Study on the current status of pediatric drug development and its improvement measures in Japan

Eiji Ueyama

Graduate School of Pharmaceutical Sciences

Department of Clinical Medicine (Pharmaceutical Medicine)

Kitasato University

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

Abstract

Drugs should ideally be made available to all patients worldwide in a timely manner regardless of whether they are adults or children. However, in reality, there is a time lag (i.e. drug lag) between the drug approvals in certain countries. This issue becomes more critical when the concerned disease is more serious. Due to this reason, the Ministry of Health, Labor and Welfare (MHLW) stressed on the necessity of promoting global clinical trials and introduced a guidance document on the basic concept of its implementation in order to eliminate drug lag.

Drugs intended for use in children should have their safety and efficacy in the pediatric population appropriately evaluated before their introduction into clinical practice. However, in routine medical practice, pediatric patients are commonly administered therapies that have not been tested in such young patients, receiving drugs designed and developed for adults. Europe and the US have established their own regulatory framework for promoting the development of pediatric drugs. Meanwhile, in Japan the MHLW has enacted various measures to promote pediatric drug development, which are different from those in US and Europe.

Pediatric drug development has not been actively implemented by pharmaceutical companies due to low profitability as a result of the followings; the number of patients is less, the dosage form and quantity needs to be specified according to each age, and child-specific consideration in conducting clinical trials such as obtaining consent is also required. In this study, we analyzed the current status of pediatric drug development in Japan in comparison with that of Europe, where pediatric plans must be considered relatively early in the development process. We also investigated the factors

influencing the approval lag between Japan and Europe for the drugs that received pediatric indication in Japan.

Our findings suggested that pediatric development has indeed been promoted even in Japan, where no laws or regulations mandating pediatric development have yet been established. However, the period from adult to pediatric indication approval was longer in Japan than in Europe and the development of pediatric drugs for certain diseases has not been very active in Japan, indicating room for further improvement in the future.

This study also showed global clinical trial to be the most effective means of shortening the approval lag in pediatric drug development. Global development is becoming the mainstream for many adult diseases, thus creating an environment for proactive participation in global clinical trials even for pediatrics drugs. For further improvement in the pediatric drug lag, more active drug development for pediatric indications is required in tandem with the US and Europe.

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Abbreviations

ATC	Anatomical Therapeutic Chemical
EMA	European Medicines Agency
EU	European Union
FDA	US Food and Drug Administration
ICH	International Conference for Harmonisation
MHLW	Ministry of Health, Labour and Welfare
PDCO	Pediatric Development Committee
PIP	Pediatric Investigation Plan
PMDA	Pharmaceuticals and Medical Devices Agency
US	United States of America
WHO	World Health Organization

1. Introduction

Drugs should ideally be made available to all patients worldwide in a timely manner regardless of whether they are adults or children. However, in reality, there is a time lag (i.e. drug lag) between the drug approvals in certain countries. Drug lag has been recognized as a major issue in Japan, especially in the 21st century.[1] This issue becomes more critical when the concerned disease is more serious. Due to this reason, in 2007, the Ministry of Health, Labor and Welfare (MHLW) stressed on the necessity of promoting global clinical trials and introducing a guidance document on the basic concept of its implementation in order to eliminate drug lag.[2] In the case of anti-cancer agents, the drug lag between the United States (US) and Japan was reported to have reduced to less than one year due to the participation of Japan in the global clinical trials.[3]

In order to establish an appropriate drug therapy for children, it is necessary to conduct clinical trials on specific pediatric patients, and then determine an appropriate dosage based on their safety and efficacy data. However, historically, clinical trials on children, unlike adults, have been perceived as difficult to conduct, mainly due to ethical and practical reasons. In case of pediatric medicines, the number of patients is less, the dosage form and quantity needs to be specified according to each age, and child-specific consideration in conducting clinical trials such as obtaining consent is also required. As a result, conducting trials are not profitable and are not being actively implemented by pharmaceutical companies. Therefore, for children, drugs approved based on only adult data without any clinical trial data for children have been used frequently for treatment without sufficient evidence.[4] Treatment of pediatric patients without such sufficient evidence not only results in insufficient efficacy but also increases the risk of side effects.[5]

This practice also reflects the unmet need for drugs developed specifically for this vulnerable population.

Given these public health concerns, establishing appropriate pharmacotherapy for children has been considered an important issue in medicine and in 2000, the Guidance on Investigation of Medicinal Products in the Pediatric Population (ICH E-11) was finalized through an agreement at the International Conference for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).[6] However, despite the fact that the establishment of the ICH E-11 increased international awareness of the need for pediatric drug development, it is not legally binding and did not significantly affect the pediatric drug development in any country/region.[7]

