Characteristics of Clinical Data Packages of Pediatric Medical Products Approved in the US and Comparison of the Approved Dosages between Pediatric and Adult Populations

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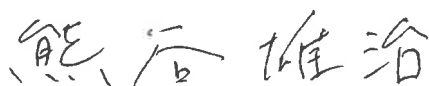
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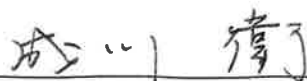School of Pharmacy
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Abstract

A medical product having both excellent efficacy and a high level of safety is required

for the treatment of pediatric patients.   However, implementation of clinical trials in

pediatric population is difficult due to the relatively small population of pediatric

patients, parents' hesitation to enroll their children in clinical trials, and also the

difficulty in building incentives for pharmaceutical industries due to insufficient returns

on investment.

In the US, Best Pharmaceuticals for Children Act (BPCA) in 2002 and Pediatric

Research Equity Act (PREA) in 2003 were established to accelerate the pediatric

medical product development.   In 2000, the International Conference on

Harmonisation of Technical Requirements for Registration of Pharmaceuticals for

Human Use (ICH) developed a guideline showing important considerations for the

pediatric medical product development, "Clinical Investigation of Medicinal Products

in the Pediatric Population" (ICH-E11).

At this time, no research on the trial design, sample size, number of trials and dosage

which are the aspects to be considered in the pediatric medical product development

plan, has been conducted.

The objective of the present research is to analyze information from labelling

(document describing information such as indication, dosage and administration,

cautions and clinical trial data) of pediatric medical products in the US to define the

characteristics useful for constructing an efficient development plan, including the

establishment of clinical data packages for new drug application of pediatric medical

products.

As a result of the analysis of pediatric medical products approved in the US from 1998

to 2013, clinical data packages submitted for pediatric approval varied widely depending on the targeted age and the therapeutic area. Adoption of blinding and types of comparators varied according to the age range of the pediatric subjects in the trials ($P<0.001$). A statistically significant difference in the sample size, the number of studies and the number of randomized controlled trials (RCT) were seen among the therapeutic areas ($P<0.001$).

Regarding the dose ratio between pediatric and adult populations, the approved dosages for pediatrics based on normalized body weight (BW) were higher than those of adults, but the ones based on body surface area (BSA) were almost the same as those of adults. The closer the age groups, the stronger the correlation of relative dosages between the groups.

The trial design, the sample size, the number of trials, the age range and the dose range to be used in pediatric drug development will affect the development cost and duration; therefore the result of this research would contribute to the more efficient and effective implementation of clinical development in pediatrics.

Table of Contents

List of tables

1

List of Figures

Abbreviations

ATC   Anatomical Therapeutic Chemical

        ATC Classification
        A: alimentary tract and metabolism
        B: blood and blood forming organs
        C: cardiovascular system
        H: systemic hormonal preparations
        J: anti-infectives for systemic use
        L: antineoplastic and immunomodulating agents
        M: musculoskeletal system
        N: nervous system
        R: respiratory system
        V: various

ARDCA   Anthropometric Reference Data for Children and Adults

BPCA   Best Pharmaceuticals for Children Act

BSA   body surface area

BW   body weight

CYP   Cytochrome P450

FDA   Food and Drug Administration

ICH   International Conference on Harmonization

IQR   interquartile range

PDF   Portable Document Format

PK   pharmacokinetic

PREA   Pediatric Research Equity Act

RCT   randomized controlled trials

1. Introduction

Superior medical products that are effective and safe are required for the treatment of disease within the pediatric population[1] and pediatric patients should be given medicines that have been appropriately evaluated.[2]   However, there are problems which are derived from the difficulty in building incentives for the pharmaceutical industry to conduct clinical trials among the pediatric population, i.e. insufficient returns on investment, parents' hesitation to enroll their children in clinical trials, and a relatively small pediatric patient populations compared with the adult populations.[3]

Several guidelines have been issued to encourage and facilitate pediatric medical product development.   Authorities in the US have introduced legislations such as the Best Pharmaceuticals for Children Act (2002, amended 2007)[4] and the Pediatric Research Equity Act (2003)[5] following the Food and Drug Administration Modernization Act (FDAMA; 1997)[6].   In Europe, the European Pediatric Rule (2008)[7] was introduced as well.   In Japan, authorities have not introduced legislations, but established a committee on pediatric pharmacotherapy to select drugs and indications to be developed for pediatric population.[8]   The ICH E11 guidance, Clinical Investigation of Medicinal Products in the Pediatric Population, which was published in 2000, provides an outline of critical issues in pediatric medical product development and approaches to safe, efficient, and ethical conduct of study of medical products in the pediatric population.[9]   The principles in study conduct, statistical considerations and choice of control groups detailed in ICH E6, E9, and E10 generally apply to pediatric studies.   There are, however, certain features unique to pediatric studies.   The ICH E11 guidance states that considerations should be given to the prevalence of the condition, the seriousness of the condition, the availability and suitability of alternative treatments for the condition and the age ranges to be treated

in the pediatric population.   But too much fine classification and examination is not always appropriate, because it might needlessly increase the number of patients to be studied.   Sometimes, it may be more appropriate to collect data over broad ranges and examine them generally.   The guidance also suggests that when a medical product is to be used in the pediatric population for the same indications as those approved in adults, extrapolation of adult efficacy data to the pediatric population may be appropriate if the disease process is similar in adults and pediatric patients, and the outcome of therapy is likely to be comparable.

Dunne et al. reviewed 370 pediatric studies submitted to the US Food and Drug Administration (FDA) between 1998 and 2008 in response to 159 written requests (166 products) issued under the Pediatric Exclusivity Provision and found that extrapolation of efficacy from the adult population occurred for 82.5% of the drug products (137 of 166).[10]   They showed extrapolating efficacy from adult to the pediatric population was useful to increase the number of approvals for pediatric use compared to the cases where there was no extrapolation.

However, the handling of several factors proposed in ICH E11 such as study design and the age of patients who participated in the trials has not been analyzed in detail so far. The purpose of the present study is to characterize key features of pediatric clinical development such as study size and design as well as potentially important factors for dosage selection for the pediatric population, by analyzing clinical data packages for newly approved pediatric products in the US, to determine a desirable way to evaluate efficacy and safety of pediatric products more efficiently.

2.   Part I: Characteristics of Clinical Data Packages of Pediatric Medical

Products Approved in the US

2.1. Part I: Introduction

The evaluation of efficacy and safety of medical products for pediatric use is difficult due to several circumstances related to conducting clinical trials in pediatric patients. The purpose of the Part I study was to analyze clinical data packages for newly approved pediatric products in the US, where various cases of pediatric drug approval have been accumulating backed by the government, to characterize key features of pediatric clinical development such as study size, study design, and adoption of extrapolation from the angles of therapeutic areas, administration route, and patient age, and others. Based on the analysis, we discuss a desirable way to evaluate efficacy and safety of pediatric products more efficiently.

2.2. Part I: Methods

2.2.1. Extraction of Key Data

All the labeling information listed in the FDA's website, New Pediatric Labeling Information Database, between February 1998 and May 2013 was used for this study.[11] In order to select appropriate labels from the database, drugs with the following criteria were excluded:

1.   Drugs for topical use (e.g. for ophthalmologic, dermatological, or otological diseases),

2.   Vaccines, diagnostic aid and combination preparations including combination packs,

3.   PDF or materials of labeling unavailable online.

In addition, labels which had the following characteristics were excluded:

