	3	2	12
	Number of subjects (total samples)	132 (292)	51 (353)	33 (107)
(2)	Measuring method	FPIA (kit)	HPLC	FPIA (kit)
(3)	Validity of sampling points [a)]	Yes	Yes	Yes
(4)	Method of confirmation of model accuracy	- Judgement by Good of fitness - Judgement by bootstrap method and OBJ function	- Judgement by 95% confidence intervals of estimates	- Judgement by ME, MAE, RMSE and OBJ function
	Model construction information [b)]	Yes	Yes	Yes
(5)	Final model formula	Yes (CL, Vc, Vp, Q)	Yes (CL/F, Vd/F)	Yes (CL)

FPIA: fluorescence polarization immunoassay, ME: mean prediction error, MAE: mean absolute error, RMSE: root mean square error, CL, CL/F: clearance, Vc: central volume of distribution, Vp: peripheral volume of distribution, Q: inter-compartmental clearance, Vd/F: distribution of volume

a) Whether or not sampling points were obtained around Tmax and/or T1/2

b) Information of software, construction and selection of PPK model, and background for covariate evaluation

3.4 Discussion

PK assessment using PPK methods was included in post-marketing clinical study in some cases, but many of them were based on observational research using TDM data at a single-center. In addition, despite the fact that PPK analysis was conducted for NDA for approval in many cases, the results are not included in Japan PI and IF. This situation is one of the backgrounds for conducting post-marketing clinical studies using PPK method. The present study suggested that PPK analyses were conducted in post-marketing clinical studies to supplement deficient PK data. However, we identified only one study, which was observational, whose PPK data was reflected in Japan IF.

In order to improve provision of PPK information in Japan PIs, quality of PPK models included in post-marketing clinical studies is important. We would propose that such studies should be designed encompassing the following criteria specified at the planning stage: (1) it is conducted as a multi-center study with sufficient subjects to construct a PPK model, (2) unified measurement of blood concentration of drug is applied among different centers and throughout the investigation period, (3) blood samples are collected at around Tmax and T1/2, and at the publishing stage: (4) information on the construction of the PPK model and on the accuracy from the base model to the final model are provided, and (5) formula of the final model is included. If sufficient post-marketing clinical studies using high-quality PPK models are performed, PPK models based on patients with diverse backgrounds, which take inter-individual variability into

consideration, can be constructed. If PPK data are subsequently described in Japan PI and/or IF, they can be used by health professionals to ensure proper administration of medicines.

A limitation of this research is that all the included data were retrieved only from the published material. In particular, the research design was estimated from the description of the data source and study method in the published paper, unless it was explicitly described as interventional or observational research.

PPK models constructed for NDA for approval are developed using data from subjects who satisfy certain inclusion criteria and therefore can't be applied to real-world patients with various characteristics. Therefore, post-marketing clinical studies are frequently undertaken by medical and academic institutions to complement the existing PK data, which are often insufficient. Furthermore, some pharmaceutical companies updated the PPK models by integrating clinical trial data, drug use survey data, and post-marketing survey data [24, 25]. Therefore, if it is possible to ensure the quality of post-marketing clinical study using PPK methods, new and/or improved PPK models using the data from these studies could be developed.

If data from PPK models that are applicable to patients in real-world settings are included in Japan PI and/or IF, by which useful PK information for the adjustment of dosage regimens would be provided, PPK information can contribute to the proper use of drugs and the promotion of individualized treatment strategies.

Chapter 4 Overall Discussion and Conclusion

The present study demonstrated that while PPK use in drug development in the US has been increasing each year, there is no similar increase occurring in Japan, and there is still insufficient provision of information about PPK to healthcare professionals. We also showed that although PK assessment using PPK methods may be included in post-marketing clinical studies, many studies are based on observational research using TDM data at a single-center. In addition, though PPK analyses are conducted for NDA for approval, the results are not included in Japan PI and IF, and this situation is one of the backgrounds for conducting post-marketing clinical studies using PPK analysis. It was suggested that PPK analyses have been conducted in post-marketing clinical studies to supplement deficient PK data. However, we identified only one study, which was observational, whose PPK data was reflected in Japan IF.

Pharmaceutical companies should conduct PK evaluation using PPK approach in clinical trials for NDA for approval and even more often in post-marketing, and actively provide these results including what PK information is not obtained from clinical trials on the published document for healthcare professionals such as US-Label, Japan PI and IF to promote proper use of drugs in medical practice. On the other hand, medical and academic institutions should plan a study to maintain quality of PPK models to meet the following points: (1) it is conducted as a multi-center study with sufficient subjects to construct a PPK model, (2) unified measurement of blood concentration of drug is applied

among different centers and throughout the investigation period, and (3) blood samples are collected at around Tmax and T1/2, and should publish the study results appropriately in such a manner that information on the construction of the PPK model, the accuracy from the base model to the final model, and formula of the final model is included. If sufficient post-marketing clinical studies using high-quality PPK models are performed, PPK models based on patients with diverse backgrounds, which take inter-individual variability into consideration, can be constructed. If PPK data are subsequently described in Japan PI and/or IF, they can be used by healthcare professionals to ensure proper administration of medicines. Furthermore, pharmaceutical companies should be able to update more useful PPK models by integrating clinical trial data, drug use survey data and post-marketing survey data, because they have a lot of PK and PD information of clinical trials. Therefore, if it is possible to ensure the quality of post-marketing clinical study using PPK methods, it is expected that new and/or improved PPK models using the data from these studies will be developed.

PPK models constructed for NDA for approval are developed using data from subjects who satisfy certain inclusion criteria and therefore can’t be applied to real-world patients with various characteristics. Therefore, post-marketing clinical studies are frequently undertaken by medical and academic institutions to complement the existing PK data, which are often insufficient. If data from PPK models that are applicable to patients in real-world settings are included in Japan PI and/or IF, by which useful PK

information for the adjustment of dosage regimens would be provided, PPK information can contribute to the proper use of drugs and the promotion of individualized treatment strategies.

References

1. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. ICH topic E7. Studies in support of special populations: Geriatrics. June 1993. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E7/Step4/E7_Guideline.pdf. Accessed 22 Dec 2015.
2. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. ICH topic E11. Clinical investigation of medicinal products in the pediatric population. July 2000. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E11/Step4/E11_Guideline.pdf. Accessed 22 Dec 2015.
3. FDA guidance for industry. Population pharmacokinetics. Rockville (MD): US Department of Health and Human Services, Food and Drug Administration, 199 9 Feb. http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm072137.pdf. Accessed 16 Feb 2016.
4. Clinical pharmacokinetic studies of pharmaceuticals: notification No. 796 issued by the Director of the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare, June 2001. http://www.pmda.go.jp/files/000206738.pdf. Accessed 16 Feb 2016.
5. Methods of Drug Interaction Studies: Notification No. 813 issued by the Director of

the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare, June 2001. http://www.pmda.go.jp/files/000206743.pdf. Accessed 16 Feb 2016.

6. Aarons L. Population pharmacokinetics: theory and practice. Brit J Clin Pharmacol. 1991;32:669–70.
7. Duan JZ. Applications of population pharmacokinetics in current drug labelling. J Clin Pharm Ther. 2007;32:57–79.
8. Nakade S, Nakanishi M, Higuchi S. Current status of population pharmacokinetics and pharmacokinetic/pharmacodynamic studies in drug development (in Japanese). Japanese Journal of Clinical Pharmacology and Therapeutics. 2003;34:329–38.
9. Marroum PJ, Gobburu J. The product label. Clin Pharmacokinet. 2002;41:161–9.
10. Lee JY, Garnett CE, Gobburu JV, Bhattaram VA, Brar S, Earp JC et al. Impact of pharmacometric analyses on new drug approval and labelling decisions. Clin Pharmacokinet. 2011;50:627–35.
11. Ogihara T, Kano T, Yamada K, Wada S, Morimoto K. Pharmacokinetics parameters in drug package inserts (1) (in Japanese). Journal of New Remedies & Clinics 2008;57:54–61.
12. Saito M, Hirata-Koizumi M, Urano T, Miyake S, Hasegawa R. Survey of hospital pharmacists' opinions of current Japanese package inserts (in Japanese). Japanese Journal of Pharmaceutical Health Care and Sciences. 2007;33:442–50.

13. Sato H, Maruyama T, Otagiri Y, Mimura E, Kawakami K, Ikeda R et al. Evaluation of usefulness of population pharmacokinetics analysis results to community pharmacy – effects of smoking and gender difference on olanzapine dosages (in Japanese). Japanese Journal of Pharmaceutical Health Care and Sciences. 2006;32:940–5.

14. Draft guideline on population pharmacokinetics and pharmacodynamics issued by the Evaluation and Licensing Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health and Welfare of Japan, 9 Dec 2015. http://search.e-gov.go.jp/servlet/Public?CLASSNAME=PCMMSTDETAIL&id=495150257&Mode=0. Accessed 9 Dec 2015.

15. Watanabe-Uchida M and Narukawa M. Utilization of population pharmacokinetics in drug development and provision of the results to healthcare professionals. Int J Clin Pharmacol Ther. 2017;55:25-31.