In Europe, the Pediatric Regulation (Reg 1901/2006/EU) was adopted for promoting the development of pediatric drugs at the end of 2006,[8] legally establishing a system to consider pediatric development during the drug development process in adults. The Pediatric Regulation requires drug companies to agree on a Pediatric Investigation Plan (PIP) with the European Medicines Agency (EMA) and its Pediatric Development Committee (PDCO) after the completion of phase 1 studies in adults and no later than the initiation of phase 2 studies (unless a product-specific or class waiver is granted by the EMA). If a pharmaceutical company completes the commitments as agreed to under the PIP, new medicinal products can receive a six-month marketing exclusivity incentive. The implementation of this regulation has forced pharmaceutical companies to consider pediatric drug development as part of the entire drug development course. Since the implementation of the Regulation, from 2007 to 2016, more than 260 new drugs for children were approved, most of them linked to the Regulation's requirements, indicating a clear positive effect. The number of agreed PIPs surpassed 1000 in 2017, of which 131

were completed at the end of 2016.[9]

Since there are no regulations legally mandating the development of pediatric drugs in Japan, the MHLW has taken various measures since 2000 to promote its development. As an incentive for companies, when a company plans clinical trials to seek a pediatric indication for a pharmaceutical product which has been approved for adults, the reexamination period (data protection period) is extended for usually 2 years (up to 10 years in total). In addition, during the reimbursement price calculation of a new drug under the National Health Insurance, if the package insert specifies that they are applicable for children, a pediatric premium is added. However, these measures have several conditions and do not necessarily apply to all pediatric drugs.[10,11] On the other hand, a leading measure different from these incentives is the establishment of the Evaluation Committee on Unapproved or Off-Label Drugs with High Medical Needs (hereafter "the Committee") in 2010.[12] The Committee targets all drugs meant not only for adults but for children as well that were approved in Western countries but not yet in Japan and solicits development requests for them from academic societies and patient groups. The drug that was judged to have a high medical need by the Committee is requested to a pharmaceutical company for development (or a development company is recruited), and then it is developed followed by the submission of an application for its approval.

The aim of this research is to present a solution to the unanswered critical questions on pediatric drug development in Japan; "Are drugs necessary for children appropriately made available to the patients in a timely manner?", "if drug lag exists, what types of pediatric drugs are?", and "are there any measures for eliminating the drug lag?" In order to answer these questions, in part 1 of the research, we evaluated the recent

status of pediatric drug approvals and their characteristics in Japan in comparison with those of Europe, where pediatric plans must be considered relatively early in the development process. Then, in prat 2, we examined the approval lag for pediatric indication between Japan and Europe, and investigated the factors potentially affecting the lag. Based on the results obtained from both research parts 1 and 2, further measures for promoting pediatric drug development were discussed.

2. Part 1

2.1 Background

In Japan, at present, no regulations legally require pediatric drug development. However, the MHLW has enacted various measures to promote pediatric drug development since 2000.[10,11]

Tsukamoto et al. reviewed the status of pediatric drug development between the periods 2006-2009 and 2010-2014 by analyzing the number of pediatric Phase 2/3 and Phase 3 trials and reported that pediatric drug development in Japan was more active after 2010 than before.[13] However, the status of pediatric drug approval in Japan has not been evaluated in detail.

In Part 1 of the research, we focused on the regulatory approval of drugs for pediatric patients in Japan, where pediatric development is not legally required and development of such drugs has been said to be lagging behind that in Western countries. We compared the status of approval of drugs for pediatric use between Europe, where pediatric plans must be considered relatively early in the development process, and Japan. To equally assess the status between the both regions, we evaluated the proportion of drugs with pediatric indication in Japan (or Europe) among the drugs approved for pediatric indications in Europe (or Japan) and their characteristics in the same period. The objective of this study (part 1) was to clarify the recent status of pediatric drug approvals and their characteristics in Japan in comparison with Europe and to identify challenges facing this development process. We then discussed how these efforts should be supported in the future based on our findings.

2.2 Method

Data Sources and Extraction of Drugs with Pediatric Indications

Drugs approved for pediatric indications between 2007 and 2015 in Europe (EMA) and Japan were included in the present study. For Europe, among the centrally authorized medicines listed in the EMA 10-year Report to the European Commission (15 November 2016) Annex, new medicines with pediatric indications (New medicines) and those approved for new pediatric indications by the addition of or change in indications (New indications) were extracted.[14] For Japan, among the drugs included in the list of approved new drugs on the PMDA's website,[15] those for which the "Indications" or "Dosage and Administration" text in the package insert clearly indicated their applicability to children (or if the applicability to children was unclear, drugs that were considered acceptable for use in children based on the details included in the review report) were extracted as drugs approved for pediatric use. Among these drugs, generic products, biosimilar products, vaccines, and combined hormone products that were available in multiple types in Japan or Europe were excluded. For drugs containing the same active ingredient that were available in multiple dosage forms, such as an injectable formulation, oral formulation, and external formulation, each dosage form was counted as separate approvals. A drug with already approved pediatric indications was counted as a single approval only if the drug was approved for use in younger children (neonates/infants [0 to <2 years of age] or toddlers/school-age children [2 to 11 years of age]) during the study period. Drugs with existing pediatric indications for which the upper age limit was changed were excluded.