1.   Only information on clinical studies (e.g. negative results, postmarketing) available,

2.   Indicated only for pediatric use (no indication for adults),

3.   For adolescents only or comparable restrictions,

4.   Recommended dosages unclear,

5.   Detailed information on clinical trials unavailable.

Then, key information for the research was obtained from the selected labeling including indications, summary of clinical data package, and study design.   Information for the pediatric patients younger than 6 months, such as preterm newborn infants and term newborn infants, was excluded because insufficient quantity of labeling information was available.   The detailed procedures are further described in the following section. The flowchart of labeling selection for the analysis is shown in Figure 2-1.

```
┌─────────────────┐   ┌──────────────────────────────────────────────────────────────┐
│ Labeling listed │   │ Excluding: 177                                               │
│ on FDA website  │   │ 1. Drugs for topical use (eg, for ophthalmologic, dermatological, or │
│ N=471           │   │    otological diseases)                                      │
└─────────────────┘   │ 2. Vaccines, diagnostic aid and combination preparations including │
         │            │    combination packs                                         │
┌─────────────────┐   │ 3. PDF or materials of labeling unavailable online           │
│ N=294           │   └──────────────────────────────────────────────────────────────┘
└─────────────────┘
         │            ┌──────────────────────────────────────────────────────────────┐
┌─────────────────┐   │ Excluding: 186                                               │
│ N=108           │   │ 1. Only information on clinical studies (eg, negative results, postmarketing) │
└─────────────────┘   │    available                                                 │
         │            │ 2. Indicated only for pediatric use (no indication for adults) │
         │            │ 3. For adolescents only or comparable restrictions           │
         │            │ 4. Recommended dosages unclear                               │
         │            └──────────────────────────────────────────────────────────────┘
         │            ┌──────────────────────────────────────────────────────────────┐
         │            │ Excluding: 7                                                 │
         │            │ Detailed information on clinical trials unavailable           │
         │            └──────────────────────────────────────────────────────────────┘
┌─────────────────┐
│ Labeling for analysis │
│ N=101           │
└─────────────────┘
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Figure 2-1
Flowchart of labeling selection for analysis.

2.2.2. Examination Based on Clinical Trial Unit

All the clinical trials except PK studies carried out for the pediatric approval were classified according to the study design in terms of randomization, blinding and types of comparator (placebo, active comparator, different dose and none).   For the classification of the comparator, for simplicity, when a placebo and an active comparator were used at the same time, it was categorized as "placebo", and when an active comparator and different doses of the test product were used, it was categorized as "active comparator". Information on the age range of pediatric subjects in each trial was extracted and classified into the following categories: under 2 years old, 2 years old – under 7 years old, 7 years old – under 12 years old, and 12 years old or older.   When the number of 12 years or older subjects is added together with adult subjects and is shown in the labeling,

the number of pediatric subjects except adults was used. Then the relationships between the age range of pediatric subjects and the study design were examined using Fisher's exact and Kruskal-Wallis tests where appropriate.

2.2.3. Examination Based on Indication Unit

We reviewed the labeling information of the selected products and listed each of their indications.   For each pediatric indication, information of the clinical data package was summarized in terms of trial size, design (implementation of randomized controlled trial (RCT) or not) and extrapolation. As for the trial size, number of clinical trials and total number of trial subjects for obtaining the pediatric approval were calculated.   In principle, PK studies were excluded from the number of clinical trials except in cases where it was approved solely on PK study data.   As for the study design, we classified it as "RCT" if more than one randomized clinical trial had been conducted to obtain the pediatric indication. Also, we classified the indication as "extrapolation" if there was a description in the labeling that adult or older pediatric patient efficacy data were extrapolated to younger pediatric populations.   Then such information was summarized by the therapeutic area (ATC classification: World Health Organization's Anatomic Therapeutic Classification system)[12], administration route, and age range for which the product was indicated (under 2 years old, 2 years old and older and 7 years old and older), and the relationships between them were examined using Fisher's exact and Kruskal-Wallis tests where appropriate.

Analyses were performed using Microsoft Excel 2010 and R (version 3.0.3)[13].   All statistical tests were 2-tailed and used a type I error rate of .01 to account for multiple comparisons across clinical trial unit and indication unit.

9

2.3. Part I: Results

Among the labeling of 471 products, we selected 101 product labeling that met the criteria described in the Methods. They consisted of 121 indications with 217 clinical trials. The number of approved indications and applied legislations between 1998 and 2013 was shown in Table 2-1.

Table 2-1 Selected Pediatric Indications Approved in the US between February 1998 and May 2013.

Year	Number of indications	Applied legislations*				
		BPCA	PREA	B&P	Rule	none
1999	4	1			3	
2000	5				5	
2001	2	1			1	
2002	3	2			1	
2003	1	1				
2004	13	8	2	3		
2005	15	8	5	2		
2006	6	1	1	4		
2007	4	2	2			
2008	17	1	7	9		
2009	8	2	2	4		
2010	11	3	6	1		1
2011	18	2	10	6		
2012	14		12	2		
Total	121	32	47	31	10	1

* BPCA, Best Pharmaceuticals for Children Act.; PREA, Paediatric Research Equity Act.; B&P, applied both BPCA and PREA; Rule, Pediatric Rule; none, no legislation applied

2.3.1. Examination Based on Clinical Trial Unit

Of the 217 clinical trials conducted for pediatric indication, 158 trials (72.8%) were randomized and 142 (65.4%) were blinded. As for the types of comparator, a placebo comparator was used in half of the trials. In the pediatric subjects under 2 years old,

neither blinding nor placebo comparators were used very frequently, whereas in the subjects of 7 years old and older, both were used in more than 70% of the trials. Adoption of blinding and types of comparators varied according to the age range of the pediatric subjects in the trials. (*P*<0.001) (Table 2-2)