16. Rogers AS. Adverse drug events: identification and attribution. Drug Intell Clin Pharm. 1987;21:915-920.

17. Doi O. Conditions for approval of pharmaceuticals. Pharmaceutical and Medical Device Regulatory Science. 2013;44:584-585.

18. Fukumoto K, Kasai H, Tsuchishita Y, Kojima N, Kamakura S, Ueno K. Population Pharmacokinetics of Bepridil in Patients with Atrial Fibrillation. The Japanese Journal of Therapeutic Drug Monitoring. 2012;29:77-82

19. Aso R, Ohashi K, Katoh T, Ogata H. Population Pharmacokinetics, protein Binding and Antiarrhythmic Effects of Disopyramide Enantiomers in Arrhythmic Patients. Jpn J Clin Pharmacol Ther. 1995;26:697-706.

20. Iwata K, Nomura K, Morikawa N, Ikeda K, Ohge H, Sueda T et al. Pharmacokinetic-pharmacodynamic target attainment analysis of cefozopran in Japanese adult patients. J Infect Chemother. 2008;14:130-136.

21. Tsuji Y, Ota Y, Kasai H, Hiraki Y, Yamada T, Matsunaga N et al. Population pharmacokinetics analysis of generic teicoplanin with MRSA or GPC infection by multicenter study. The Japanese Journal of Therapeutic Drug Monitoring. 2015;32:188-197.

22. Ishida K, Motoyama O, Shishido S, Tsuzuki K, Hashimoto Y. Population pharmacokinetics of mizoribine in pediatric recipients of renal transplantation. Clin Exp Nephrol. 2012;16:799-804.

23. Miyoshino S, Tateishi M, Eda I, Shimomura M, Koike Y, Ebihara A et al. Setting of population pharmacokinetic parameters for optimal dose regimens of digoxin in patients with Duchenne type muscular dystrophy. Annual report of the research on nervous and mental disorders. 1990;288-292.

24. Sato N, Miura Y, Mitomi N, Hayashi H, Suzuki H, SHibasaki S et al. Population Pharmacokinetic Analysis of Arbekacin Suldate inAdult Patients. The Japanese Journal of Therapeutic Drug Monitoring. 2010;27:98-110.

25. Nishimura K, Tanaka K, Osaki M, Morita K, Tanigawara Y. Population Pharmacokinetics of Theophylline: Postmarketing Study for a Once-Daily Administered Preparation (Uniphyl®). The Japanese Journal of Therapeutic Drug Monitoring. 2002;19:107-108.

Acknowledgements

My heartfelt appreciation goes to my supervisor Professor Mamoru Narukawa, Ph.D., Graduate School of Pharmaceutical Sciences, Department of Clinical Medicine (Pharmaceutical Medicine), Kitasato University, whose comments and suggestions were invaluable for my study.

For this dissertation, I would like to thank my reading committee members: Prof. Yuji Yoshiyama, Prof. Hiroshi Homma, and Dr. Kohichi Shinozaki for their time, interests and valuable advice.

My special thanks go to Ms. Akane Takayama (ex-assistant professor), Mr. Masayuki Kaneko (assistant professor) and Ms. Takako Nakata (ex-assistant). Graduate School of Pharmaceutical Sciences, Department of Clinical Medicine (Pharmaceutical Medicine), Kitasato University, for their administrative assistance throughout this study.

Last but certainly not least, I would like to grateful thank my husband Tatsuya for his understanding and encouragement for my study.

Appendix

Appendix 1-1: Database for Study 1 (US)

Approval year	ATC code	Drug name (active ingredient)	Utilization of PPK		Descriptive contents of PPK [a]	No PPK results in US-Label despite having PPK results in US-CPBR		Comfirmed by FDA pharmacometrics team (If "Reason" is other than 1 to 5)
			[Label] 0: No 1: Yes	[CPBR] 0: No 1: Yes	Label	Reason [b]		0: No 1: Yes
2012	-	Aubagio (teriflunomide)	1	1	5	-	-	-
2012	-	Fulyzaq (crofelemer)	0	0	-	-	-	-
2012	-	Sirturo (bedaquiline fumarate)	1	1	4	-	-	-
2012	-	Stribild (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate)	1	1	3	-	-	-
2012	-	Zioptan (tafluprost)	0	0	-	-	-	-
2012	A	Myrbetriq (mirabegron)	0	1	-	X	1	1
2012	A	Neutroval (tbo-filgrastim)	0	0	-	-	-	-
2012	A	Perjeta (pertuzumab)	1	1	3	-	-	-
2012	A	Signifor (pasireotide diaspartate)	1	1	4	-	-	-
2012	A	Stendra (avanafil)	0	0	-	-	-	-
2012	B	Juxtapid (lomitapide mesylate)	0	0	-	-	-	-
2012	B	Surfaxin (lucinactant)	0	0	-	-	-	-
2012	C	Gattex (teduglutide recombinant)	0	1	-	X	1	0
2012	D	Voraxaze (glucarpidase)	0	0	-	-	-	-
2012	G	Amyvid (florbetapir F-18)	0	0	-	-	-	-
2012	G	Belviq (lorcaserin hydrochloride)	0	1	-	X	2	1
2012	H	Raxibacumab (raxibacumab)	1	1	4	-	-	-
2012	J	Eliquis (apixaban)	0	1	-	X	4	1
2012	J	Iclusig (ponatinib hydrochloride)	0	1	-	X	1	1
2012	J	Zaltrap (ziv-aflibercept)	1	1	4	-	-	-
2012	L	Bosulif (bosutinib monohydrate)	0	1	-	X	1	1

Approval year	ATC code	Drug name (active ingredient)	Utilization of PPK		Descriptive contents of PPK [a]	No PPK results in US-Label despite having PPK results in US-CPBR		Comfirmed by FDA pharmacometrics team (If "Reason" is other than 1 to 5)
			[Label] 0: No 1: Yes	[CPBR] 0: No 1: Yes	Label	Reason [b]		0: No 1: Yes
2012	L	Choline C 11 Injection (choline C-11)	0	0	-	-	-	-
2012	L	Cometriq (cabozantinib S-malate)	1	1	3	-	-	-
2012	L	Elelyso (taliglucerase alfa)	0	0	-	-	-	-
2012	L	Fycompa (perampanel)	1	1	2	-	-	-
2012	L	Inlyta (axitinib)	1	1	4	-	-	-
2012	L	Linzess (linaclotide)	0	0	-	-	-	-
2012	L	Picato (ingenol mebutate)	0	0	-	-	-	-
2012	L	Prepopik (sodium picosulfate/magnesium oxide/citric acid)	0	0	-	-	-	-
2012	L	Synribo (omacetaxine mepesuccinate)	0	1	-	X	1	1
2012	L	Tudorza Pressair (aclidinium bromide)	0	0	-	-	-	-
2012	L	Xeljanz (tofacitinib citrate)	1	1	4	-	-	-
2012	L	Xtandi (enzalutamide)	1	1	4	-	-	-
2012	N	Jetrea (ocriplasmin)	0	0	-	-	-	-
2012	R	Erivedge (vismodegib)	1	1	4	-	-	-
2012	R	Kyprolis (carfilzomib)	1	1	4	-	-	-
2012	S	Kalydeco (ivacaftor)	1	1	4	-	-	-
2012	S	Stivarga (regorafenib)	1	1	4	-	-	-
2012	V	Omontys (peginesatide acetate)	1	1	4	-	-	-
2013	-	Brintellix (vortioxetine hydrobromide)	0	1	-	X	1	1
2013	-	Imbruvica (ibrutinib)	0	1	-	X	1	1
2013	A	Tecfidera (dimethyl fumarate)	0	0	-	-	-	-
2013	C	Adempas (riociguat)	1	1	6	-	-	-

Approval year	ATC code	Drug name (active ingredient)	Utilization of PPK		Descriptive contents of PPK [a]	No PPK results in US-Label despite having PPK results in US-CPBR		Comfirmed by FDA pharmacometrics team (If "Reason" is other than 1 to 5)
			[Label] 0: No 1: Yes	[CPBR] 0: No 1: Yes	Label	Reason [b]		0: No 1: Yes
2013	C	Duavee (bazedoxifene acetate/estrogens conjugated)	1	1	4	-	-	-
2013	C	Nesina (alogliptin benzoate)	0	1		X	1	1
2013	G	Kadcyla (ado-trastuzumab emtansine)	1	1	3	-	-	-
2013	J	Gilotrif (afatinib dimaleate)	1	1	4	-	-	-
2013	J	Luzu (luliconozole)	0	0	-	-	-	-
2013	J	Olysio (simeprevir sodium)	1	1	4	-	-	-
2013	L	Aptiom (eslicarbazepine acetate)	1	1	3	-	-	-
2013	L	Kynamro (mipomersen sodium)	0	1		X	1	1
2013	L	Mekinist (trametinib dimethyl sulfoxide)	1	1	4	-	-	-
2013	L	Pomalyst (pomalidomide)	0	0		-	-	-
2013	L	Tafinlar (dabrafenib mesylate)	1	1	4	-	-	-
2013	L	Vizamyl (flutemetamol F-18)	0	0	-	-	-	-
2013	L	Xofigo (radium Ra 223 dichloride)	0	0	-	-	-	-
2013	N	Dotarem (gadoterate meglumine)	0	1		X	2	0
2013	N	Gazyva (obinutuzumab)	1	1	3	-	-	-
2013	N	Tivicay (dolutegravir sodium)	1	1	3	-	-	-
2013	R	Invokana (canagliflozin)	1	1	4	-	-	-
2013	R	Sovaldi (sofosbuvir)	1	1	3	-	-	-
2013	V	Anoro Ellipta (umeclidinium bromide/vilanterol trifenatate)	1	1	4	-	-	-
2013	V	Breo Ellipta (fluticasone furoate/vilanterol trifenatate)	0	1	-	X	2	1
2013	V	Lymphoseek (technetium Tc 99m tilmanocept)	0	0		-	-	-
2013	V	Opsumit (macitentan)	0	0	-	-	-	-