Summarization of Drugs with Pediatric Indications in Europe and Japan

Pediatric drugs summarized as above were classified by target disease (in both adults and children or only in children) and by form of approval (initial approval or supplemental approval). Drugs were considered to be available in pediatric formulations if the pediatric formulation fell into the following categories: oral solution, oral suspension, oral soluble film, scored tablets, orally disintegrating tablet, chewable tablet, mini-tablets, sprinkle capsule, powder for oral solution, powder for oral suspension, granules for oral suspension, oral powder, oral granules, tablet, dispersible tablet, dispersible scored tablet, or tablet for oral suspension.[16] Drugs approved in Japan were additionally checked to determine whether or not the pediatric development had been initiated at the request of the Committee.[12]

In the comparison of characteristics of the approved pediatric drugs between Europe and Japan, Fisher's exact test was performed using StatsDirect (StatsDirect LTD., Cheshire, UK). A statistically significant difference was defined as p value < 0.05.

Identification and Classification of Drugs with Pediatric Indications in Europe and Japan

Proportion and Characteristics of Drugs with Pediatric Indications in Japan among the Drugs Approved for Pediatric Indications in Europe (EMA)

Among the drugs approved for pediatric indications in Europe (EMA) between 2007 and 2015, we identified those for which the same products were available in the Japanese market in March 2018, based on the PMDA's website. The proportion of drugs with pediatric indications in Japan was determined by the Anatomical Therapeutic Chemical (ATC) classification,[17] and the status of the development of pediatric formulations was examined.

Proportion and Characteristics of Drugs with Pediatric Indications in Europe among the Drugs Approved for Pediatric Indications in Japan

Among the drugs approved for pediatric indications in Japan between 2007 and 2015, we identified those for which the same products were available in the EU market in March 2018 based on the EMA's website. When determining the presence of approved pediatric indications in the EU, relevant medicinal products that were not centrally authorized by the EMA but instead nationally authorized were considered to be approved if they were approved either in the United Kingdom, France, or Germany. The proportion of drugs with pediatric indications in the EU was determined by the ATC classification, and the status of the development of pediatric formulations was examined.

Time from the Approval of the Adult Indication to that of the Pediatric Indication

For drugs with both adult and pediatric indications, the time from the approval of the therapeutic indication in adults to that in children was calculated for both Europe and Japan. In this calculation, we focused on the first pediatric indication for a drug in cases where the drug obtained pediatric indication for different age ranges on several occasions.

2.3 Result

Drugs with Pediatric Indications in Europe and Japan

The demographics of the drugs studied are summarized in Table 1. A total of 135 drugs were approved for pediatric indications in Europe, with 208 approved in Japan. When drugs were stratified by target disease, drugs approved for diseases in both adults and children accounted for least 90% of the drugs in both Europe and Japan, with no marked difference between the regions. When drugs were stratified by form of approval (initial approval or supplemental approval), the proportion of drugs with supplemental approval was higher (67.3%) in Japan than in Europe (55.6%) (p=0.0304). When drugs were stratified by the presence of new formulations for children, the proportion of drugs with such formulations was higher in Europe (23.0%) than in Japan (9.6%) (p=0.0010). Thirteen drugs in Europe and 4 drugs in Japan, which already had pediatric indication, obtained additional indication for younger ages; the rest 122 drugs in Europe and 204 in Japan obtained pediatric indication for the first time. When drugs were stratified by ATC classification, both regions showed a similar trend, and J (Antiinfectives for systemic use) was the most frequently approved category. While the number of approved drugs for pediatric indications increased in the second half of the study period (2011-2015) compared to the first half (2007-2010) in Japan, the number seemed stable throughout the period in Europe (Figure 1).

Table 1. Number of drugs approved for pediatric indications in Europe (EMA) and Japan between 2007 and 2015.

	Europe n=135	Japan n=208	*p* value*
Target disease, n (%)			
In both adults and children	125 (92.6)	194 (93.2)	0.8309
Only in children	10 (7.4)	14 (6.8)	
Form of approval, n (%)			
Initial	60 (44.4)	68 (32.7)	0.0304
Supplemental	75 (55.6)	140 (67.3)	
With new formulations for children, n (%)			
Yes	31 (23.0)	20 (9.6)	0.0010
No	104 (77.0)	188 (90.4)	
Requests from the Evaluation Committee on Unapproved or Off-Label Drugs with High Medical Needs, n (%)			
Yes	—	57 (27.4)	—
No	—	151 (72.6)	

EMA, European Medicines Agency.

*Fisher's Exact Test.