Table 2-2 Relationship between the age range of pediatric subjects and the study design.

Age range of pediatric subjects	Randomized		Blind		Comparator							
					Placebo		Active		Different dose		None	
All (n=217)	158	(72.8) [66.4-78.6]	142	(65.4) [58.7-71.7]	108	(49.8) [42.9-56.6]	30	(13.8) [9.5-19.1]	45	(20.7) [15.5-26.7]	34	(15.7) [11.1-21.2]
<2years (n=72)	43	(59.7) [47.5-71.1]	35	(48.6) [36.7-60.7]	16	(22.2) [13.3-33.6]	18	(25.0) [15.5-36.6]	23	(31.9) [21.4-44.0]	15	(20.8) [12.2-32.0]
>=2years (n=116)	89	(76.7) [68.0-84.1]	81	(69.8) [60.6-78.0]	69	(59.5) [50.0-68.5]	10	(8.6) [4.2-15.3]	21	(18.1) [11.6-26.3]	16	(13.8) [8.1-21.4]
>=7years (n=11)	10	(90.9) [58.7-99.8]	10	(90.9) [58.7-99.8]	8	(72.7) [39.0-94.0]	2	(18.2) [2.3-51.8]	0		1	(9.1) [0.2-41.3]
>=12years (n=18)	16	(88.9) [65.3-98.6]	16	(88.9) [65.3-98.6]	15	(83.3) [58.6-96.4]	0		1	(5.6) [0.1-27.3]	2	(11.1) [1.4-34.7]
P value	0.013		<0.001		<0.001							

2.3.2. Examination Based on Indication Unit

Of the 121 indications, 5 were approved only with PK study data. Characteristics of clinical data package, i.e. number of clinical trials and total number of trial subjects, study design (implementation of RCT), and data extrapolation (presence or absence of extrapolation), were examined according to the ATC classifications. The number of clinical trials, total number of trial subjects, and study design varied depending on the ATC classifications. (*P*<0.001) More pediatric patients were enrolled in the clinical trials for M, N, R and J ATC classifications, but less for L and H classes. The median number of clinical trials per indication was distributed between 1 and 5. Only 1 clinical trial was conducted for almost all indications, but in A, M, N and R classes, two or more clinical trials were conducted.

RCT was adopted more frequently (nearly 90% of the indications) in B, C, H, N and R

classes, and less in L and M classes. ATC classifications with more than 8 indications were extracted and the median number of subjects and RCT adoption ratio by the ATC classifications were plotted in Figure 2-2. L class had a lower RCT adoption ratio and fewer subjects, whereas N and R classes had a higher RCT adoption ratio and a greater number of subjects.

Among the 121 indications, the approach of extrapolating efficacy data of adult or older pediatric population to the younger pediatric population was taken in 44 (36.4%) indications. Tendency of more extrapolation was shown in R, J and M classes, and less extrapolation in L and N classes, but no statistically significant difference was observed among the ATC classifications. As for the examination by the administration route and the indicated age range, no statistically significant difference was found except in the case between administration route and the number of trial subjects. (Table 2-3)

Table 2-3 Characteristics of the clinical data package for pediatric approval by ATC classification, administration route, and indicated age.

| Agent/Indication Characteristic	No.	Number of patients Median (IQR*)	Number of trials Median	Trial Design RCT		Extrapolation	
All indications	121	205 (101-471)		87	(71.9) [63.0-79.7]	44	(36.4) [27.8-45.6]
ATC classifications							
A: alimentary tract and metabolism	17	90 (49-249)	2	10	(58.8) [32.9-81.6]	6	(35.3) [14.2-61.7]
B: blood and blood forming organs	3	131 (66-143)	1	3	(100) [29.2-100]	1	(33.3) [0.8-90.6]
C: cardiovascular system	8	161 (111-297)	1	7	(87.5) [47.3-99.7]		0
H: systemic hormonal preparations	3	60 (29-149)	1	3	(100) [29.2-100]		0
J: anti-infectives for systemic use	40	279 (109-656)	1	26	(65.0) [48.3-79.4]	18	(45.0) [29.3-61.5]
L: antineoplastic and immunomodulating agents	8	48 (20-104)	1	2	(25.0) [3.2-65.1]	1	(12.5) [0.3-52.7]
M: musculoskeletal system	2	621 (401-840)	5	1	(50.0) [1.3-98.7]	1	(50.0) [1.3-98.7]
N: nervous system	17	392 (164-682)	2	15	(88.2) [63.6-98.5]	4	(23.5) [6.8-49.9]
R: respiratory system	21	316 (211-1722)	2	20	(95.2) [76.2-99.9]	12	(57.1) [34.0-78.2]
V: various	2	71 (11-130)	1	0		1	(50.0) [1.3-98.7]
P value		<0.001	<0.001	<0.001		0.052	
Administration Route							
Oral	78	236 (105-499)	1	56	(71.8) [60.5-81.4]	27	(34.6) [24.2-46.2]
Injection	30	113.5 (50.0-326.0)	1	18	(60.0) [40.6-77.3]	13	(43.3) [25.5-62.6]
Inhalation	11	316 (187-630)	1	11	(100) [71.5-100]	4	(36.4) [10.9-69.2]
Nasal	2	2008 (1874-2142)	4	2	(100) [15.8-100]		0
P value		0.004	0.138	0.048		0.681	
Indicated age							
<2years	54	222 (85-499)	2	36	(66.7) [52.5-78.9]	24	(44.4) [30.9-58.6]
>=2years	63	199 (107-448)	1	47	(74.6) [62.1-84.7]	19	(30.2) [19.2-43.0]
>=7years	4	238.5 (108.5-627.5)	1	4	(100) [39.8-100]	1	(25.0) [0.6-80.6]
P value		0.998	0.611	0.340		0.225	
IQR: interquartile range							
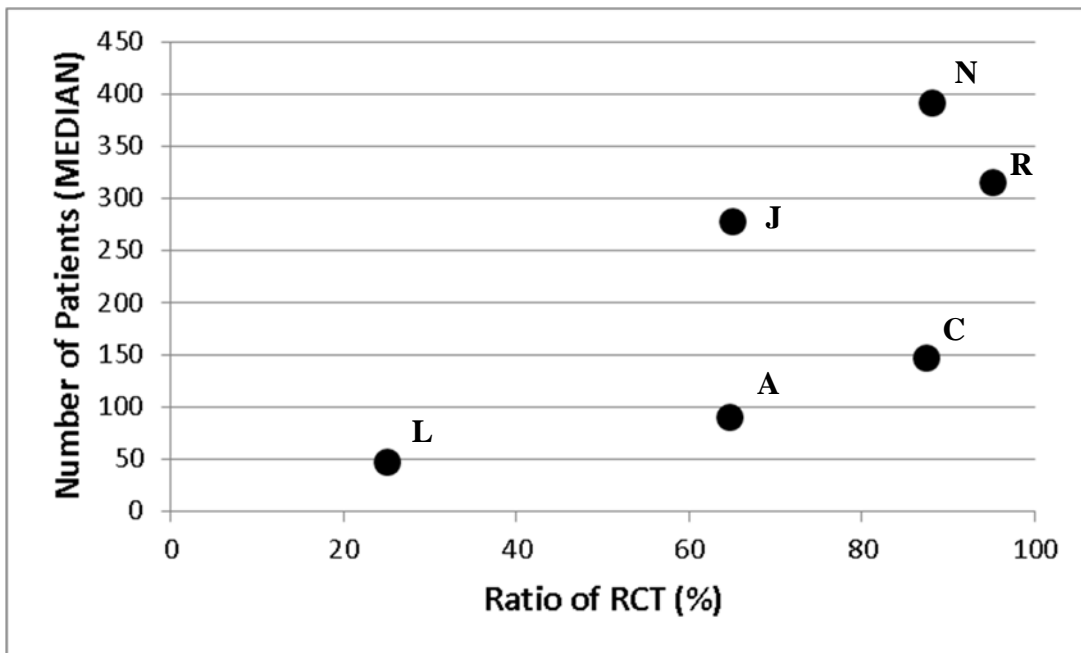
Figure 2-2　Relationship between the number of trial subjects and ratio of RCT adoption by ATC classification.
A: alimentary tract and metabolism, C: cardiovascular system, J: anti-infective for systemic use, L: antineoplastic, N: nervous system, R: respiratory system

2.4. Part I: Discussion

As a result of the analysis of the approved pediatric medical products from 1998 through 2013 in the US, it was shown that there was wide variability in the request level for the clinical data package such as total number of trial subjects, number of clinical trials, and adoption of RCT by the ATC classifications and drug administration route to obtain pediatric approval.　Examination based on clinical trial unit shows that adoption of blinding and the types of comparators varied according to the age range of the pediatric subjects in the trials.　More specifically, less blinding and placebo comparators were observed with younger pediatric subjects, whereas in older subjects an increased usage of blinding and placebo was seen.　It was thought that this phenomenon was conspicuously influenced by the pediatric clinical trial characteristics such as the difficulty of obtaining

parental consent to enroll their children in clinical trials, the small pediatric patient population and the concern for the risk of unconfirmed side effects for young pediatric patients.

In the examination based on indication unit, total number of trial subjects, number of clinical trials and ratio of RCT adoption were different according to the ATC classifications with statistical significance. Particularly, both the total number of subjects and the ratio of RCT adoption of L class were lower than those of others. Medical products in L class are used for the purpose of the treatment of serious and/or life-threatening diseases for which no or limited treatment options are available. When a medical product will be used to treat rare and severe diseases with great medical needs, it may be approved with a special clinical data package. This might account for the differences in the number of clinical trials and number of subjects. On the other hand, products in N and R classes have a large number of subjects and high ratio of RCT adoption. Clinical efficacy of products in N class is often difficult to show, and many clinical trials have failed to verify the efficacy. For some products in R class, adverse effects on bone growth are a concern in young pediatric patients. In these therapeutic areas, reaction to medical products may vary depending on the development stage of the children and it is supposed that more clinical trial data in pediatric patients was required to prove the efficacy and safety.