Approval year	ATC code	Drug name (active ingredient)	Utilization of PPK		Descriptive contents of PPK [a]	No PPK results in US-Label despite having PPK results in US-CPBR		Comfirmed by FDA pharmacometrics team (If "Reason" is other than 1 to 5)
			[Label] 0: No 1: Yes	[CPBR] 0: No 1: Yes	Label		Reason [b]	0: No 1: Yes
2013	V	Osphena (ospemifene)	1	1	3	-	-	-
2014	-	Beleodaq (belinostat)	0	1		X	2	1
2014	-	Blincyto (blinatumomab)	1	1	4	-	-	-
2014	-	Cerdelga (eliglustat tartrate)	1	1	4	-	-	-
2014	-	Dalvance (dalbavancin hydrochloride)	1	1	6	-	-	-
2014	-	Esbriet (pirfenidone)	1	1	4	-	-	-
2014	-	Farxiga (dapaglifozin propanediol)	1	1	4	-	-	-
2014	-	Harvoni (ledipasvi/sofosbuvir)	1	1	3	-	-	-
2014	-	Jublia (efinaconazole)	0	0		-	-	-
2014	-	Lumason (sulfur hexafluoride lipid-type a microspheres)	0	0		-	-	-
2014	-	Lynparza (olaparib)	0	1		X	1	1
2014	-	Movantik (naloxegol oxalate)	0	1		X	5	1
2014	-	Northera (droxidopa)	1	1	4	-	-	-
2014	-	Orbactiv (oritavancin diphsphate)	1	1	3	-	-	-
2014	-	Rapivab (peramivir)	1	1	3	-	-	-
2014	-	Sivextro (tedizolid phosphate)	1	1	4	-	-	-
2014	-	Tanzeum (albiglutide)	1	1	4	-	-	-
2014	-	Trulicity (dulaglutide)	0	1		X	2	1
2014	-	Viekira Pak (ombitasvir/paritaprevir/ritonavir/dasabuvir sodium)	1	1	3	-	-	-
2014	-	Vimizim (elosulfase alfa)	0	0		-	-	-
2014	-	Zerbaxa (ceftolozane sulfate/tazobactam sodium)	1	1	4	-	-	-
2014	A	Hetlioz (tasimelteon)	0	0		-	-	-

Approval year	ATC code	Drug name (active ingredient)	Utilization of PPK		Descriptive contents of PPK [a]	No PPK results in US-Label despite having PPK results in US-CPBR		Comfirmed by FDA pharmacometrics team (If "Reason" is other than 1 to 5)
			[Label] 0: No 1: Yes	[CPBR] 0: No 1: Yes	Label		Reason [b]	0: No 1: Yes
2014	A	Keytruda (pembrolizumab)	1	1	3	-	-	-
2014	A	Opdivo (nivolumab)	1	1	3	-	-	-
2014	A	Otezla (apremilast)	0	1		X	2	1
2014	A	Plegridy (peginterferon beta-1a)	0	1		X	2	1
2014	A	Striverdi Respimat (olodaterol hydrochloride)	0	1		X	2	1
2014	B	Zykadia (ceritinib)	1	1	4	-	-	-
2014	J	Entyvio (vedolizumab)	1	1	3	-	-	-
2014	J	Jardiance (empagliflozin)	1	1	3	-	-	-
2014	L	Belsomra (suvorexant)	1	1	4	-	-	-
2014	L	Cyramza (ramucirumab)	1	1	4	-	-	-
2014	L	Impavido (miltefosine)	1	1	6	-	-	-
2014	L	Kerydin (tavaborole)	0	0		-	-	-
2014	L	Neuraceq (florbetaben F-18)	0	0		-	-	-
2014	L	Ofev (nintedanib esylate)	1	1	4	-	-	-
2014	L	Sylvant (siltuximab)	1	1	3	-	-	-
2014	L	Xtoro (finafloxacin)	0	0		-	-	-
2014	L	Zontivity (vorapaxar sulfate)	0	1		X	3	1
2014	R	Zydelig (idelalisib)	1	1	4	-	-	-
2014	V	Akynzeo (netupitant/palonosetron hydrochloride)	1	1	4	-	-	-
2014	V	Myalept (metreleptin)	0	0		-	-	-
2015	-	Bridion (sugammadex sodium)	1	1	5	-	-	-
2015	-	Cosentyx (secukinumab)	1	1	4	-	-	-

Approval year	ATC code	Drug name (active ingredient)	Utilization of PPK		Descriptive contents of PPK [a]	No PPK results in US-Label despite having PPK results in US-CPBR		Comfirmed by FDA pharmacometrics team (If "Reason" is other than 1 to 5)
			[Label] 0: No 1: Yes	[CPBR] 0: No 1: Yes	Label	Reason [b]		0: No 1: Yes
2015	-	Darzalex (daratumumab)	1	1	3	-	-	-
2015	-	Kanuma (sebelipase alfa)	1	1	2	-	-	-
2015	-	Kengreal (canegrelor)	0	1		X	2	1
2015	-	Ninlaro (ixazomib citate)	1	1	4	-	-	-
2015	-	Odomzo (sonidegib phosphate)	1	1	6	-	-	-
2015	-	Orkambi (lumacaftor/ivacaftor)	1	-	3	-	-	-
2015	-	Savaysa (edoxaban tosylate)	1	1		-	-	-
2015	-	Tagrisso (osimertinib mesylate)	1	1	3	-	-	-
2015	-	Unituxin (dinutuximab)	1	1	3	-	-	-
2015	-	Viberzi (eluxadoline)	0	1		X	2	1
2015	-	Vraylar (cariprazine hydrochloride)	0	1		X	2	1
2015	-	Xuriden (uridine triacetate)	0	0		-	-	-
2015	-	Yondelis (trabectedin)	1	1	4	-	-	-
2015	A	Alecensa (alectinib hydrochroride)	0	1		X	2	1
2015	A	Aristada (aripiprazole lauroxil)	1	1	3	-	-	-
2015	A	Corlanor (ivabradine hydrochloride)	0	1		X	2	1
2015	A	Nucala (mepolizumab)	1	1	3	-	-	-
2015	B	Zurampic (lesinurad)	1	1	4	-	-	-
2015	C	Kybella (deoxycholic acid)	0	1		X	2	1
2015	C	Rexulti (brexpiprazole)	1	1	5	-	-	-
2015	C	Varubi (rolapitant hydrochloride)	1	1	3	-	-	-
2015	G	Repatha (evolocumab)	0	1		X	2	1

Approval year	ATC code	Drug name (active ingredient)	Utilization of PPK		Descriptive contents of PPK [a]	No PPK results in US-Label despite having PPK results in US-CPBR		Comfirmed by FDA pharmacometrics team (If "Reason" is other than 1 to 5)
			[Label] 0: No 1: Yes	[CPBR] 0: No 1: Yes	Label	Reason [b]		0: No 1: Yes
2015	H	Ibrance (palbociclib)	1	1	4	-	-	-
2015	J	Addyi (flibanserin)	0	0		-	-	-
2015	J	Cotellic (cobimetinib fumarate)	1	1	3	-	-	-
2015	J	Cresemba (isavuconazonium sulfate)	1	1	3	-	-	-
2015	L	Avycaz (ceftazidime/avibactam sodium)	1	1	4	-	-	-
2015	L	Cholbam (cholic acid)	0	0		-	-	-
2015	L	Daklinza (daclatasvir gihydrochloride)	1	1	3	-	-	-
2015	L	Empliciti (elotuzumab)	1	1	6	-	-	-
2015	L	Farydak (panobinostat lactate)	1	1	4	-	-	-
2015	L	Genvoya (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fumarate)	1	1	3	-	-	-
2015	L	Lenvima (lenvatinib mesylate)	1	1	4	-	-	-
2015	L	Natpara (parathyroid horomone)	1	1	4	-	-	-
2015	L	Portrazza (necitumumab)	1	1	3	-	-	-
2015	L	Strensiq (asfotase alfa)	1	1	5	-	-	-
2015	L	Tresiba (insulin degludec)	0	1		X	5	1
2015	N	Lonsurf (trifluridine/tipiracil hydrochloride)	1	1	4	-	-	-
2015	N	Praluent (alirocumab)	1	1	4	-	-	-
2015	N	Praxbind (idarucizumab)	1	1	4	-	-	-
2015	R	Entresto (sacubitril/valsartan)	0	1		X	2	1
2015	V	Uptravi (selexipag)	0	1		X	2	1
2015	V	Veltassa (patiromer sorbitex calcium)	0	0		-	-	-