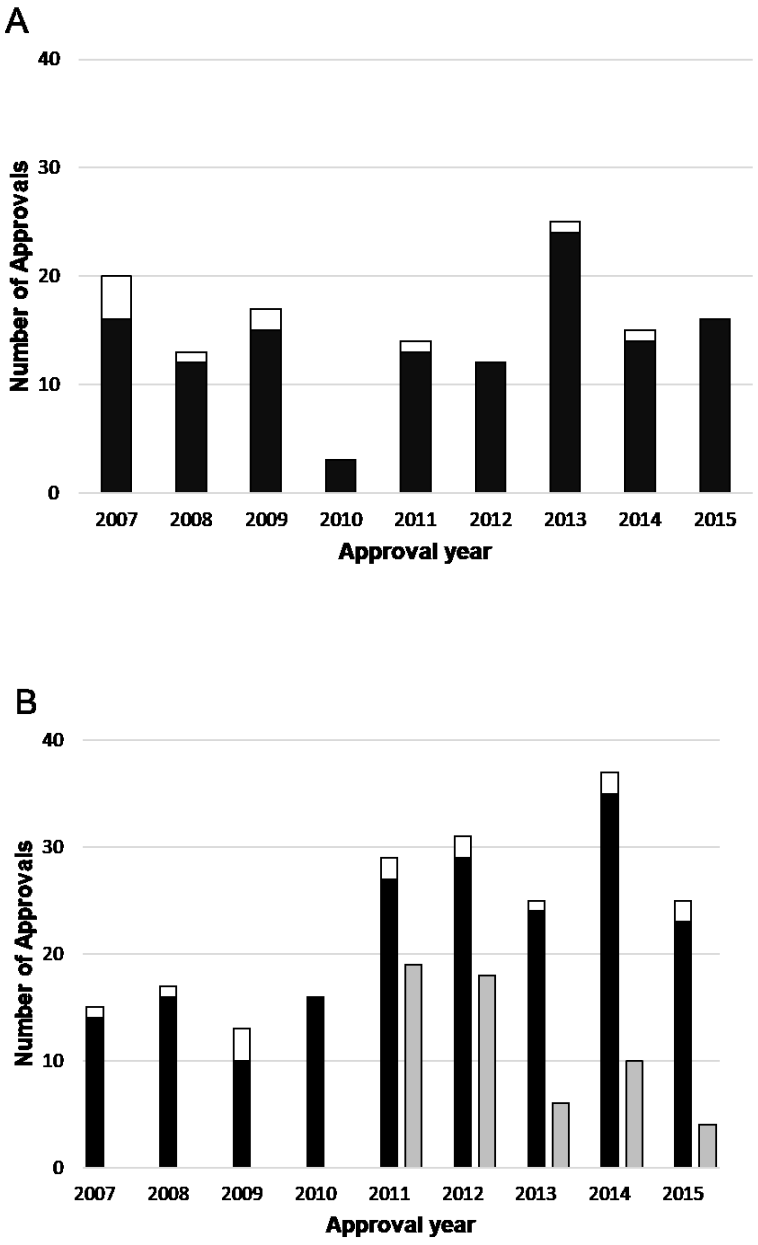

Figure 1. Transition of the number of drugs approved for pediatric indications in (A) Europe and (B) Japan.

Black bar: For both adults and children, White bar: Only for children, Gray bar (B only): Based on requests from the Evaluation Committee on Unapproved or Off-Label Drugs with High Medical Needs.

In Japan, drugs approved for pediatric indications based on requests from the Committee accounted for approximately 35% to 40% of all the drugs approved for pediatric indications from 2011 onward. When the number of approved drugs for pediatric indications was stratified by form of approval (initial approval or supplemental approval) and compared between the first half (2007-2010) and the second half (2011-2015) of the study period, the number of initial approval increased from 22 to 46, whereas the number of supplemental approval nearly tripled, from 39 to 101.

Proportion and Characteristics of Drugs with Pediatric Indications in Japan among Drugs with Pediatric Indications in Europe (EMA)

Among the drug products approved for pediatric indications in Europe (EMA), 92 were also marketed with the same indications in Japan, with 55 (60%) approved for pediatric indications. When evaluated by ATC classification, less than 50% of drugs in N (Nervous system) and J (Antiinfectives for systemic use) were approved for pediatric indications in Japan. Among the 24 drugs approved in Europe with new formulations for children, only 12 drugs (50%) were available in Japan (Table 2).

Table 2. Proportion of drugs with pediatric indications in Japan among the drugs approved for pediatric indications in Europe (EMA) between 2007 and 2015 by ATC classification and status of development of pediatric formulations.

	Total	Pediatric indications in Japan		Proportion of approval in Japan (%)
	n=92	Present n=55	Absent n=37	60 [55/92]
ATC classification				
A	12 (2*)	10	2	83
B	4	3	1	75
C	4 (1*)	3	1	75
D	1	1	0	100
G	1	1	0	100
H	0	0	0	-
J	29 (9*)	13	16	45
L	19 (4*)	12	7	63
M	1	1	0	100
N	14 (7*)	5	9	36
P	0	0	0	-
R	5 (1*)	5	0	100
S	0	0	0	-
V	2	1	1	50
New formulations for children				
Present	24	12	12	50
Absent	68	43	25	63

*Number of new formulations for children.

ATC, anatomical therapeutic chemical.

ATC classification: A, Alimentary tract and metabolism; B, Blood and blood-forming organs; C, Cardiovascular system; D, Dermatologicals; G, Genito-urinary system and sex hormones; H, Systemic hormonal preparations, excluding sex hormones and insulins; J, Antiinfectives for systemic use; L, Antineoplastic and immunomodulating agents; M, Musculo-skeletal system; N, Nervous system; P, Antiparasitic products, insecticides and repellents; R, Respiratory system; S, Sensory organs; V, Various.