As for the extrapolation of efficacy data of adult or older pediatric population to the younger pediatric population, it was unexpected that a significant difference was not seen by the ATC classifications and patient age, but we found some interesting characteristics in the results. When the extrapolation ratio calculated by dividing the number of extrapolation by the total number of indications was compared by the ATC classification,

the ratios of L and N classes were lower than those in others.   It is thought that extrapolation was difficult in L and N classes because there were many cases in which the treatment results were not the same in adults and pediatric patients due to different disease progression.   In addition, when the extrapolation ratio was compared among different pediatric ages, the ratio in younger pediatric patients was higher than that in older patients.   This may show the difficulty in conducting clinical trials in younger pediatric patients compared to in the older pediatric patients.

A statistically significant difference was seen between the route of drug administration and the number of trial subjects.   However, more cases would be necessary to generalize the results of the relationship between the route of drug administration and other factors. The database used in the present study was established based on the US labeling information and does not necessarily reflect all the information submitted to the FDA with the application.   However, the labeling includes reliable safety and efficacy information evaluated by the FDA, and the result of the present study is considered to show a characteristic tendency of clinical data package of pediatric medical products.

Clinical data package of medical products for which pediatric indication was approved by the FDA showed a tendency specific to the age range of pediatric subjects and the therapeutic area in terms of the number of clinical trials and number of subjects, and study design.   The result of the present study would provide useful information in planning future pediatric development.

2.5. Brief Summary

A tendency specific to the age range of pediatric subjects and the therapeutic area was

seen in the clinical data package for pediatric indication approved in the US from 1998 to 2013.　　This should be taken into consideration to implement pediatric medical product development more efficiently and effectively.

3. Part II: Comparison of Approved Dosages for Pediatric and Adult Populations Based on US Labeling Information

3.1. Part II: Introduction

Efforts to establish the appropriate dosages in pediatric medicines have been made for a long time.   The passing of legislation to promote pediatric drug development in the US and EU has led to a number of approval of dosages for pediatric use.   Factors influencing pediatric dosages and limitations of the existing methods for dosage scaling should be clarified to mitigate the risk of pediatric drug treatments as well as to make appropriate development plans for pediatrics.   Finding potentially important factors for dosage selection for the pediatric population was the primary goal of this Part II study.

3.2. Part II: Methods

3.2.1. Extraction of Key Data

The labeling information listed in the FDA's webpage, New Pediatric Labeling Information Database, between February 1998 and May 2013[11], was used for this study. In order to select appropriate labels from the database, drugs with the following criteria were excluded:

1.   Drugs for topical use (e.g. for ophthalmologic, dermatological, or otological diseases),

2.   Vaccines, diagnostic aid and combination preparations including combination packs,

3.   PDF or materials of labeling unavailable online.

In addition, labels that had the following characteristics were excluded:

1.   Only information on clinical studies (e.g. negative results, postmarketing)

available,

2.   Indicated only for pediatric use (no indication for adults)

3.   For adolescents only or comparable restrictions,

4.   Recommended dosages unclear.

We then obtained key information for the research, such as dosage for pediatric and adult patients, indications, pharmacokinetic parameters, therapeutic categories, formulation, administration routes, and approval date.   The dosages for the pediatric patients younger than 6 months, such as preterm newborn infants and term newborn infants, were excluded because there was insufficient labeling information available. Additionally, we decided to remove labeling that was limited to adolescents, or comparable restrictions.   If there were ranges in dosages in labeling, the higher dosages were selected.   When different dosages were used between the start and the maintenance phase, the highest dosage for maintenance was chosen.   Labeling for 108 drugs for pediatric patients 6 months and older were extracted for analysis.

3.2.2.   Mutual Conversion into Dosage Expressed by Age, BW, and BSA

In the labeling, dosages for the pediatric population are expressed either in terms of age, BW, or BSA.   Using the data on age, BW, and body height (length) from Anthropometric Reference Data for Children and Adults (ARDCA; FDA CDC; 2007-2010),[14] the dosages in the individual labels were standardized to be comparable among groups.   The basal level for weight and height were derived from the 50th percentile population values from ARDCA.   The BSA was calculated from height and weight according to equations proposed by Mosteller.[15]   The ratio of pediatric-to-adult dosage was used to analyze differences across age groups, ATC classification groups, and drug

clearance groups.

3.2.3. Comparison across Age Groups

The dosages for different age groups were calculated and converted into dosages expressed by age, normalized BW, and normalized BSA. Dosage ratios at several ages - 6 months, 2 years, 6 years, 11 years, and 16 years - were calculated as the ratio of pediatric patients at each stage to adult dosage as expressed by age, BW, and BSA. There are recommended categories for drug treatments, as shown in the age classification of pediatric patients of the ICH-E11.[9] They are defined by age bands, for example, preterm newborn infants, term newborn infants (0-27 days), infants and toddlers (28 days-23 months), children (2-11 years), and adolescents (12 to 16-18 years [depending on the region]). In order to make a database to compare age groups, representative values of each category need to be created. However, appropriate representative values cannot be calculated using wide age bands owing to developmental issues (e.g. physical, cognitive, and psychosocial) across age categories.

3.2.4. Comparison across ATC Groups