ATC: anatomical therapeutic chemical, PPK: population pharmacokinetics, CPBR: Clinical Pharmacology Biopharmaceutics Reviews report, -: not applicable

a) Categories 1: Individual patient pharmacokinetic parameters can be calculated from the model equation; 2: pharmacokinetic parameters are listed according to a patient background (such as weight or creatinine clearance); 3: pharmacokinetic parameters are listed, but not according to a patient background; 4: covariate is identified, and the necessity of dose adjustment by its covariate is stated; 5: covariate is identified, but the whether it is necessary to adjust the dosage cannot be determined; 6: only information that does not apply to categories 1–5 is shown, or only the fact that population pharmacokinetic analysis was performed is shown, without further information

b) Reasons 1: inappropriate PPK model/construction process; 2: dose adjustment was unnecessary; 3: more information than that provided by the PPK analysis was obtained from other analysis results; 4: there was inconsistency between PPK and the results of standard PK study; 5: unknown

Appendix 1-2: Database for Study 1 (Japan)

Approval year	ATC code	Drug name (active Ingredient)	Utilization of PPK				Descriptive content of PPK [a)]	
			[CTD] 0: No 1: Yes	[NDA RR] 0: No 1: Yes	[IF] 0: No 1: Yes	[PI] 0: No 1: Yes	PI	IF
2012	-	Azilva tablets 20mg & 40mg (azilsartan)	1	1	0	0	-	-
2012	-	Imovax polio subcutaneous injection (inactivated poliomyelitis vaccine (salk vaccine))	0	0	0	0	-	-
2012	-	Kiklin capsules 250mg (bixalomer)	0	0	0	0	-	-
2012	-	Kolbet tablets 25mg Careram tablets 25mg (iguratimod)	0	0	0	0	-	-
2012	-	Lotriga granular capsules 2g (omega-3-Acid ethyl esters)	0	0	0	0	-	-
2012	-	Poteligeo injection 20mg (mogamulizumab (genetical recombination))	1	1	1	0	-	4
2012	-	Quattrovac subcutaneous injection syringe (adsorbed diphtheria-purified pertussis-tetanus-inactivated polio (sabin strain) combined vaccine)	0	0	0	0	-	-
2012	-	Regnite tablets 300mg (gabapentin enacarbil)	1	1	1	0	-	5
2012	-	Rotateq oral solution (a live, oral pentavalent vaccine that contains 5 live reassortant rotaviruses)	0	0	0	0	-	-
2012	-	Suiny tablets 100mg Beskoa tablets 100mg (anagliptin)	0	0	0	0	-	-
2012	-	Tenelia tablets 20mg (Teneligliptin hydrobromide hydrate)	0	0	0	0	-	-
2012	-	Tetrabik subcutaneous injection syringe (adsorbed diphtheria-purified pertussis-tetanus-inactivated polio (sabin strain) combined vaccine)	0	0	0	0	-	-
2012	A	Brazaves capsules 100mg (miglustat)	1	1	0	0	-	-
2012	A	Ameparomo capsules 250mg (paromomycin sulfate)	0	0	0	0	-	-
2012	A	Amitiza capsules 24μg (lubiprostone)	0	0	0	0	-	-
2012	A	Buphenyl tablets 500mg Buphenyl granule 94% (sodium phenylbutyrate)	0	0	0	0	-	-
2012	A	L-Cartin FF oral solution 10% L-Cartin FF injection 1000mg (levocarnitine)	0	0	0	0	-	-

Approval year	ATC code	Drug name (active Ingredient)	Utilization of PPK				Descriptive content of PPK [a)]	
			[CTD] 0: No 1: Yes	[NDA RR] 0: No 1: Yes	[IF] 0: No 1: Yes	[PI] 0: No 1: Yes	PI	IF
2012	A	Tresiba flextouch Tresiba penfill (insulin degludec (genetical recombination))	1	1	1	0	-	4
2012	B	Eliquis tablets 2.5mg & 5mg (apixaban)	1	1	1	0	-	5
2012	B	Xarelto tablets 10mg & 15mg (rivaroxaban)	1	1	1	0	-	3
2012	D	Aiphagan ophthalmic solution 0.1% (brimonidine tartrate)	0	0	0	0	-	-
2012	G	Toviaz tablets 4mg & 8mg (fesoterodine fumarate)	1	1	1	0	-	5
2012	H	Somatuline subcutaneous injection 60mg, 90mg & 120mg (lanreotide acetate)	1	1	0	0	-	-
2012	J	Cancidas for intravenous drip infusion 50mg & 70mg (caspofungin acetate)	1	1	1	1	5	4
2012	J	Edurant tablets 25mg (rilpivirine hydrochloride)	1	1	1	1	3	3
2012	J	Tygacil injection 50mg (tigecycline)	1	1	1	0	-	4
2012	L	Cimzia syringe for subcutaneous injection 200mg (Certolizumab pegol (genetical recombination))	1	1	1	1	5	3
2012	L	Eylea intravitreal injection 40mg/mL Eylea intravitreal injection kit 40mg/mL (aflibercept (genetical recombination))	0	0	0	0	-	-
2012	L	Gliadel for intracerebral implant 7.7mg (carmustine)	0	0	0	0	-	-
2012	L	Gonax subcutaneous injection 80mg & 120mgr (degarelix acetate)	1	1	1	1	5	5
2012	L	Inlyta tablets 1mg & 5mg (axitinib)	1	1	1	1	2	2
2012	L	Votrient tablets 200mg (pazopanib hydrochloride)	1	1	1	1	4	4
2012	L	Xalkori capsules 200mg & 250mg (crizotinib)	1	1	1	0	-	5
2012	M	Ranmark subcutaneous injection 120mg (denosumab (genetical recombination))	1	1	1	0	-	5
2012	N	Apokyn subcutaneous injection 30mg (apomorphine hydrochloride hydrate)	1	1	1	0	-	4
2012	N	Choreazine tablets 12.5mg (tetrabenazine)	1	1	1	0	-	5
2012	N	Diacomit drysyrup 250mg (stiripentol)	1	1	1	0	-	5
2012	N	Emla cream (lidocaine/propitocaine)	0	0	0	0	-	-

Approval year	ATC code	Drug name (active Ingredient)	Utilization of PPK				Descriptive content of PPK [a)]	
			[CTD] 0: No 1: Yes	[NDA RR] 0: No 1: Yes	[IF] 0: No 1: Yes	[PI] 0: No 1: Yes	PI	IF
2012	N	Lunesta tablets 1mg, 2mg & 3mg (eszopiclone)	0	0	0	0	-	-
2012	N	Methapain tablets 5mg & 10mg (methadone hydrochloride)	1	0	-	0	-	-
2012	N	Neupro patch 2.25mg, 4.5mg, 9mg & 13.5mg (rotigotine)	1	1	1	0	-	4
2012	P	Malarone combination tablets (atovaquone/proguanil hydrochloride)	1	0	1	0	-	3
2012	P	Samtirel oral suspension 15% (atovaquone)	1	1	1	0	-	5
2012	R	Pulmozyme inhalation solution 2.5mg (dornase alfa (genetical recombination))	0	0	0	0	-	-
2012	R	Seebri inhalation capsules 50μg (glycopyrronium bromide)	1	1	0	0	-	-
2013	-	Acofide tablets 100mg (acotiamide hydrochloride Hydrate)	1	1	1	0	-	3
2013	-	Adsorbed influenza virus vaccine (H5N1) "Seiken" 1mL (adsorbed influenza virus vaccine (H5N1))	0	0	0	0	-	-
2013	-	Cell cultured influenza vaccine (Prototype) "Baxter" 1mL Cell cultured influenza vaccine (Prototype) "TAKEDA" 1mL (cell cultured influenza vaccine (Prototype))	-	0	-	0	-	-
2013	-	Cell cultured influenza vaccine H5N1 (Prototype) "Baxter" 1mL Cell cultured influenza vaccine H5N1 (Prototype) "TAKEDA" 1mL (cell cultured influenza vaccine (H5N1))	-	0	-	0	-	-
2013	-	Hizentra 20% sbcutaneous injection 1g/5mL (immune globlin (human))	0	0	0	0	-	-
2013	-	Metreleptin [SHIONOGI] subcutaneous injection 11.25mg (metreleptin (genetical recombination))	0	0	0	0	-	-
2013	-	Normosang infusion 250mg (Hemin)	0	0	0	0	-	-
2013	-	Nouriast tablets 20mg (istradefylline)	1	1	1	0	-	4
2013	-	Oblean tablets 120mg (cetilistat)	0	0	-	0	-	-
2013	-	Stribild combination tablets (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate)	1	1	1	0	-	3
2013	-	Topiloric tablets 20mg, 40mg & 60mg Uriadec tablets 20mg, 40mg & 60mg (topiroxostat)	0	0	0	0	-	-
2013	-	Unitalc intrapleural 4g (talc)	0	0	0	0	-	-
2013	A	Lyxumia subcutaneous injection 300μg (lixisenatide)	1	1	1	0	-	5
2013	A	Onglyza tablets 2.5mg (saxagliptin hydrate)	1	1	1	0	-	3