Proportion and Characteristics of Drugs with Pediatric Indications in Europe among Drugs with Pediatric Indications in Japan

Among the drug products approved for pediatric indications in Japan, 155 were also marketed with the same indications in Europe, with 137 (88%) approved for pediatric indications. When evaluated by ATC classification, the proportion of drugs approved for pediatric indications in Europe exceeded 75% in all the ATC classification ($n \geq 2$). There was no marked difference in the proportion of drugs with pediatric indications with or without new formulations for children (Table 3).

Table 3. Proportion of drugs with pediatric indications in Europe among drugs with pediatric indications in Japan by ATC classification and status of development of pediatric formulations.

	Total	Pediatric indications in Europe		Proportion of approval in Europe (%)
	n=155	Present n=137	Absent n=18	88 [137/155]
ATC classification				
A	23 (1*)	22	1	96
B	14	13	1	93
C	9 (1*)	8	1	89
D	0	0	0	-
G	0	0	0	-
H	3 (1*)	3	0	100
J	37 (3*)	29	8	78
L	19 (1*)	17	2	90
M	2	2	0	100
N	19 (7*)	19	0	100
P	2	2	0	100
R	15 (4*)	13	2	87
S	1	0	1	0
V	11	9	2	82
New formulations for children				
Present	18	17	1	94
Absent	137	120	17	88

*Number of new formulations for children.

ATC, anatomical therapeutic chemical.

ATC classification: A, Alimentary tract and metabolism; B, Blood and blood-forming organs; C, Cardiovascular system; D, Dermatologicals; G, Genito-urinary system and sex hormones; H, Systemic hormonal preparations, excluding sex hormones and insulins; J, Antiinfectives for systemic use; L, Antineoplastic and immunomodulating agents; M, Musculo-skeletal system; N, Nervous system; P, Antiparasitic products, insecticides and repellents; R, Respiratory system; S, Sensory organs; V, Various.

Time from Adult Indication Approval to Pediatric Indication Approval

For drugs with both adult and pediatric indications in Europe (EMA), the time from the approval of the therapeutic indication in adults to that in pediatrics is shown in Figure 2A. Among the 112 drug products, 88 (79%) were approved for pediatric indications concurrently with adult indications. For the remaining drugs, 3 to 6 years was the most commonly (9%) observed period from the adult indication approval to the pediatric indication approval.

For drugs with both adult and pediatric indications in Japan, the time from the approval of therapeutic indications in adults to that in pediatrics is shown in Figure 2B. Among the 190 drug products, 146 (77%) were approved for pediatric indications concurrently with adult indications. For the remaining drugs, the most commonly observed period from the adult indication approval to the pediatric indication approval was more than 12 years (7%), followed by 9 to 12 years. This trend was not different between the drugs with and without the request from the Committee.

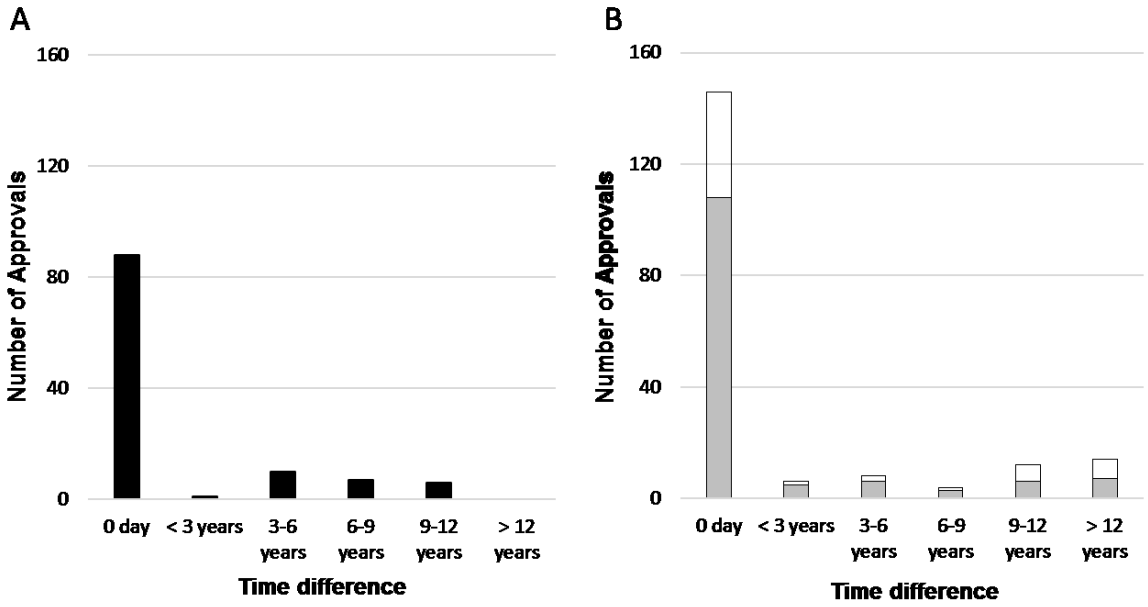

Figure 2. Period from adult indication to pediatric indication approval for drugs approved for pediatric indications in (A) Europe and (B) Japan.