Drugs in the database were categorized according to the ATC classification system controlled by the Collaborating Centre for Drug Statistics Methodology, World Health Organization.[12] Although the dosage ratios for analysis were calculated at several age stages for each ATC classification category in terms of BW and BSA, attention was focused on ratio of pediatric-to-adult dosage at 6 months and 2 years of age, where pediatric metabolism may move into different phases.[16]

3.2.5. Categorization of Clearance Group Based on Pharmacologic Findings

The information on drug clearance of the products was collected from the labeling by applying the method of Rodriguez et al[2] , which was conducive to handling of various descriptions of drug clearance in the labeling.   The observations of drug clearance (or apparent oral clearance) were grouped into the following 3 categories: I = lower drug clearance (or apparent oral clearance) in younger patients, II = drug clearance (or apparent oral clearance) increases with the increasing body weight (up to adult values), and III = higher apparent oral clearance (or higher drug clearance) in younger patients. Then, each group was compared by dosage ratio to adults normalized by BW and BSA.

3.3. Part II: Results

3.3.1. Characteristics of Labeling Information for Pediatric Patients

The flowchart of labeling selection for analysis is shown in Figure 3-1.   Figure 3-2 shows the indication methods of the dosage information in the labels.   Dosage information indicated by BW accounted for over 70% of the labeling.   Cases in which dosages were indicated by a mix of age and BW or BSA were categorized as either BW or BSA.   Table 3-1 shows the results, with cumulative percentages for each age group, up to the 11-year age group, in parentheses.
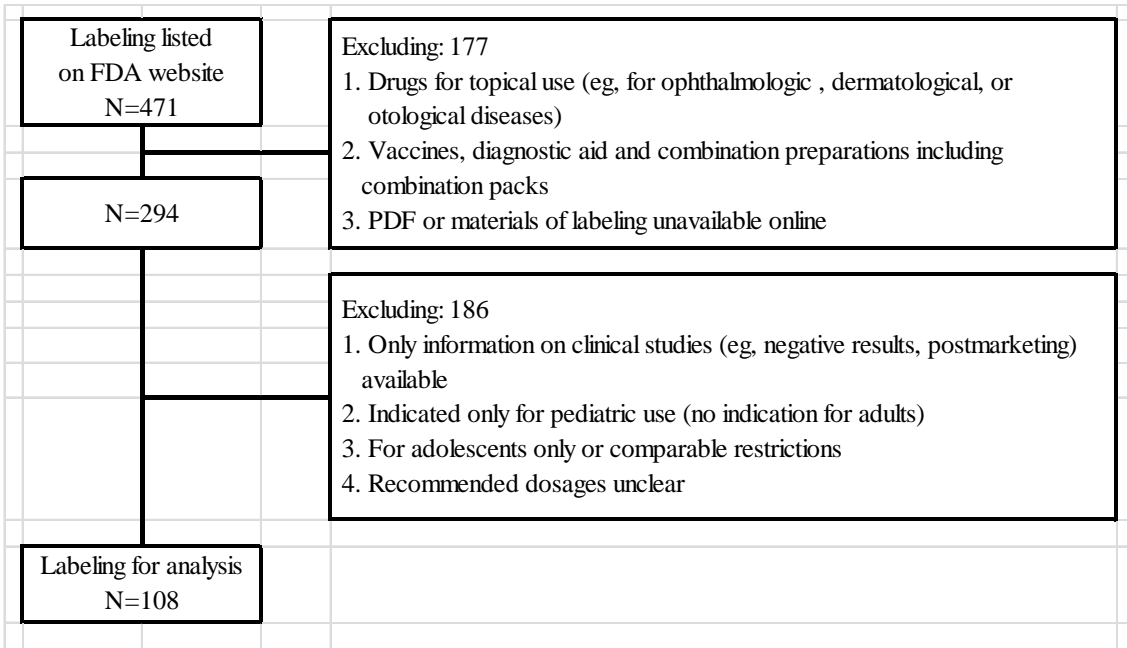
Figure 3-1
Flowchart of labeling selection for analysis.

Labeling listed on FDA website N=471

Excluding: 177
1. Drugs for topical use (eg, for ophthalmologic , dermatological, or otological diseases)
2. Vaccines, diagnostic aid and combination preparations including combination packs
3. PDF or materials of labeling unavailable online

N=294

Excluding: 186
1. Only information on clinical studies (eg, negative results, postmarketing) available
2. Indicated only for pediatric use (no indication for adults)
3. For adolescents only or comparable restrictions
4. Recommended dosages unclear
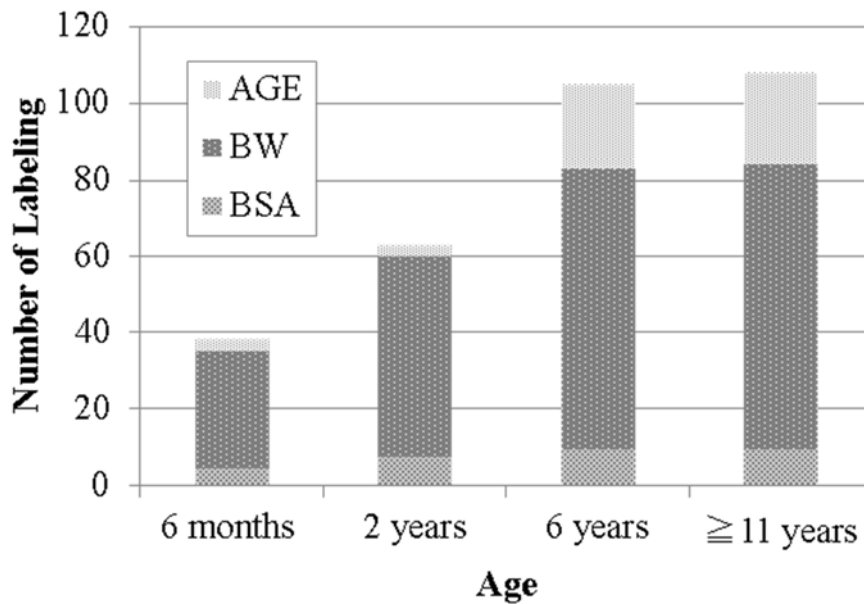
Labeling for analysis N=108

Figure 3-2 Indication methods of dosage information in the labeling.
AGE, dosage expressed by age; BSA, Dosage expressed by body surface area; BW, dosage expressed by body weight.

Table 3-1   Anatomical Therapeutic Chemical (ATC) Classification System of Database Across Ages.

ATC Classification	Age Group, n (%)[a]							
	6months		2years		6years		>11years	
A: alimentary tract and metabolism	6	(40)	11	(73)	14	(93)	15	(100)
B: blood and blood forming organs	2	(50)	3	(75)	4	(100)	4	(100)
C: cardiovascular system	1	(13)	2	(25)	8	(100)	8	(100)
H: systemic hormonal preparations	6	(75)	6	(75)	8	(100)	8	(100)
J: anti-infectives for systemic use	15	(46)	25	(76)	32	(97)	33	(100)
L: antineoplastic and immunomodulating agents	1	(13)	4	(50)	8	(100)	8	(100)
M: musculoskeletal system	1	(50)	2	(100)	2	(100)	2	(100)
N: nervous system	2	(14)	5	(36)	14	(100)	14	(100)
R: respiratory system	3	(21)	3	(21)	13	(93)	14	(100)
V: various	1	(50)	2	(100)	2	(100)	2	(100)
Total	38	(35)	63	(58)	105	(97)	108	(100)

[a]Cumulative percentage of each age group to 11-year of age group.

3.3.2.   Comparison across Age Groups

Figure 3-3 shows box plots illustrating ratio of pediatric-to-adult dosage by age group in terms of age, BW, and BSA.   The dosage ratios to adults were as follows: in terms of age, they ranged from 0.21 at 6 months to 0.94 at 16 years; in terms of BW, they ranged from 2.15 at 6 months to 1.19 at 16 years; and in terms of BSA, they ranged from 1.09 at 6 months to 1.10 at 16 years.   Although the dosages of pediatric patients based on BW were higher than those of adults, the ones based on BSA were almost the same as those of adults.   The ratios of pediatric-to-adult dosages at age 6 months were compared to those at ages 2, 6, and 11 years, and all individual data on dosage ratios in the database were plotted in a scatter diagram based on BW and BSA.
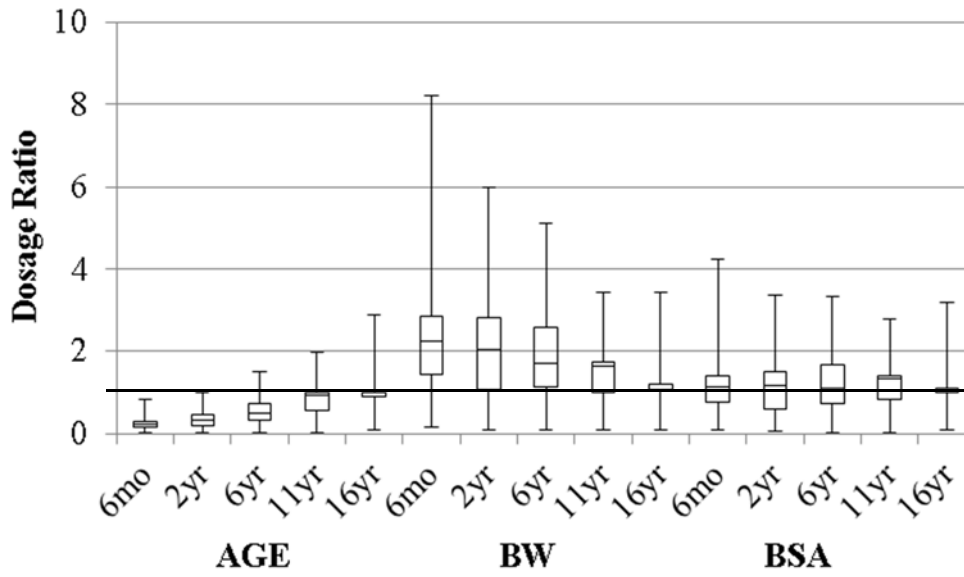
Figure 3-3 Ratio of pediatric-to-adult dosage by age.
AGE, dosage expressed by age; BSA, dosage expressed by body
surface area; BW, dosage expressed by body weight; 6mo, 6 months
of age; 2yr, 2 years of age; 6yr, 6 years of age; 11ys, 11 years of age;
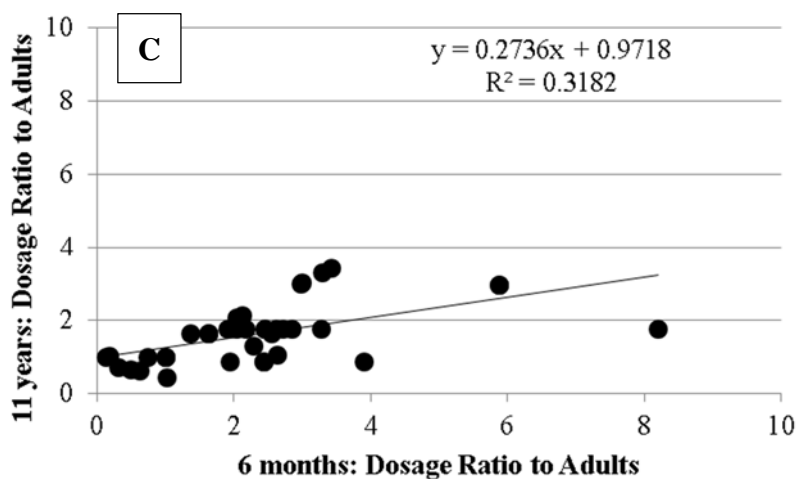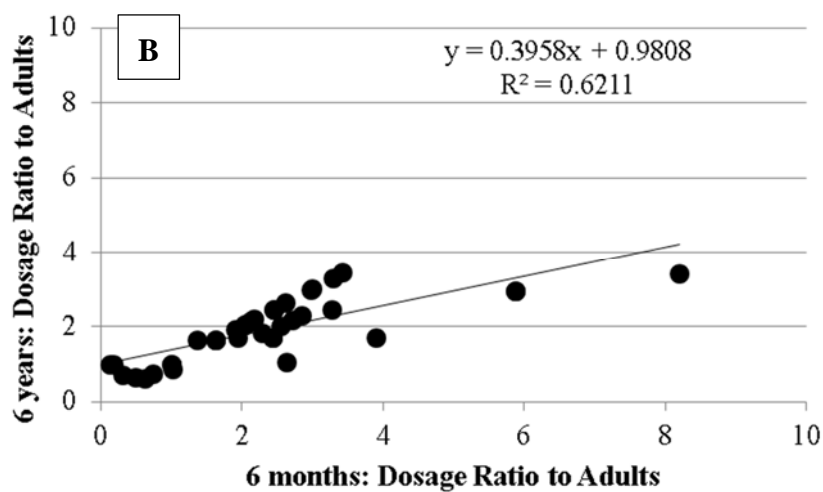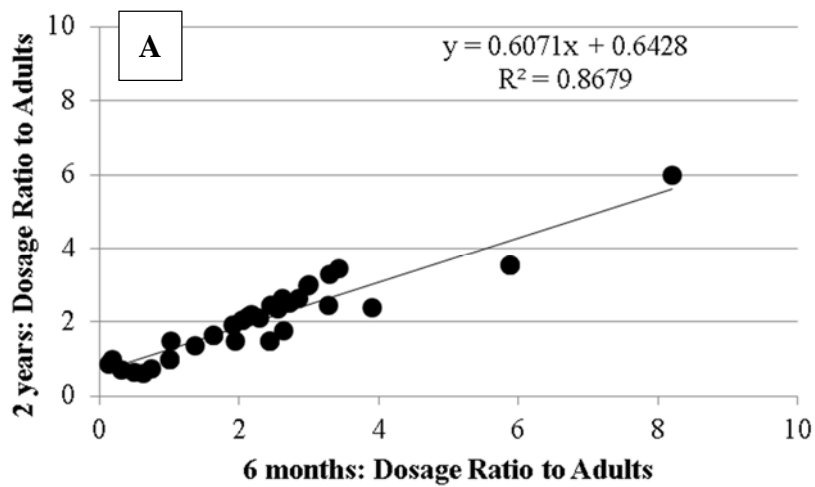16yr, 16 years of age.

Figure 3-4 Relationship of dosage expressed by body weight for patients between (A) 6 months and 2 years of age, (B) 6 months and 6 years of age, and (C) 6 months and 11 years of age.
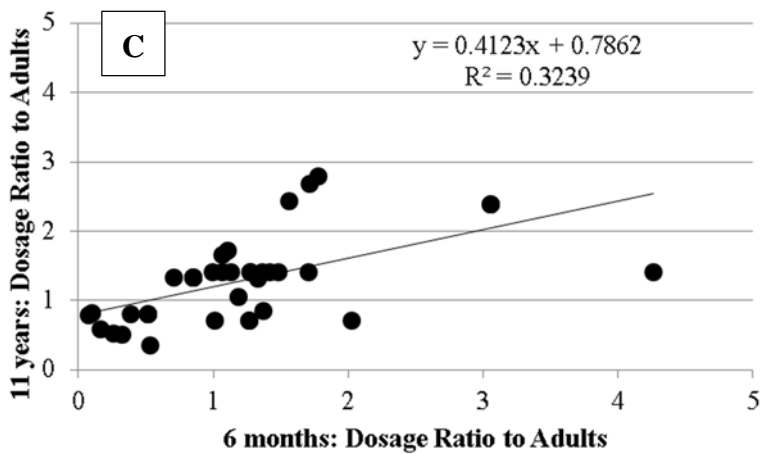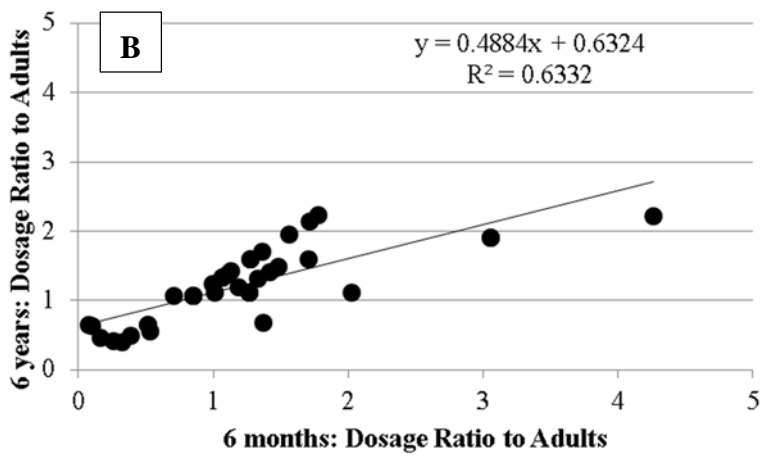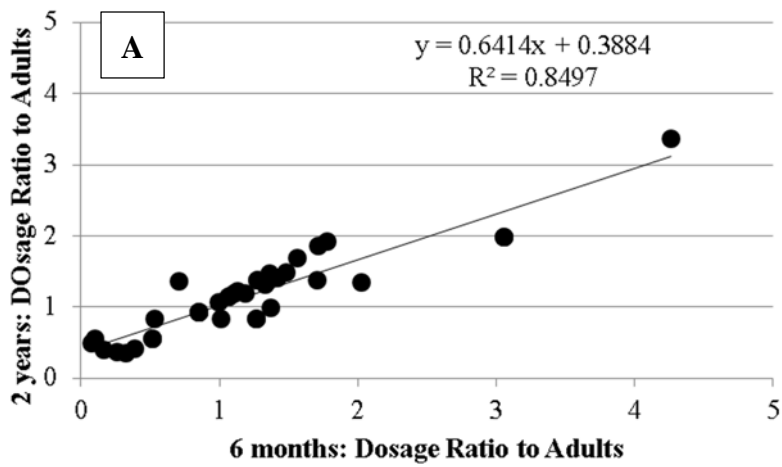
Figure 3-5 Relationship of dosage expressed by body surface area
between (A) 6 months and 2 years of age, (B) 6 months and 6 years of
age, and (C) 6 months and 11 years of age.

The relationships of dosages between age groups were analyzed in terms of coefficient of correlation values.　The results are shown in Figure 3-4 and Figure 3-5.　Relative dosages at 6 months of age showed a stronger correlation with those at age 2 years compared to those at 6 or 11 years of age.　In addition, no significant differences of correlation at corresponding age groups between BW base and BSA base were observed.

3.3.3.　Comparison across ATC Groups

The results comparing dosage ratios based on BW and BSA at 6 months and 2 years of age are shown as box plots in Figure 3-6 and Figure 3-7.　At both ages, the dosage ratios for the H, J, and L ATC classifications were higher than 1; on the contrary, those for ATC classes B and C were below 1.　When the dosage ratios at age 6 months were compared to those at age 2 years, the dosage ratios for the L and R classes at 6 months were higher than those at 2 years, and the dosage ratios for the B, C, M, and N classes at 6 months were lower than those at 2 years.

Figure 3-6 Ratio of pediatric (6 months) to adult dosage based on (A) BW by ATC and (B) BSA by ATC. ATC, Anatomical Therapeutic Chemical classification groups; BSA, dosage expressed by body surface Area; BW, dosage expressed by body weight.
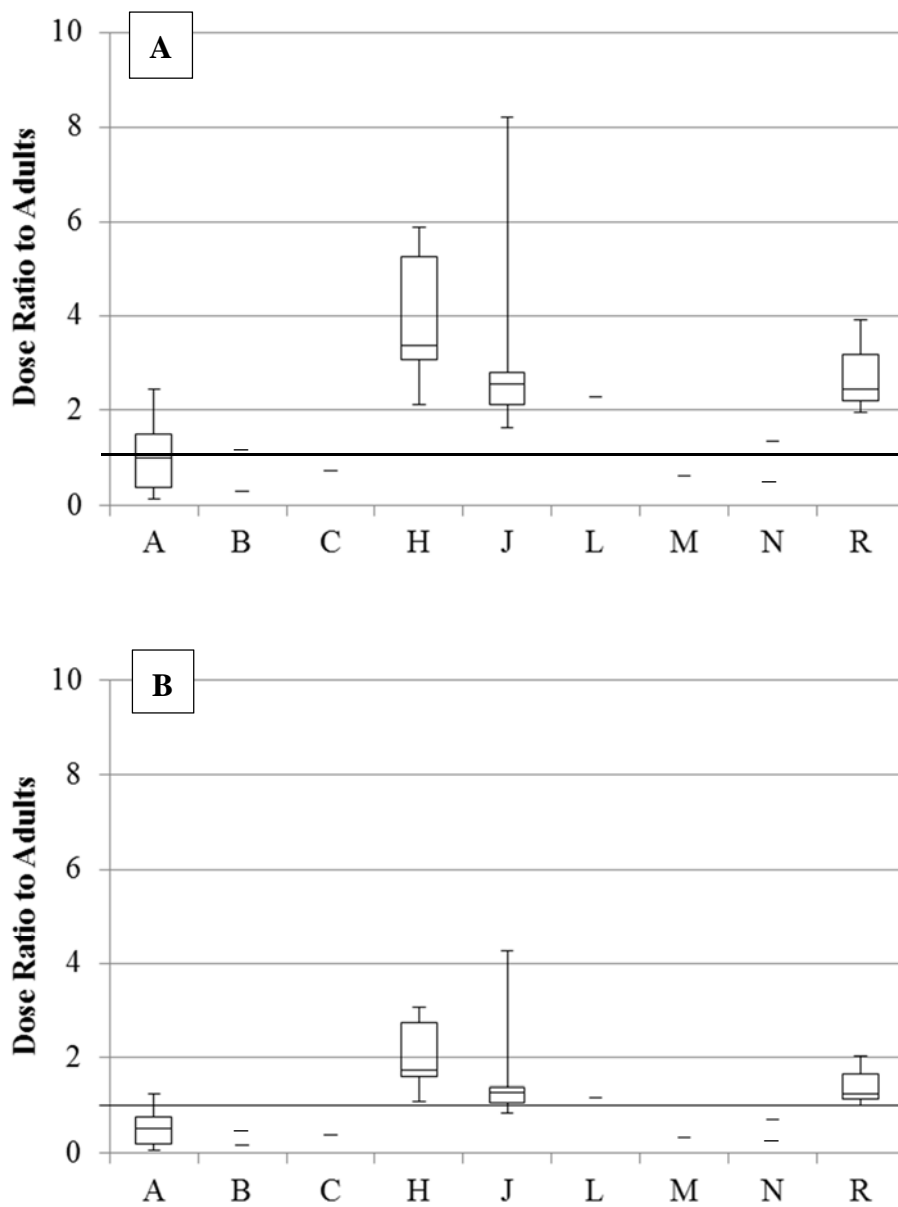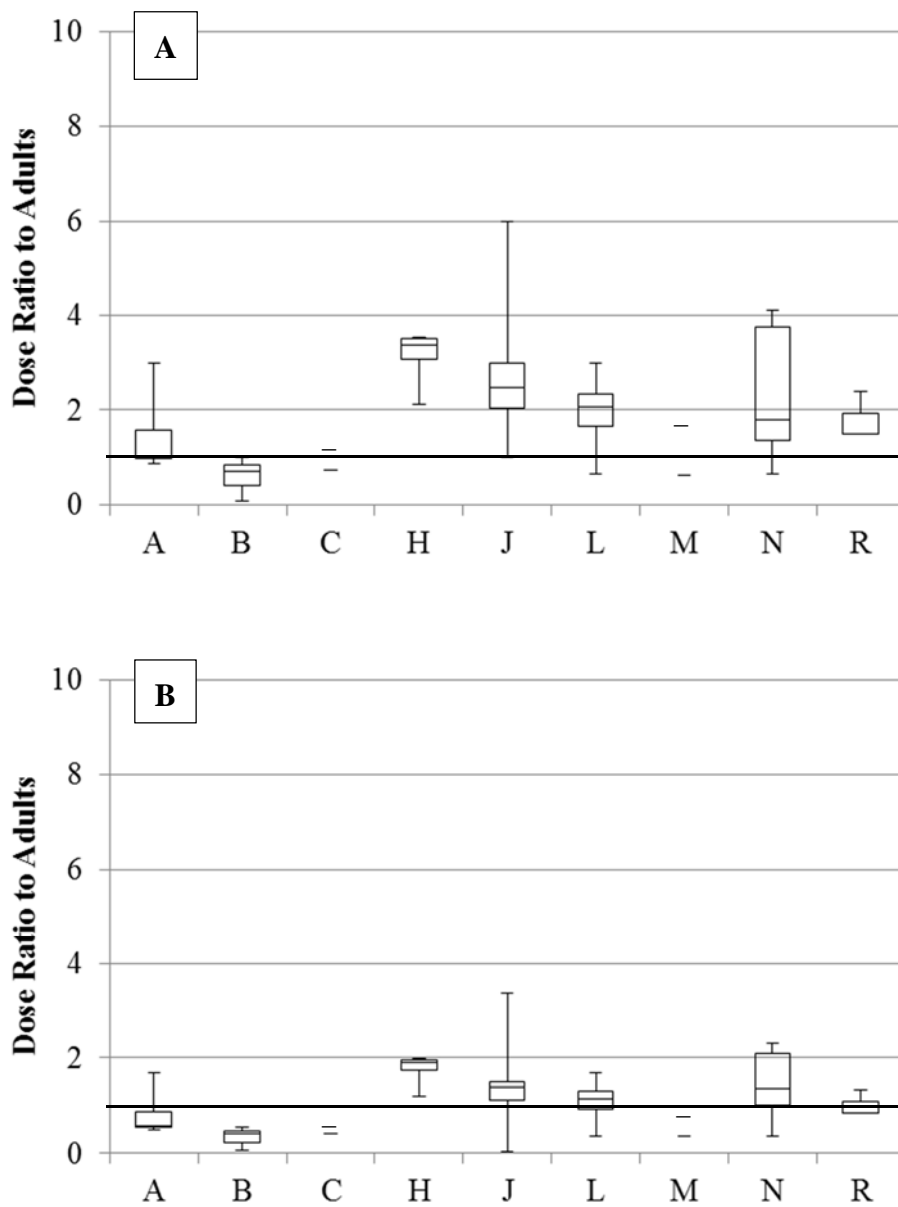
Figure 3-7 Ratio of pediatric (2 years) to adult dosage based on BW by ATC and (B) BSA by ATC. ATC, Anatomical Therapeutic Chemical classification groups; BSA, dosage expressed by body Surface Area; BW, dosage expressed by body weight.

3.3.4. Comparison across Clearance Groups

Figure 3-8 shows the ratio of pediatric-to-adult dosage by BW and BSA in terms of drug clearance category seen in patients 6 months to 16 years of age. The data in category III indicate that some young patients in the groups had larger dosage ratios by BW and BSA than did adults. On the contrary, the dosage ratios of some young patients in categories I and II were smaller than those of adults based on BW and BSA. However, in each category, some young patients showed opposite results in dosage ratio. The data in categories I, II, and III stratified by ATC classification are shown in Table 3-2. Data were distributed widely across classifications, but category III labeling was frequently seen in the J and N classes.