Approval year	ATC code	Drug name (active Ingredient)	Utilization of PPK				Descriptive content of PPK [a]	
			[CTD] 0: No 1: Yes	[NDA RR] 0: No 1: Yes	[IF] 0: No 1: Yes	[PI] 0: No 1: Yes	PI	IF
2013	B	Voluven 6% solution for infusion (poly (O-2-hydroxyethyl) starch)	0	0	0	0	-	-
2013	C	Bisono tape 4mg & 8mg (bisoprolol)	0	0	0	0	-	-
2013	J	Prevenar13 suspension liquid for injection (pneumococcal 13-valent conjugate vaccine (diphtheria CRM197 protein))	0	0	0	0	-	-
2013	J	Sovriad capsules 100mg (simeprevir sodium)	1	1	1	1	3	3
2013	L	Alabel oral 1.5g Alaglio oral 1.5g (aminolevulinic acid hydrochloride)	0	0	0	0	-	-
2013	L	Arzerra for intravenous infusion 100mg & 1000mg (ofatumumab (genetical recombination))	1	1	1	0	-	4
2013	L	Evoltra intravenous injection 20mg (clofarabine)	1	1	1	1	5	4
2013	L	Kadcyla intravenous injection 100mg & 160mg (trastuzumab emtansine (genetical recombination))	1	1	1	0	-	4
2013	L	Perjeta intravenous injection 420mg/14mL (pertuzumab (genetical recombination))	1	1	1	1	3	3
2013	L	Stivarga tablets 40mg (regorafenib hydrate)	1	1	1	0	-	6
2013	L	Xeljanz tablet 5mg (tofacitinib citrate)	1	1	1	1	3	3
2013	M	Bonviva injection syringe 1mg (ibandronate sodium hydrate)	1	1	1	0	-	4
2013	N	Inovelon tablets 100mg & 200mg (rufinamide)	1	1	1	1	5	5
2013	N	Regtect tablets 333mg (acamprosate calcium)	0	0	0	0	-	-
2013	N	Vyndaqel capsules 20mg (tafamidis meglumine)	1	1	1	1	5	3
2013	N	Xeplion aqueous suspension for intramuscular injection syringe 25mg, 50mg, 75mg, 100mg & 150mg (paliperidone palmitate)	1	1	1	1	4	3
2013	R	Relvar 100 ellipta14 Relvar 100 ellipta30 Relvar 200 ellipta14 Relvar 200 ellipta30 (vilanterol trifenatate/fluticasone furoate)	1	1	1	0	-	2
2013	V	Datscan injection (Iofluipan (^{123}I))	0	0	0	0	-	-
2014	-	Adsorbed cell culture-derived influenza vaccine H5N1 for intramuscular injection 30μg/mL"Kitasato Daiichi Sankyo" (adsorbed cell culture-derived influenza vaccine (H5N1))	0	0	-	0	-	-

Approval year	ATC code	Drug name (active Ingredient)	Utilization of PPK				Descriptive content of PPK [a]	
			[CTD] 0: No 1: Yes	[NDA RR] 0: No 1: Yes	[IF] 0: No 1: Yes	[PI] 0: No 1: Yes	PI	IF
2014	-	Alecensa capsule 20mg & 40mg (alectinib hydrochloride)	1	1	1	0	-	5
2014	-	Allergen extract for scratch test - HDM "TORII" 100,000JAU/mL (Dermatophagoides farinae extract bulk powder,Dermatophagoides pteronyssinus extract bulk powder)	-	-	0	0	-	-
2014	-	Allergen extract for subcutaneous injection-HDM "TORII" 100,000JAU/mL & 10,000JAU/mL (dermatophagoides farinae extract)	0	0	0	0	-	-
2014	-	Alprolix intravenous 250, 500, 1000, 2000 & 3000 (eftrenonacog alfa (genetical recombination))	1	1	1	0	-	5
2014	-	Avigan tablet 200mg (favipiravir)	-	0	-	-	-	-
2014	-	Belsomra tablets 10mg (suvorexant)	1	1	1	0	-	3
2014	-	Byclot combination intravenous injection (freeze-dried activated human blood coagulation factor VII concentrate containing factor X)	-	-	-	0	-	-
2014	-	Cell culture-derived influenza emulsion HA vaccine H5N1 for intramuscular injection"Kaketsuken" (cell culture-derived influenza emulsion HA vaccine (H5N1))	0	0	-	0	-	-
2014	-	Clenafin topical solution for nail 10% (efinaconazole)	0	0	0	0	-	-
2014	-	Deberza tablets 20mg Apleway tablets 20mg (tofogliflozin hydrate)	1	0	1	0	-	3
2014	-	Eloctate Intravenous 250, 500, 750, 1000, 1500, 2000 & 3000 (efraloctocog alfa (genetical recombination))	1	1	1	0	-	5
2014	-	Glanatec ophthalmic solution 0.4% (ripasudil hydrochloride hydrate)	0	0	0	0	-	-
2014	-	Lusefi tablet 2.5mg & 5mg (luseogliflozin hydrate)	1	1	1	0	-	5
2014	-	Nicystagon capsules 50mg & 150mg (cysteamine bitartrate)	1	0	0	0	-	-
2014	-	NovoEight intravenous injection 250, 500, 1000, 1500, 2000 & 3000 (turoctocog alpha (genetical recombination))	0	0	0	0	-	-
2014	-	Opdivo intravenous infusion 20mg & 40mg (nivolumab (genetical recombination))	1	1	1	0	-	4
2014	-	Rixubis Intravenous 250, 500, 1000, 2000, 3000 (Nonacog gamma (genetical recombination))	-	-	-	-	-	-
2014	-	Suglat tablets 25mg & 50mg (ipragliflozin L-proline)	1	1	1	0	-	5
2014	-	Takecab tablets 10mg & 20mg (vonoprazan fumarate)	1	1	1	0	-	4

Approval year	ATC code	Drug name (active Ingredient)	Utilization of PPK				Descriptive content of PPK [a]	
			[CTD] 0: No 1: Yes	[NDA RR] 0: No 1: Yes	[IF] 0: No 1: Yes	[PI] 0: No 1: Yes	PI	IF
2014	-	Vanihep capsules 150mg (vaniprevir)	0	0	0	0	-	-
2014	A	Canaglu tablets 100mg (canagliflozin hydrate)	1	1	1	0	-	5
2014	A	Cystadane (betaine)	0	0	0	0	-	-
2014	A	Forxiga tablets 5mg & 10mg (dapagliflozin propylene glycolatehydrate)	1	1	1	0	-	3
2014	A	Jardiance tablets 10mg & 25mg (empagliflozin)	1	1	1	1	5	3
2014	A	Orfadin capsules 2mg, 5mg & 10mg (nitisinone)	1	0	1	0	-	3
2014	A	Vimizim intravenous infusion 5mg (elosulfase alfa (genetical recombination))	0	0	0	0	-	-
2014	A	Vpriv for intravenous injection 400U (Velaglucerase alfa (genetical recombination))	0	0	0	0	-	-
2014	B	Efient tablets 3.75mg & 5mg (prasugrel hydrochloride)	1	1	1	0	-	4
2014	B	Riona tablets 250mg (ferric citrate hydrate)	0	0	0	0	-	-
2014	B	Treprost for injection 20mg, 50mg, 100mg & 200mg (treprostinil)	0	0	0	0	-	-
2014	C	Adempas tablets 0.5mg, 1.0mg & 2.5mg (riociguat)	1	1	1	1	5	3
2014	D	Bepio gel 2.5% (benzoyl peroxide)	0	0	0	0	-	-
2014	J	Daklinza tablets 60mg (daclatasvir hydrochloride)	1	1	1	0	-	4
2014	J	Deltyba tablets 50mg (delamanid)	1	1	1	0	-	3
2014	J	Menactra intramuscular injection (meningococcal quadrivalent vaccine (diphtheria toxoid conjugate))	0	0	0	0	-	-
2014	J	Sunvepra capsules 100mg (asunaprevir)	1	1	1	0	-	4
2014	J	Tenozet tablets 300mg (tenofovir disoproxil fumarate)	0	0	0	0	-	-
2014	J	Tivicay tablets 50mg (dolutegravir sodium)	1	1	1	1	3	1
2014	L	Adcetris for intravenous drip infusion 50mg (brentuximab vedotin (genetical recombination))	1	1	1	0	-	4
2014	L	Agrylin capsules 0.5mg (anagrelide hydrochloride hydrate)	0	0	0	0	-	-
2014	L	Bosulif tablets 100mg (bosutinib hydrate)	1	1	1	0	-	4