Black bar: Total, White bar: Based on requests from the Evaluation Committee on Unapproved or Off-Label Drugs with High Medical Needs (the Committee). Gray bar: No requests from the Committee.

2.4 Discussion

The number of drugs approved for pediatric indications from 2007 to 2015 was greater in Japan (208 drugs) than in Europe (135 drugs). The number in Japan increased from 2011 onward, while the number was numerically stable in Europe. This increase in Japan was generally consistent with the number of drugs for which development was initiated at the request of the Committee, suggesting the Committee exerted a substantial influence on the development and approval of drugs that had remained unapproved in Japan. When we looked into the approval date of drugs with the same pediatric indication in both Europe (EMA) and Japan, the majority had been approved earlier in Europe than in Japan, indicating that access to medicine for pediatric patients in Japan is lagging behind that in Europe.

Among the drugs approved for pediatric indications from 2007 to 2015, the number of supplemental approvals was about two times greater in Japan than in Europe, while the number of initial approvals did not differ markedly between the two. The increase in the number of pediatric drugs from 2011 onward in Japan was due mainly to supplemental approvals, suggesting that efforts to develop pediatric drugs have progressed substantially even in Japan, where no laws or regulations mandating pediatric drug development are currently in place. Of note, approval with the development of pediatric formulations was more frequent in Europe than in Japan, suggesting that drug development was likely conducted meticulously with consideration of the age of patients in Europe, where pediatric drug development is explicitly legislated.

Regarding the approved pediatric drugs classified by ATC classification, the proportion of drugs with pediatric indications in Japan among those approved for

pediatric indications in Europe (EMA) was 36% for N (Nervous system) and 45% for J (Antiinfectives for systemic use) categories, which was less than 50% and lower than the respective proportions of such drugs with pediatric indications in Europe among those approved for pediatric indications in Japan (N: 100%, J: 78%), highlighting the potential need to close the gap for these specific categories. In addition, the present study showed that Japan had a significantly lower proportion of development of pediatric formulations, indicating the need to specifically promote the development of pediatric formulations in future regulatory initiatives.

Our investigation of the period from adult to pediatric indication approval showed that the most commonly observed period for drugs approved in Europe (EMA), except for cases in which the pediatric and adult indications were approved at the same time, was 3 to 6 years, with 12 years being the longest. The mean period from the approval of therapeutic indications in adults to the availability of pediatric data in the US was reportedly 6.5 years for new drugs that lacked any pediatric data at their initial approval,[18] suggesting no major difference between Europe and the US in terms of the period from adult to pediatric indication approval. In contrast, a period of more than 12 years was the most common for drugs to receive such approval in Japan. Given that, in many cases, pediatric development for drugs that had lacked pediatric indication for many years was stimulated by a request from the Committee, this finding suggested that this initiative was somewhat effective in promoting pediatric development. However, the period from adult to pediatric indication approval in Japan tended to be longer than that in Europe. Because the request by the Committee is based on the fact that the approval of the drug or the pediatric indication has been confirmed in other countries, current regulations in Japan and efforts to establish an environment to facilitate pediatric drug development are not

sufficient with respect to achieving timely access to medicine for pediatric patients.

The introduction of measures such as the establishment of the Committee has promoted pediatric drug development in Japan. However, further improvement may yet be achieved in terms of the period from adult to pediatric indication approval and the development of pediatric drugs for certain diseases. The present study suggests the need for effective measures to promote and incentivize pediatric development, with an aim to achieve more timely access to medicine for pediatric patients.

Several limitations associated with the present study warrant mention. When comparing drugs with pediatric indications in Japan and Europe, focus was placed on the drugs approved during the period from 2007 to 2015, not including the data in and after 2016; this was because we referred to the product lists in the EMA 10-year report about the Pediatric Regulation. In addition, when we determined the presence of pediatric indications in Europe among the drugs approved in Japan, for drugs approved before the centrally authorized approval system was implemented by EMA, we considered nationally authorized products. In this judgement, we referred to the information in the United Kingdom, France, and Germany, not that in all the European countries due to difficulties in assessing the source data in other European countries. As for the pediatric formulation, because there was no clear and established definition of pediatric formulations, we referred to a review article to select those.[16] Therefore, we may have missed some drugs with pediatric formulations.

3. Part 2

3.1 Background

Drugs should ideally be made available to all patients worldwide in a timely manner regardless of whether they are adults or children. However, in reality, there is a time lag (i.e. drug lag) between the drug approvals in certain countries. Drug lag has been recognized as a major issue in Japan, especially in the 21st century.