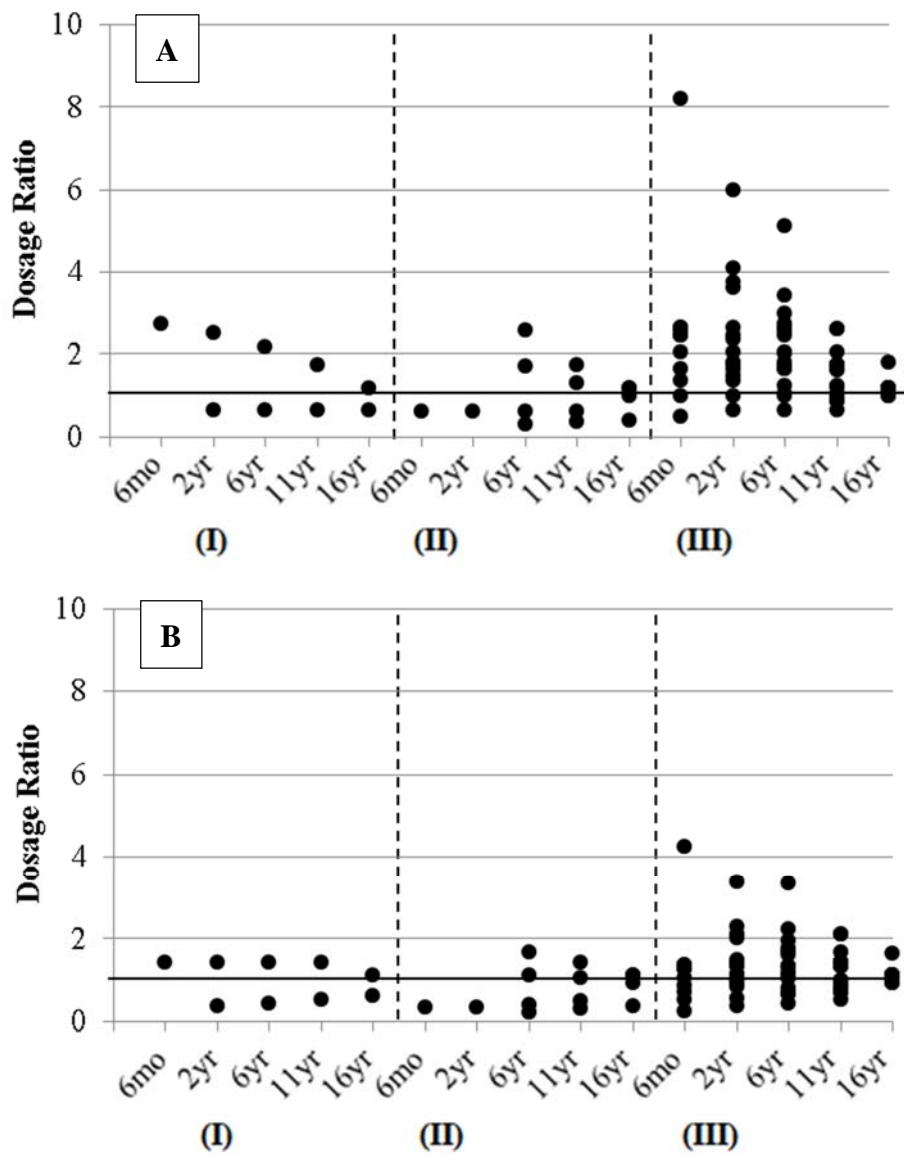
Figure 3-8 Ratio of pediatric to adult dosage based on (A) BW by drug clearance group and (B) BSA by drug clearance group. BSA, dosage expressed by body surface area; BWS, dosage expressed by body weight; I, lower drug clearance in younger patients; II, drug clearance increases with increasing body weight; III, higher apparent oral clearance in younger patients.

Table 3-2   Drug Clearance Category Information by Anatomical Therapeutic Chemical (ATC) Classification.

ATC Classification	Drug clearance Category[a]		
	I	II	III
A: alimentary tract and metabolism		1	2
B: blood and blood forming organs			
C: cardiovascular system		1	1
H: systemic hormonal preparations			
J: anti-infectives for systemic use	1		7
L: antineoplastic and immunomodulating agents	1		
M: musculoskeletal system		1	
N: nervous system		1	6
R: respiratory system			2
V: various			
Total	2	4	18

[a]Category I, lower drug clearance in younger patients;

Category II, drug clearance increases with increasing body weight;

Category III, higher apparent oral clearance in younger patients.

Drug clearance group: Trade name (generic name) of products; ATC

(I)   Cancidas (caspofungin); J, Faslodex (fulvestrant); L

(II)   Concerta (methylphenidate); N, Protonix (pantoprazole); A, Toprol (metoprolol); C, Zemuron (rocuronium); M

(III)   Accolate (zafirlukast); R, Adderall (amphetamine mixed salts); N, Epivir (lamivudine); J, Invanz (ertapenem); J, Keppra (levetiracetam); N, Lamictal (lamotrigine); N, Levaquin (levofloxacin); J, Lexiva (fosamprenavir); J, Lotensin (benazepril); C, Norvir (ritonavir); J, TamiFlu (oseltamivir); J, Topamax (topiramate); N, Trileptal (oxcarbazepine); N, Ultiva (remifentanil); N, Xyzal (levocetirizine dihydrochloride); R, Zantac (ranitidine); A, Zofran   (ondansetron); A, Zyvox (linezolid); J

3.4. Part II: Discussion

In this study, dosage information in the pediatric population was investigated based on the FDA's New Pediatric Labeling Information Database.   In previous studies related to dosage scaling in pediatric subjects, some studies used pharmacokinetic and

clearance data derived from the literature, and some used mixed data from both unlicensed drugs and licensed drugs.[16,17]   There are few studies on dosage selection that refer solely to approved drugs in pediatric patients.[2,10,17]   All of the information in the present study was derived from the pediatric drug labels that were evaluated and approved by FDA in terms of efficacy and safety.   Therefore, the approved dosages in pediatric patients can be assumed to be more appropriate to compare to dosage selection in adults.   There is a possibility that dosages for the pediatric clinical trials were set based on conventional methods such as BSA referring to adult dosages, which may have resulted in a good correlation between pediatric and adult dosages.   However, we emphasize the fact that those pediatric dosages have been approved and widely used in clinical practice.

In the present study, 108 labels of pediatric drugs for patients 6 months and older were extracted for analysis.   Although the topic of dosages for preterm newborn infants and term newborn infants is attracting attention for pediatric drug treatments, information pertaining to those groups for the purpose of analysis is very limited at the moment. After standardizing the individual dosages based on age, BW, and BSA, the ratios of pediatric-to-adult dosage were calculated and compared across ages, ATC classification, and drug clearance groups.   From the results of the differences in ratios of pediatric-to-adult dosage based on BW, it was found that the dosage ratios to adults were between 1.19 and 2.15.   This means that approved dosages for pediatric patients increased more than those of adults in general.   Bartelink et al[18] reported that for many drugs, body weight–normalized drug clearance in children exceeds that of an adult and suggested an increase of the dosage based on body weight for most drugs.   The results of the present study strongly support the suggestion.   On the other hand, the dosage

ratios to adults based on BSA were between 1.09 and 1.10, almost the same as those of adults in this study.　It was reported that although scaling methods based on BSA can be considered to overpredict clearance in neonates and infants after 6 months of age, BSA is a good marker as a basis of drug dosing[18,19]; our results are consistent with those findings.

The relationship of dosages at 6 months to those at other ages was analyzed using ratios of pediatric-to-adult dosages.　Relative dosages at 6 months of age showed a stronger correlation with those at age 2 years compared to those at age 6 or 11 years.　It may be due to metabolism and renal function, because it was known that the half-life of drugs in young pediatric patients, 6 months to 2 years of age, becomes significantly short compared to adults for renally cleared substrate, Cytochrome P450 (CYPs) substrates, and glucuronidation substrates.[16]　　Reasons for the differences in correlation tendencies among those age groups remain largely speculative, but some specific factors may affect a variety of relationships at 6 months of age group with other age groups in terms of dosage ratios to those of adults.　　The present study suggests that when dosage is selected in young pediatric patients, it is important to take into consideration the fact that the closer the age groups, the stronger the correlation of relative dosages between the groups.

The dosage ratios across ATC classification were extremely varied.　　At both 6 months and 2 years of age based on BW and BSA, labels for drugs in the H, J, and L groups had ratios higher than 1, and dosage ratios in the B and C groups were below 1. In order to interpret the evidence, information on drug clearance by ATC group is shown in Table 3-2.　　In the H and B groups, there was neither high nor low clearance labeling.　　In J and L groups, there was some high clearance labeling, but not all.　　In

the C group, there was 1 category II and 1 category III labeling, but the remaining 6 labels were standard or not characterized.   Therefore, this observed variety cannot be explained by clearance.   It was thought that the variety might be derived from the characteristics of the compound such as hydrophilicity/lipophilicity and/or the change of volume of distribution in the development process in children.   There still remain unclear factors that may influence dosage selection.   Future research should attempt to clarify such factors on dosage selection and to reflect them on optimization of pediatric drug dosing.

3.5.   Part II: Brief Summary