Approval year	ATC code	Drug name (active Ingredient)	Utilization of PPK				Descriptive content of PPK [a]	
			[CTD] 0: No 1: Yes	[NDA RR] 0: No 1: Yes	[IF] 0: No 1: Yes	[PI] 0: No 1: Yes	PI	IF
2014	L	Cosentyx for subcutaneous injection syringe 150mg Cosentyx for subcutaneous injection 150mg (secukinumab (genetical recombination))	1	1	1	1	3	3
2014	L	Giotrif tablets 20mg, 30mg, 40mg & 50mg (afatinib maleate)	1	1	1	1	5	4
2014	L	G-Lasta subcutaneous injection 3.6mg (pegfilgrastim (genetical recombination))	0	0	0	0	-	-
2014	L	Jakavi tablets 5mg (ruxolitinib phosphate)	1	1	1	0	-	2
2014	L	Jevtana intravemous infusion 60mg (cabazitaxel acetonate)	1	1	1	1	5	5
2014	L	Lonsurf combination tablet T15 & T20 (trifluridine/tipiracil hydrochloride)	0	0	1	0	-	4
2014	L	MabCampath intravenous infusion 30mg (alemtuzumab (genetical recombination))	1	1	1	0	-	5
2014	L	Rapalimus tablets 1mg (sirolimus)	1	1	0	0	-	-
2014	L	Tysabri for intravenous infusion 300mg (natalizumab (geneticalrecombination))	1	1	1	0	-	5
2014	L	Xtandi capsules 40mg (enzalutamide)	1	1	1	1	5	5
2014	L	Zanosar for intravenous injection 1g (streptozocin)	0	0	0	0	-	-
2014	L	Zelboraf tablet 240mg (vemurafenib)	1	1	1	1	3	3
2014	L	Zytiga tablets 250mg (abiraterone acetate)	1	1	1	1	3	3
2014	N	Tapenta tablets 25mg, 50mg & 100mg (tapentadol hydrochloride)	1	0	-	0	-	-
2014	R	Anoro Ellipta 7doses & 30doses (umeclidinium bromide/vilanterol trifenatate)	1	1	1	0	-	2
2014	V	Fomepizole intravenous infusion 1.5g (fomepizole)	0	0	0	0	-	-
2014	V	Methylene blue intravenous injection "Daiichi sankyo" 50mg (methylthioninium chloride hydrate)	0	0	0	0	-	-
2014	V	Nopicor capsules 2.5μg (nalfurafine hydrochloride)	1	0	0	0	-	-
2014	V	Savene injectable 500mg (dexrazoxane)	1	0	0	0	-	-
2015	-	Acoalan injection 600 (antithrombin gamma (genetical recombination))	0	0	0	0	-	-
2015	-	Loqoa tape (esflurbiprofen/menthaoil)	0	0	0	0	-	-
2015	-	Marizev tablets 12.5mg & 25mg (omarigliptin)	1	1	1	1	5	2

Approval year	ATC code	Drug name (active Ingredient)	Utilization of PPK				Descriptive content of PPK [a)]	
			[CTD] 0: No 1: Yes	[NDA RR] 0: No 1: Yes	[IF] 0: No 1: Yes	[PI] 0: No 1: Yes	PI	IF
2015	-	Mulpleta tablets 3mg (lusutrombopag)	1	1	1	1	4	3
2015	-	Olanedine antiseptic solution 1.5% Olanedine solution 1.5% antiseptic applicator 10 mL & 25mL (olanexidine gluconate)	0	0	0	0	-	-
2015	-	Zafatek tablets 50mg & 100mg (trelagliptin succinate)	1	1	1	0	-	5
2015	-	Zebiax lotion 2% (ozenoxacin)	0	0	0	0	-	-
2015	A	Cerdelga capsule 100mg (eliglustat tartrate)	1	1	1	1	5	5
2015	A	Strensiq subcutaneous injection 12mg/0.3mL, 18mg/0.45mL, 28mg/0.7mL, 40mg/1mL & 80mg/0.8mL (asfotase alfa (genetical recombination))	1	1	1	0	-	3
2015	A	Trulicity subcutaneous injection 0.75mg Ateos (dulaglutide (genetical recombination))	1	1	1	1	5	5
2015	B	NovoThirteen intravenous injection 2500 (catridecacog (genetical recombination))	0	0	0	0	-	-
2015	B	P-Tol chewable tablet 250mg & 500mg (sucroferricoxy hydroxide)	0	0	0	0	-	-
2015	B	Ventavis inhalation solution 10μg (iloprost)	0	0	0	0	-	-
2015	C	Opsumit tablet 10mg (macitentan)	0	0	0	0	-	-
2015	D	Duac combination gel (clindamycin phosphate hydrate/benzoyl peroxide)	0	0	0	0	-	-
2015	J	Cell culture-derived influenza emulsion HA vaccine (prototype) for intramuscular injection“Kaketsuken” (cell culture-derived influenza emulsion HA vaccines (prototype))	0	0	0	0	-	-
2015	J	Harvoni combination tablets (ledipasviracetonate/sofosbuvir)	1	1	1	1	3	4
2015	J	Sovaldi tablets 400mg (sofosbuvir)	1	1	1	1	3	4
2015	J	Synflorix aqueous suspension for intramuscular injection (Pneumococcal 10-valent conjugatevaccine adsorbed (Non-typeable Haemophilus influenzae (NTHi) protein D, diphtheria ortetanus toxoidconjugates))	0	0	0	0	-	-
2015	J	Viekirax combination tablets (ombitasvirhydrate/paritaprevirhydrate/ritonavir)	1	1	1	1	3	3
2015	L	Caprelsa tablets 100mg (vandetanib)	1	1	1	0	-	4
2015	L	Copaxone subcutaneous injection syringe 20mg (glatiramer acetate)	0	0	0	0	-	-
2015	L	Cyramza injection 100mg & 500mg (ramucirumab (genetical recombination))	1	1	1	0	-	3

Approval year	ATC code	Drug name (active Ingredient)	Utilization of PPK				Descriptive content of PPK [a)]	
			[CTD] 0: No 1: Yes	[NDA RR] 0: No 1: Yes	[IF] 0: No 1: Yes	[PI] 0: No 1: Yes	PI	IF
2015	L	Farydak capsules 10mg & 15mg (panobinostat lactate)	1	1	1	0	-	3
2015	L	Lenvima capsules 4mg & 10mg (lenvatinib mesilate)	1	1	1	0	-	5
2015	L	Ofev capsules 100mg & 150mg (nintedanib ethanesulfonate)	1	1	1	1	5	4
2015	L	Pomalyst capsules 1mg, 2mg, 3mg & 4mg (pomalidomide)	1	1	1	0	-	5
2015	L	Yervoy injection 50mg (ipilimumab (genetical recombination))	1	1	1	0	-	4
2015	L	Yondelis intravenous infusion 0.25mg & 1mg (trabectedin)	1	1	1	0	-	4
2015	M	Xiaflex Injection (collagenase (Clostridium histolyticum))	0	0	0	0	-	-
2015	N	Effexor SR capsules 37.5mg & 75mg (venlafaxine hydrochloride)	1	1	1	0	-	4
2015	P	Plaquenil tablets 200mg (hydroxychloroquine sulfate)	1	1	1	1	2	2
2015	R	Eklira 400μg Genuair 30doses Eklira 400μg Genuair 60doses (aclidinium bromide)	0	0	0	0	-	-
2015	R	Spiolto respimat 28puffs & 60puffs (tiotropium bromidehydrate/olodaterol hydrochloride)	0	0	0	0	-	-
2015	V	Actair 100 IR sublingual tablets-HDM Actair 300 IR sublingual tablets-HDM (Dermatophagoides farinae extract bulk powder,Dermatophagoides pteronyssinus extract bulk powder)	0	0	0	0	-	-
2015	V	Gadovist intravenous injection 1.0mol/L 7.5 mL Gadovist intravenous injection 1.0 mol/L syringe 5mL, 7.5mL & 10mL (gadobutrol)	1	1	1	0	-	5
2015	V	Miticure house dust mite sublingual tablets 3,300 JAU & 10,000 JAU (Dermatophagoides farinae extract, Dermatophagoides pteronyssinus extract)	0	0	0	0	-	-
2015	V	Octreoscan injection (indium pentetoreotide (^{111}In))	0	0	0	0	-	-

ATC: anatomical therapeutic chemical, PPK: population pharmacokinetics, CTD: common technical document, NDA RR: new drug applications review report, IF: interview form, PI: package insert, -: not applicable

a) Categories 1: Individual patient pharmacokinetic parameters can be calculated from the model equation; 2: pharmacokinetic parameters are listed according to a patient background (such as weight or creatinine clearance); 3: pharmacokinetic parameters are listed, but not according to a patient background; 4: covariate is identified, and the necessity of dose adjustment by its covariate is stated; 5: covariate is identified, but the whether it is necessary to adjust the dosage cannot be determined; 6: only information that does not apply to categories 1–5 is shown, or only the fact that population pharmacokinetic analysis was performed is shown, without further information