In our previous study (part 1), we investigated the status of pediatric drug approvals and their characteristics in Japan in comparison to Europe, where pediatric development plans must be considered relatively early in the development process. The result showed that the number of drugs that obtained pediatric indications between 2007 and 2015 was higher in Japan. However, when we looked at the approval date of drugs with the same pediatric indication in both Europe and Japan, we found that majority of the drugs had been approved earlier in Europe, indicating that the access to medicine for pediatric patients in Japan is lagging behind that in Europe.[19]

The objective of this study is to examine the current status and characteristics of pediatric drug development in Japan using the information on the approval lag between in Japan and Europe for drugs that obtained pediatric indication in Japan from 2007 to 2018. This information is useful for clinicians and patients as well as drug developers and regulatory stakeholders. Based on the results, further measures for eliminating the approval lag have also been discussed.

3.2 Method

Data sources and extraction of drugs with pediatric indications

This study analyzes the drugs approved for pediatric indications in Japan between 2007 and 2018. From the list of newly approved drugs on the PMDA's website,[15] those with "Indications" or "Dosage and Administration" text in the package insert indicating their applicability to children (or if the applicability to children was unclear, drugs that were considered acceptable for use for children based on the details included in the review report), were selected as drugs approved for pediatric use. Influenza vaccines, combined vaccines, and combined hormonal products that were available in multiple variations in Japan or Europe were excluded. For drugs containing the same active ingredient that was available in multiple dosage forms, such as an injectable formulation, oral formulation, and external formulation, each dosage form was counted as a separate approval. Drugs with already approved pediatric indication for which the lower or upper age limit was changed were also excluded.

Extraction of information from the drugs that obtained pediatric indications

For drugs with pediatric indications selected by the method described above, the approval date, target disease, ATC classification,[17] dosage form, company name, development request from the Committee,[12] orphan disease, and clinical data package (use of foreign data, and existence of global clinical trial) were investigated. The target diseases were classified into "adults and children" (diseases affecting adults and children) and "children only" (diseases affecting children only). Drugs were considered to be available in pediatric formulations if the dosage form fell in the following categories: oral

solution, oral suspension, oral soluble film, scored tablets, orally disintegrating tablet, chewable tablet, mini-tablets, sprinkle capsule, powder for oral solution, powder for oral suspension, granules for oral suspension, oral powder, oral granules, tablet, dispersible tablet, dispersible scored tablet, or tablet for oral suspension.[16] Development companies were classified into Japanese and foreign-affiliated companies. Regarding the clinical data package, the cases where foreign clinical trial data were utilized for the drug approval were judged.

Search for approval information in Europe

Using the information on the European Medicines Agency (EMA) website[20] and the information on the review report of the drugs approved in Japan, we checked the drugs with pediatric indication in Japan and identified those which have the same indication in Europe. Then, for each product on the EMA's website, the status and date of approval for relevant medicinal product in Europe was investigated from "Procedural steps taken and scientific information after the authorization." Whether they are approved in the European region was checked based on the information as of March 31, 2019.

Classification and aggregation based on the above information

Breakdown of Drugs with Pediatric Indications and Calculation of Approval Lag between Japan and Europe

For the drugs to be investigated, the breakdown by target disease, dosage form, pediatric drug development, development request from the Committee, orphan drug, company (Japanese or foreign-affiliated), foreign clinical trial data, global clinical trial, ATC classification, and approval time (2007-2010, 2011-2014, 2015-2018) was

summarized. The approval lag between Japan and Europe was calculated (the case where the approval date in Europe was earlier than in Japan is indicated as a plus).

Examination of the factors affecting approval lag

Approval lag was examined by dosage form, pediatric formulation, orphan drug, company nationality (domestic or foreign affiliated), foreign clinical trial data, and global clinical trial.

Characteristics of drugs approved based on global clinical trial data

For the drugs approved for pediatric indications in Japan based on the global clinical trial data, we counted the number of annual approvals. The proportion of approvals for each ATC category was also calculated.

Statistical Analysis

A Mann-Whitney U test was performed using StatsDirect (StatsDirect LTD., Cheshire, UK) for the examination of factors affecting approval lag for pediatric indications. A statistically significant difference was defined as p value < 0.05.

3.3 Result

Characteristics of drugs with pediatric indications

The demographics of the drugs studied are summarized in Table 4. A total of 274 drugs were approved for pediatric indications in Japan between 2007 and 2018. When the drugs were classified according to target disease, the drugs approved for diseases in both adults and children accounted for more than 90%. The percentage of approvals with pediatric formulation development was less than 10%. Approximately 30% of drugs received pediatric indications at the request of the Committee, which has been 38.1% (82/215) since 2011, when the Committee initiated its activities. By ATC classification, category J had the highest proportion at 23%, followed by category L. The number of drugs approved for pediatric indications was the highest in 2011-2014, followed by 2015-2018, and 2007-2010.

Table 4. Characteristics of drugs approved for pediatric indications in Japan.