In this study, comparison of the dosage of approved pediatric drugs from 6 months to 16 years of age with those of adult drugs was performed by referring to labeling listed in the FDA's New Pediatric Labeling Information Database and standardizing dosage based on BW and BSA.   The resulting comparison of ratios of pediatric-to-adult dosage in terms of BW and BSA are consistent with available evidence.   From the correlation analysis of the relationship of pediatric to adult dosages, the closer the age groups, the stronger the correlation of relative dosages between the groups.

4. Overall Discussion

The ICH E11 guidance states that, in proceeding with a pediatric development program for a medical product, considerations should be given to the prevalence of the condition, the seriousness of the condition, the availability and suitability of alternative treatments for the condition, and the age ranges to be treated in the pediatric population.

As a result of the analysis of the approved pediatric medical products from 1998 through 2013 in the US, the present study showed some important points to be considered for pediatric medicine development. There was wide variability in the request level for the clinical data package such as total number of trial subjects, number of clinical trials, and adoption of RCT by the ATC classifications and drug administration route to obtain pediatric approval. Examination based on clinical trial unit shows that adoption of blinding and the types of comparators varied according to the age range of the pediatric subjects in the trials. It was thought that this phenomenon was conspicuously influenced by the pediatric clinical trial characteristics such as the difficulty in obtaining parents' consent to enroll their children in clinical trials, the small pediatric patient population, and the concern for the risk of unconfirmed side effects for young pediatric patients. In the examination based on indication unit, total number of trial subjects, number of clinical trials and ratio of RCT adoption were different by the ATC classifications with statistical significance. In some therapeutic areas, reaction to medical products may change more significantly depending on the development stage of children and it is supposed that more clinical trial data in pediatric patients was required to prove the efficacy and safety.

Also, in this study, the relationship of dosages at 6 months to those at other older pediatric ages was analyzed using ratios of pediatric-to-adult dosages and it was

suggested that the closer the age groups, the stronger the correlation of relative dosages between the groups.　This should be taken into consideration when dosage is selected in younger pediatric patients and also when extrapolation of efficacy/safety data from adult or older pediatric patients to younger pediatric patients is attempted.

The database used in the present study was established based on the US labeling information and does not necessarily reflect all the information submitted to the FDA with the application.　However, the labeling includes reliable safety and efficacy information evaluated by the FDA, and the result of the present study showed a characteristic tendency of clinical data package of pediatric medical products.　The findings concerning trial design, sample size, number of trials, age range and dose range are important factors to be considered to implement efficient clinical studies in pediatric populations, because they will affect the development cost and duration.　The Japanese regulatory authorities encourage pharmaceutical companies to develop drugs and indications including pediatric use that have been approved for use in the Western countries but not yet in Japan.　There are many risk factors to be considered related to the development stage of children when clinical trials involving pediatric patients are being planned.　The result of the present study would provide practical and useful information in planning future pediatric development in Japan as well as in the US.

5.　Conclusions

A tendency specific to the age and the ATC classifications was seen in the clinical data package of pediatric medical products approved in the US from 1998 to 2013. Relationship of relative dosages at different pediatric ages showed a stronger correlation between the groups of closer ages.　These points should be considered to implement

pediatric medical product development more efficiently and effectively.

6. References

1. Munzenberger PJ, McKercher P. Pediatric dosing: the pharmacist dilemma. Contemp Pharm Pract. 1980;3(1):11-14.

2. Rodriguez W, Selen A, Avant D, et al. Improving pediatric dosing through pediatric initiatives: what we have learned. Pediatrics. 2008:121;530.

3. Caldwell PH, Murphy SB, Butow PN, Craig JC. Clinical trials in children. Lancet. 2004;364:803-11.

4. Best Pharmaceuticals for Children Act. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049876.htm. January 4, 2002. Accessed May 3, 2014.

5. The Paediatric Research Equity Act. http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM077853.pdf. 2003. Accessed June 22, 2014.

6. Guidance for Industry. Qualifying for pediatric exclusivity under section 505A of the Federal Food, Drug and Cosmetic Act. http://www.fda.gov/downloads/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDAMA/FullTextofFDAMAlaw/UCM089145.pdf. November 21, 1997. Accessed May 3, 2014.

7. Communication from the Commission: guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies. Official Journal of the European Union. 2008;c243/01-12.

8. Ministry of Health, Labour and Welfare, The committee on Pediatric Pharmacotherapy. http://www.mhlw.go.jp/stf/shingi/other-iyaku.html?tid=128694 Accessed May 10, 2015.

9. International Conference on Harmonisation; Guidance on E11 Clinical Investigation of Medicinal Products in the Pediatric Population; Availability. Department of health and human services. Food and Drug Administration. Published December 15, 2000. http://www.fda.gov/ohrms/dockets/98fr/121500a.htm. Accessed May 3, 2014.

10. Dunne J, Rodriguez WJ, Murphy MD, et al. Extrapolation of adult data and other data in pediatric drug-development programs. Pediatrics. 2011;128:e1242-e1249. doi:10.1542/peds.2010-3487.

11. U.S. Food and Drug Administration. New pediatric labeling information database. U.S. Food and Drug Administration. http://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=labelingdatabase&displayAll=true#.UNUrMgqbFbQ.email. Updated May 21, 2013. Accessed June 15, 2013.

12. ATC/DDD index 2014. WHO Collaborating Centre for Drug Statistics Methodology. http://www.whocc.no/atcddd/indexdatabase/. Updated December 19, 2013. Accessed January 14, 2014.

13. R Core Team (2014). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/ Accessed May 20, 2015.

14. Fryar CD, Gu Q, Ogden CL. Anthropometric reference data for children and adults: United States, 2007-2010. National Center for Health Statistics. Vital

Health Stat. Published October, 2012.
http://www.cdc.gov/nchs/data/series/sr_11/sr11_252.pdf. Accessed October 28, 2013.

15. Mosteller RD. Simplified calculation of body-surface area. N Engl J Med 1987 ; 317(17):1098.