Appendix 2: Database for Study 2

Drug name	Therapeutic category	TDM		Journal title	Research design 1: Interventional 2: Observational 3: Unknown	Research purpose [a]	Number of centers 1: Single-center 2: Multiple-center 3: Unknown	Number of subjects	Number of total sampling points	New findings_1 [b]	New findings_2 [c] (If "New finding_1" are 1 to 3,)	PPK information in application data	Reflecting the PPK results obtained from the report in PI and IF (If "PPK information in application data" is X,)
mycophenoic acid	87399	X	1	The Japanese Journal of Therapeutic Drug Monitoring (2015) 22;11-21	1	1, 4	1	29	372	1, 2	1	-	-
docetaxel	87424	-	1	Cancer Science (2009) 100;144-149	1	5-3	3	200	-	2, 3	7	X	No
			2	Cancer Science (2007) 98;1985-1992	1	5-3	1	62	-	4	-	X	No
			3	Yakugaku Zasshi (2009) 129;1565-1572	2	1	3	-	-	4	-	X	No
etoposide	87424	-	1	The St. Marianna Medical Journal (1998) 26;393-400	1	1	1	7	-	1	1	-	-
pranlukast	87449	-	1	Allergology International (2003) 52;213-218	1	5-1	3	22	54	2, 3	7	X	No
itraconazole	87629	-	1	The Japanese Journal of Antibiotics (2013) 66;159-168	2	1	1	51	236	1	1	-	-
phenytoin	871132	X	1	Journal of Pharmaceutical Science and Technology, Japan (1990) 50;292-299	2	5-5	2	217	750	1	1	-	-
			2	Japanese Journal of Clinical Pharmacology and Therapeutics (1990) 21;181-182	2	5-4	1	70	149	1, 2	1	-	-
			3	Journal of Japanese Society of Hospital Pharmacists (1990) 26;169-171	1	4	3	5	-	1, 2	5	-	-
			4	Japanese Journal of National Medical Services (1989) 43;433-438	2	1	2	98	370	1, 2	2	-	-
			5	Japanese Journal of Clinical Pharmacology and Therapeutics (1992) 23;171-172	3	5-5	1	19	63	4	-	-	-
clobazam	871139	X	1	The Japanese Journal of Therapeutic Drug Monitoring (2015) 32;85-93	2	4	1	48	363	1, 2	1	-	-
risperidone	871179	-	1	Recent Advances in Clinical Pharmacology (2012) 33;115-121	1	1	2	50	-	3	1	X	No
digoxin	872113	X	1	The Japanese Journal of Therapeutic Drug Monitoring (2010) 27;78-84	2	6	3	143	269	4	-	X	No

Drug name	Therapeutic category	TDM		Journal title	Research design 1: Interventional 2: Observational 3: Unknown	Research purpose [a]	Number of centers 1: Single-center 2: Multiple-center 3: Unknown	Number of subjects	Number of total sampling points	New findings_1 [b]	New findings_2 [c] (If "New finding_1" are 1 to 3,)	PPK information in application data	Reflecting the PPK results obtained from the report in PI and IF (If "PPK information in application data" is X,)
			2	The Japanese Journal of Therapeutic Drug Monitoring (2001) 18;277-285	2	3	1	19	45	4	-	X	No
			3	Japanese Journal of Pharmaceutical Health Care and Sciences (2001) 27;426-431	2	5-1	1	147	340	2, 3	7	X	No
			4	Annual report of the research, the foundation for Growth Science (2003) 26;379-384	2	5-1	1	71	129	2, 3	7	X	No
			5	Annual report of the research on nervous and mental disorders (1990) 288-292	2	5-4	2	33	107	2, 3	7	X	No
			6	Annual report of the research on nervous and mental disorders (1988) 310	2	1	2	21	-	3	9	X	No
			7	The Japanese Journal of Therapeutic Drug Monitoring (1999) 16;292-298	2	3	1	12	110	4	-	X	No
olprinone	872119	-	1	Journal of Anesthesia (2013) 27;243-250	1	5-4, 6	3	37	123	1, 2	1	-	-
landiolol	872123	-	1	Journal of Infection and Chemotherapy (2015) 21;123-129	1	1, 5-4	1	9	126	1	1	-	-
amiodarone	872129	X	1	The Japanese Journal of Therapeutic Drug Monitoring (2014) 31;93-100	2	5-5	1	47	137	3	5	X	No
			2	Progress in Medicine (2006) 26(Suppl.1);1469-1472	2	4	1	23	151	2, 3	7	X	No
bepridil	872129	X	1	The Japanese Journal of Therapeutic Drug Monitoring (2012) 29;77-82	1	5-4	2	95	101	1, 2	1	-	-
disopyramide	872129	X	1	Japanese Journal of Clinical Pharmacology and Therapeutics (1995) 26;697-706	1	1	2	33	108	1, 2	1	-	-
pilsicainide	872129	-	1	The Japanese Journal of Therapeutic Drug Monitoring (2010) 27;85-97	2	4	1	76	101	1, 2	1	-	-
carvedilol	872149	-	1	Biological & Pharmaceutical Bulletin (2007) 30;537-542	2	4	3	41	373	1, 2	1	-	-
			2	Biological & Pharmaceutical Bulletin (2010) 33;1378-1384	1	1, 4	3	58	155	1, 2	1	-	-

Drug name	Therapeutic category	TDM		Journal title	Research design 1: Interventional 2: Observational 3: Unknown	Research purpose [a]	Number of centers 1: Single-center 2: Multiple-center 3: Unknown	Number of subjects	Number of total sampling points	New findings_1 [b]	New findings_2 [c] (If "New finding_1" are 1 to 3,)	PPK information in application data	Reflecting the PPK results obtained from the report in PI and IF (If "PPK information in application data" is X,)
theophylline	872251	X	1	Yakugaku Zasshi (2008) 128;635-640	2	4, 6	1	52	90	1, 2	2	-	-
			2	The Japanese Journal of Therapeutic Drug Monitoring (2003) 20;249-256	2	2, 4	1	128	205	4	-	-	-
			3	Japanese Journal of Clinical Pharmacology and Therapeutics (2001) 32;113-118	2	5-5	2	174	-	1, 2	1	-	-
			4	Yakugaku Zasshi (1999) 119;861-867	2	3, 4	3	148	178	1, 2	1	-	-
			5	The Japanese Journal of Therapeutic Drug Monitoring (1993) 10;146-148	2	4, 5-4	1	52	354	1, 2	1	-	-
			6	Japanese Journal of Clinical Pharmacology and Therapeutics (1986) 17;81-82	1	4	1	46	-	1	1	-	-
			7	The Japanese Journal of Therapeutic Drug Monitoring (2010) 27;151-157	2	2	1	71	-	4	-	-	-
			8	The Japanese Journal of Therapeutic Drug Monitoring (2009) 26;59-65	2	3	1	54	81	1, 2	3	-	-
thiamazole	872432	-	1	Japanese Journal of Clinical Pharmacology and Therapeutics (1987) 18;271-272	1	6	3	28	-	1	1	-	-
febuxostat	873949	-	1	Recent Advances in Clinical Pharmacology (2015) 36;112-118	2	1, 5-3	1	26	126	1	1	-	-
			2	Journal of Shiga University of Medical Science (2014) 27;a9-a11	1	4	1	15	30	1, 2	1	-	-
cyclosporine	873999	X	1	Biological & Pharmaceutical Bulletin (2015) 38;1265-1271	2	5-4	1	36	89	1, 2	1	-	-
			2	The Japanese Journal of Therapeutic Drug Monitoring (2009) 26;52-58	2	1	1	-	-	4	-	-	-
mizoribine	873999	-	1	Clinical and Experimental Nephrology (2016) 20;757-763	1	5-1, 5-3, 5-4	2	105	984	1, 2	2, 4	-	-
			2	Clinical and Experimental Nephrology (2012) 16;799-804	2	5-1	2	51	353	1	2	-	-
			3	Clinical and Experimental Nephrology (2011) 15;900-906	2	5-4	2	114	449	1, 2	1	-	-

Drug name	Therapeutic category	TDM		Journal title	Research design 1: Interventional 2: Observational 3: Unknown	Research purpose [a]	Number of centers 1: Single-center 2: Multiple-center 3: Unknown	Number of subjects	Number of total sampling points	New findings_1 [b]	New findings_2 [c] (If "New finding_1" are 1 to 3,)	PPK information in application data	Reflecting the PPK results obtained from the report in PI and IF (If "PPK information in application data" is X,)
			4	Therapeutic Research (2005) 26;642-646	2	5-4	2	46	87	1	1	-	-
tacrolimus	873999	X	1	Annual report of the research, the Uehara memorial Foundation (2008) 22;1-4	3	5-4	1	60	-	2, 3	7	X	No
			2	The Japanese Journal of Therapeutic Drug Monitoring (2009) 26;52-58	→ cf. cyclosporine-2								
			3	Japanese Journal of Clinical Pharmacology and Therapeutics (2002) 33;127S-128S	2	3	1	47	-	4	-	X	No
busulfan	874213	-	1	Japanese Journal of Pharmaceutical Health Care and Sciences (2009) 35;1-10	2	5-1	2	103	-	2, 3	7	X	No
cisplatin	874291	-	1	Japanese Journal of Clinical Oncology (2001) 31;179-184	1	4	1	27	-	1, 2	1	-	-
nedaplatin	874291	-	1	Kitasato Medicine (2009) 39;35-39	1	2	3	10	115	1, 2	1	-	-
vancomycin	876113	X	1	The Japanese Journal of Therapeutic Drug Monitoring (2015) 32;109-115	2	3	1	55	124	1, 2	1	-	-
			2	The Japanese Journal of Therapeutic Drug Monitoring (2011) 28;45-50	2	4	1	65	-	1	2	-	-
			3	Journal of Japanese Society of Hospital Pharmacists (2008) 44;935-937	2	3	1	119	-	1	3	-	-
			4	Biological & Pharmaceutical Bulletin (2002) 25;1333-1338	3	5-2	3	41	66	1, 2	1	-	-
			5	Recent Advances in Clinical Pharmacology (2013) 34;33-39	2	3	1	25	-	1, 2	2	-	-
			6	The Japanese Journal of Therapeutic Drug Monitoring (2016) 33;181-190	2	3	2	95	268	1, 2	1	-	-
			7	Japanese Journal of Environmental Infections (2014) 29;117-121	1	6	1	65	-	4	-	-	-
			8	Yakugaku Zasshi (2012) 132;125-133	2	4	1	90	-	1, 2	1	-	-
			9	Journal of Infection and Chemotherapy (2005) 11;182-188	2	2	1	8	16	1, 2	4	-	-