16. Ginsberg G, Hattis H, Sonawane B, et al. Evaluation of child/adult pharmacokinetic differences from a database derived from the therapeutic drug literature. Toxicol Sci 2002;66(2):185-200.

17. Johnson TN. The problems in scaling adult drug doses to children. Arch Dis Child 2008;93:207-211. doi:10.1136/adc.2006.114835.

18. Bartelink HI, Rademaker CMA, Schobben AFAM. Guidelines on paediatric dosing on the basis of developmental physiology and pharmacokinetic considerations. Clin Pharmacokinet 2006;45(11):1077-1097.

19. Hawcutt DB, Smyth RL. One size does not fit all: getting drug doses right for children. Arch Dis Child 2008;93(3):190-191.

7. Appendix

Selected Labeling for Analysis. 1 of 3

Part 1	Part 2	Number of products	Number of indications	Trade name	Generic name	Approved year	ATC	Clearance category*
Part 1	Part 2							
101 products (121 indications) for Part 1	108 products for Part 2	1	1	Accolate Tablets	zafirlukast	1999	R	III
		2	2	Adderall XR	amphetamines mixed salts	2005	N	III
		3	3	Afinitor	everolimus	2010	L	
		4	4	Agenerase Capusles and Oral Solution	amprenavir	2001	J	
		5	5	Agrylin	anagrelide	2004	L	
		6	6	Allegra	fexofenadine	2006	R	
		7	7	Amaryl	glimepiride	2005	A	
		8	8	AmBisome Injection	amphotericin B	2000	J	
			9	AmBisome Injection	amphotericin B	2000	J	
		9	10	Aptivus	tipranavir	2008	J	
		10	11	Asmanex Twisthaler 110mcg inhalation powder	mometasone furoat	2008	R	
			12	Asmanex Twisthaler 110mcg inhalation powder	mometasone furoat	2008	R	
		11	13	Atacand	candesartan	2009	C	
		12	14	Benicar	olmesartan	2010	C	
		13	15	Cancidas	caspofungin	2008	J	I
			16	Cancidas	caspofungin	2008	J	
		14	17	CellCept	mycophenylate	2000	L	
		15	18	Cipro	ciprofloxacin	2004	J	
		16	19	Clarinex	desloratadine	2004	R	
		17	20	Colazal	balsalazide	2006	A	
		18	21	Concerta	methylphenidate	2004	N	II
		19	22	Corlopam	fenoldopam	2004	C	
		20	23	Cozaar	losartan	2004	C	
		21	24	Creon	pancrelipase	2011	A	
		22	25	Diovan	valsartan	2007	C	
		23	26	Emtriva	emtricitabine	2006	J	
		24	27	Epivir	lamivudine	2002	J	III
		25	28	Epivir-HBV	lamivudine	2001	J	
		26	29	Faslodex Injection	fulvestrant	2011	L	I
		27	30	Ferrlecit	sodium ferric gluconate complex	2004	B	
		28	31	Flovent Diskus Inhalation Powder	fluticasone	2000	R	
			32	Flovent Diskus Inhalation Powder	fluticasone	2000	R	
		29	33	Flovent HFA	fluticasone propionate	2008	R	
			34	Flovent HFA	fluticasone propionate	2008	R	
		30	35	Focalin XR	dexmethylphenidate	2009	N	
		31	36	Fuzeon	enfuvirtide	2006	J	
		32	37	Gadavist	gadobutrol	2011	V	
		33	38	GAMMAGARD LIQUID	immune gobulin infusion (human)	2011	J	
			39	GAMMAGARD LIQUID	immune gobulin infusion (human)	2011	J	
		34	40	Gleevec	imatinib mesylate	2006	L	
		35	41	Intelence	etravirine	2012	J	
		36	42	Invanz	ertapenem	2005	J	III
			43	Invanz	ertapenem	2005	J	
		37	44	Isentress	raltegravir	2011	J	
		38	45	Keppra	levetiracetam	2011	N	III
			46	Keppra	levetiracetam	2011	N	
		39	47	Kytril Injection	granisetron hydrochloride	2011	A	
		40	48	Lamictal	lamotrigine	2009	N	III
								cont.

Part 1 Part 2		Number of products	Number of indications	Trade name	Generic name	Approved year	ATC	Clearance category*
101 products (121 indications) for Part 1	108 products for Part 2	41	49	Levaquin	levofloxacin	2012	J	III
		42	50	Lexiva	fosamprenavir	2012	J	III
		43	51	Lotensin	benazepril	2004	C	III
		44	52	Maxalt and Maxalt-MLT	rizatriptan	2011	N	
		45	53	Merrem I.V.	meropenem	2005	J	
			54	Merrem I.V.	meropenem	2005	J	
		46	55	Myfortic Delayed-Release Tablets	mycophenolic acid	2004	L	
		47	56	Nexium	esomeprazole	2011	A	
		48	57	Nexium IV	esomeprazole	2011	A	
		49	58	Norvir	ritonavir	2005	J	III
		50	59	Ofirmev	acetaminophen	2010	M	
		51	60	Omnaris Nasal Spray	ciclesonide	2010	R	
		52	61	Omnicef	cefdinir	1999	J	
			62	Omnicef	cefdinir	1999	J	
		53	63	Oxtellar XR	oxcarbazepine	2012	N	
		54	64	Pancreaze	pancrelipase	2010	A	
		55	65	Patanase	olopatadine	2009	R	
		56	66	PEGASYS	peginterferon alfa-2a	2011	L	
		57	67	PegIntron	peginterferon alfa-2b	2008	L	
		58	68	Pertzye	pancrelipase	2012	A	
		59	69	Prevacid	lansoprazole	2008	A	
		60	70	Prezista	darunavir	2011	J	
		61	71	Prilosec	omeprazole	2008	A	
			72	Prilosec	omeprazole	2008	A	
		62	73	Prinivil	lisinopril	2003	C	
		63	74	Protonix	pantoprazole	2009	A	II
		64	75	Protopam	pralidoxime	2010	V	
		65	76	QUILLIVANT XR	methylphenidate hydrochloride	2012	N	
		66	77	Relenza	zanamivir	2006	J	
		67	78	Retrovir	zidovudine	2009	J	
		68	79	Reyataz	atazanavir	2011	J	
		69	80	Sandostatin and Sandostatin LAR	octreotide	2010	H	
		70	81	Serevent	salmeterol	2010	R	
		71	82	Singulair Oral Granules, Tablets	montelukast	2012	R	
			83	Singulair Oral Granules, Tablets	montelukast	2012	R	
			84	Singulair Oral Granules, Tablets	montelukast	2012	R	
			85	Singulair Oral Granules, Tablets	montelukast	2012	R	
		72	86	Strattera	atomoxetine	2002	N	
		73	87	TamiFlu	oseltamivir	2010	J	III
			88	TamiFlu	oseltamivir	2010	J	
		74	89	Topamax	topiramate	2011	N	III
			90	Topamax	topiramate	2011	N	
		75	91	Toprol XL	metoprolol	2007	C	II
		76	92	Trileptal	oxcarbazepine	2005	N	III
			93	Trileptal	oxcarbazepine	2005	N	
		77	94	Ultiva	remifentanil	2004	N	III
		78	95	Ultresa	pancrelipase	2012	A	
		79	96	Valtropin	somatropin (rDNA origin)	2007	H	
		80	97	Venofer	iron sucrose	2012	B	
								cont.

Part 1 Part 2		Number of products	Number of indications	Trade name	Generic name	Approved year	ATC	Clearance category*
101 products (121 indications) for Part 1	108 products for Part 2	81	98	Ventolin HFA	albuterol	2008	R	
		82	99	Videx EC	didanosine	2008	J	
		83	100	Viracept	nelfinavir	2004	J	
		84	101	Viramune Tablets 200	nevirapine	2008	J	
		85	102	VIRAMUNE XR	nevirapine	2012	J	
		86	103	Viread	tenofovir disoproxil fumarate	2012	J	
		87	104	Voluven	6% Hydroxyethyl Starch in 0.9% Sodium Chloride Injection	2007	B	
		88	105	Vyvanse Capsules	lisdexamfetamine	2010	N	
		89	106	Xopenex HFA Inhalation Aerosol	levalbuterol	2005	R	
		90	107	Xopenex Inhalation Solution	levalbuterol	2002	R	
		91	108	Xyzal	levocetirizine dihydrochloride	2009	R	III
			109	Xyzal	levocetirizine dihydrochloride	2009	R	
		92	110	Zantac	ranitidine	1999	A	III
		93	111	Zemplar	paricalcitol	2004	H	
		94	112	Zemuron	rocuronium	2008	M	II
		95	113	Zenpep	pancrelipase	2011	A	
		96	114	Ziagen	abacavir	2008	J	
		97	115	Zithromax Tablets	azithromycin	2004	J	
		98	116	Zmax Oral Susp	azithromycin	2008	J	
		99	117	Zofran	ondansetron	2005	A	III
			118	Zofran	ondansetron	2005	A	
		100	119	Zoloft	sertraline	2005	N	
		101	120	Zyvox	linezolid	2005	J	III
			121	Zyvox	linezolid	2005	J	
		102		Doryx Delayed-Release Tablets	doxycycline	2005	J	
		103		Genotropin Injection	somatropin (rDNA origin)	2006	H	
		104		HEMACORD	hematopoietic progenitor cells, cord blood	2011	B	
		105		Humatrope for injection	somatropin (rDNA origin)	2006	H	
		106		Norditropin Cartridges	somatropin (rDNA origin)	2007	H	
		107		Tirosint capsules	levothyroxine	2006	H	
		108		Unithroid Tablets	levothyroxine	2000	H	

* I: Lower drug clearance in younger patients.

II: Drug clearance increases with increasing body weight.

III: Higher apparent oral clearance in younger patients.

the English of my manuscripts.

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