Drug name	Therapeutic category	TDM		Journal title	Research design 1: Interventional 2: Observational 3: Unknown	Research purpose [a]	Number of centers 1: Single-center 2: Multiple-center 3: Unknown	Number of subjects	Number of total sampling points	New findings_1 [b]	New findings_2 [c] (If "New finding_1" are 1 to 3,)	PPK information in application data	Reflecting the PPK results obtained from the report in PI and IF (If "PPK information in application data" is X,)
			10	The Japanese Journal of Therapeutic Drug Monitoring (2002) 19;191-192	2	3	1	23	42	1	1	-	-
			11	Japanese Journal of Chemotherapy (2002) 50;363-370	2	3	1	14	28	1	1	-	-
			12	The Japanese Journal of Therapeutic Drug Monitoring (2001) 18;286-290	2	2	1	9	17	4	-	-	-
			13	The Japanese Journal of Therapeutic Drug Monitoring (2001) 18;337-342	2	3	1	23	84	4	-	-	-
arbekacin	876119	X	1	Journal of Infection and Chemotherapy (2016) 22;436-443	2	2	1	170	331	2, 3	7	X	No
			2	Japanese Journal of Chemotherapy (2011) 59;597-604	1	2	2	49	146	4	-	X	No
			3	Japanese Journal of Chemotherapy (2006) 54;520-525	2	5-1	1	19	31	3	2, 8	X	No
teicoplanin	876119	X	1	The Japanese Journal of Therapeutic Drug Monitoring (2015) 32;188-197	2	6	2	132	292	2, 3	7	X	No
			2	Japanese Journal of Chemotherapy (2007) 55;17-22	2	5-1	1	63	111	3	2, 8	X	No
			3	Japanese Journal of Chemotherapy (2006) 54;1-6	2	6	1	120	305	4	-	X	Yes
			4	Japanese Journal of Pharmaceutical Health Care and Sciences (2013) 39;587-598	2	2, 3	2	74	-	4	-	X	No
			5	Japanese Journal of Pharmaceutical Health Care and Sciences (2007) 33;710-718	2	3	1	45	59	4	-	X	No
isepamicin	876123	X	1	Japanese Journal of Chemotherapy (1994) 42;202-213	2	2	1	48	418	4	-	-	-
cefotiam	876132	-	1	The Japanese Journal of Therapeutic Drug Monitoring (2008) 25;75-81	1	1	1	8	-	4	-	-	-
cefozopran	876132	-	1	The Japanese Journal of Antibiotics (2009) 62;435-444	2	5-1	2	31	110	1, 2	2	-	-
			2	Recent Advances in Clinical Pharmacology (2009) 30;118-127	1	1, 2	1	36	-	1	1	-	-

Drug name	Therapeutic category	TDM		Journal title	Research design 1: Interventional 2: Observational 3: Unknown	Research purpose [a]	Number of centers 1: Single-center 2: Multiple-center 3: Unknown	Number of subjects	Number of total sampling points	New findings_1 [b]	New findings_2 [c] (If "New finding_1" are 1 to 3,)	PPK information in application data	Reflecting the PPK results obtained from the report in PI and IF (If "PPK information in application data" is X,)
			3	Journal of Infection and Chemotherapy (2008) 14;130-136	1	1, 5-4	2	32	145	1, 2	1	-	-
gentamicin	876134	X	1	The Japanese Journal of Therapeutic Drug Monitoring (2016) 33;91-99	2	2	1	104	321	1, 2	1	-	-
biapenem	876139	-	1	Journal of Infection and Chemotherapy (2013) 19;98-102	1	5-2	3	20	-	4	-	X	No
meropenem	876139	-	1	Japanese Journal of Chemotherapy (2012) 60;335-341	1	1, 5-1	1	29	-	4	-	X	No
			2	Journal of Infection and Chemotherapy (2010) 16;139-143	2	5-1	3	40	229	2, 3	7	X	No
			3	Journal of Infection and Chemotherapy (2010) 16;25-32	1	1, 5-5	3	42	265	2, 3	1	X	No
piperacillin	876139	-	1	The Japanese Journal of Antibiotics (2013) 66;189-203	2	2	2	53	157	3	8	X	No
sulbactam	876139	-	1	Journal of Infection and Chemotherapy (2015) 21;284-289	1	6	2	66	188	3	5	X	No
tazobactam	876139	-	1	The Japanese Journal of Antibiotics (2013) 66;189-203	→ cf. piperacillin-1								
micafungin	876179	-	1	Medicine and Drug Journal (2009) 45;751-755	3	2	1	-	-	3	9	X	No
levofloxacin	876241	-	1	Internal Medicine (2008) 47;375-378	1	2, 5-5	1	8	20	3	9	X	No
			2	Journal of Japanese Society of Hospital Pharmacists (2008) 44;897-900	2	2, 3	1	567	-	2, 3	7	X	No
moxifloxacin	876241	-	1	Antibiotics & Chemotherapy (2010) 26;2452-2459	1	5-4, 5-5	1	15	-	3	1	X	No
linezolid	876249	-	1	Journal of Infection and Chemotherapy (2011) 17;70-75	3	1	1	12	20	2, 3	7	X	No
morphine	878114	-	1	The Japanese Journal of Therapeutic Drug Monitoring (2002) 19;253-261	2	3	1	38	76	1	1, 5	-	-
carbamazepine	871139 871179	X	1	Journal of Pharmaceutical Science and Technology, Japan (1989) 49;304-312	2	4, 5-5	2	122	432	1, 2	1	-	-
			2	Japanese Journal of Pharmaceutical Health Care and Sciences (2005) 31;410-416	2	2, 6	1	60	-	1, 2	1	-	-

Drug name	Therapeutic category	TDM		Journal title	Research design 1: Interventional 2: Observational 3: Unknown	Research purpose [a]	Number of centers 1: Single-center 2: Multiple-center 3: Unknown	Number of subjects	Number of total sampling points	New findings_1 [b]	New findings_2 [c] (If "New finding_1" are 1 to 3,)	PPK information in application data	Reflecting the PPK results obtained from the report in PI and IF (If "PPK information in application data" is X,)
valproic acid	871139 871179	X	1	The Japanese Journal of Therapeutic Drug Monitoring (2007) 24;175-178	2	1	3	58	130	1, 2	1	-	-
			2	Journal of Pharmaceutical Science and Technology, Japan (1989) 49;148-156	2	5-5	2	194	739	1	1	-	-
			3	Japanese Journal of Clinical Pharmacology and Therapeutics (1985) 16;211-212	1	1, 5-1	1	20	-	4	-	-	-
ephedrine	872221 872118	-	1	Kampo Medicine (1992) 43;275-283	1	4	3	8	-	1, 2	6	-	-
methotrexate	873999 874222	X	1	Biological & Pharmaceutical Bulletin (2014) 37;916-921	2	4	1	79	462	4	-	-	-
			2	The Japanese Journal of Therapeutic Drug Monitoring (2005) 22;220-227	2	3	1	12	-	1	1	-	-
			3	Japanese Journal of Clinical Pharmacology and Therapeutics (1990) 21;55-56	3	1	1	7	109	1	2	-	-
			4	The Japanese Journal of Therapeutic Drug Monitoring (1989) 6;27-29	2	5-1	1	13	142	1	2	-	-
indocyanine green	877224 877222 87729	-	1	Japanese Pharmacology & Therapeutics (1990) 18(Suppl.1);45-53	1	3	1	-	-	4	-	-	-
			2	Japanese Journal of Clinical Pharmacology and Therapeutics (1990) 38;906-910	3	1	1	143	-	4	-	-	-

TDM: therapeutic drug monitoring, PPK: population pharmacokinetics, -: not applicable

a) 1: No or insufficient reports/studies on PPK and PPK/PD, 2: It is necessary to search for suitable dosage, 3: Over/under estimation by the current model (including software), 4: Insufficient consideration of influence factors, 5: PK in the special population is not examined/insufficient, [-1: Pediatric, -2: Geriatric, -3: Hepatic/renal impairment, -4: Patient (including under special circumstances), -5: Japanese], 6: Others

b) 1: Development of a new PPK model in patients in clinical practice, 2: Identification of factors requiring dose adjustment, 3: Development of a modification of PPK model, 4: Others

c) 1: Patient, 2: Pediatric, 3: Geriatric, 4: Renal impairment, 5: Japanese, 6: First PK information, 7: Different covariates, 8: Different age groups, 9: Different diseases