	Total, n=274
Target disease, n (%)	
Only in children	23 (8.4)
In both adults and children	251 (91.6)
Formulation, n (%)	
Injections	140 (51.1)
Oral and external agents	134 (48.9)
With new formulations for children, n (%)	
Yes	25 (9.1)
No	249 (90.9)
Requests from the Evaluation Committee on Unapproved or Off-Label Drugs with High Medical Needs, n (%)	
Yes	82 (29.9)
No	192 (70.1)
Orphan drug, n (%)	
Yes	60 (21.8)
No	214 (78.1)
Company nationality, n (%)	
Japanese	126* (45.5)
Foreign affiliated	151* (54.5)
Foreign clinical data, n (%)	
Yes	106 (38.7)
No	168 (61.3)
Global clinical trial, n (%)	
Yes	37 (13.5)
No	237 (86.5)
ATC classification, n (%)	
A, Alimentary tract and metabolism	32 (11.7)
B, Blood and blood-forming organs	24 (8.8)
C, Cardiovascular system	15 (5.5)
D, Dermatologicals	6 (2.2)

G, Genito-urinary system and sex hormones	3 (1.1)
H, Systemic hormonal preparations, excluding sex hormones and insulins	8 (2.9)
J, Anti-infectives for systemic use	64 (23.4)
L, Antineoplastic and immunomodulating agents	38 (13.9)
M, Musculoskeletal system	6 (2.2)
N, Nervous system	32 (11.7)
P, Antiparasitic products, insecticides and repellents	4 (1.5)
R, Respiratory system	18 (6.6)
Approval time, n (%)	
2007-2010	59 (21.5)
2011-2014	120 (43.8)
2015-2018	95 (34.7)

*Three approvals were made by both types of companies.

Examination using approval lag data

Approval lag for pediatric indications between Japan and Europe

The approval lag (median, the same below) for 105 drugs that obtained pediatric indication in both Japan and Europe was 1017 days. The approval lag for a drug without a request from the Committee was 712 days, which was significantly shorter than that with the request (2260 days) (p=0.0004) (Table 5). Since the Committee targets only drugs approved in Western countries and their development is initiated based on the Committee's request, the drugs developed without a request can be considered to have been voluntarily developed by companies. Therefore, a subsequent study was performed using the data of drugs developed without the Committee's request.

Table 5. Approval lag for pediatric indications between Japan and Europe (EMA).

	n	Approval lag (median), days	*p* value*
Total	105	1017	—
Requests from the Committee	82	712	0.0004
Without requests from the Committee	23	2260	

*Mann-Whitney U test.

Examination of approval lag by approval time and ATC classification

When the approval lag between Japan and Europe was calculated by approval time, it was shown to have been gradually reduced over time (1217 days: 2007-2010, 1140 days: 2011-2014, 348 days: 2015-2018) (Figure 3). The approval lag for each ATC classification showed that it was relatively short for the drugs of categories A and B (n = 4 or more) (A: 269 days, B: 140 days). This analysis also showed that the time lag for category B improved significantly after 2011, and for category L since 2015, which was less than half a year (Table 6).

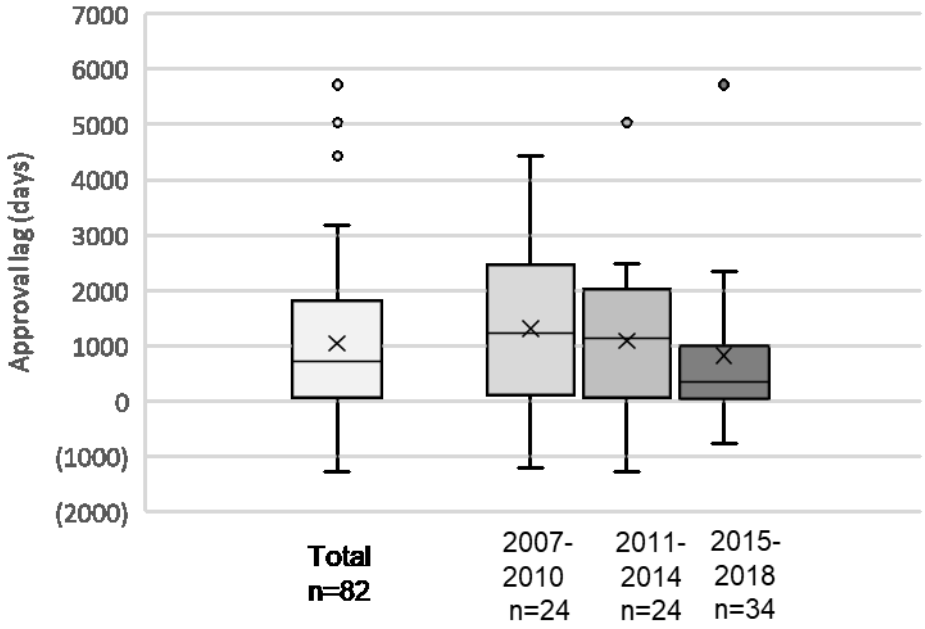

Figure 3. Approval lag for pediatric indications between Japan* and Europe (EMA) (*drugs developed based on the Committee's requests are excluded).

In this box plot, the top, the middle, and the bottom line in a box represent the 75th percentile, the median and the 25th percentile, respectively. The mean is shown as an ×. The upper whisker of the box plot is the maximum value smaller than 1.5 interquartile range above the third quartile (open circles show outliers). The lower whisker of the box plot is the minimum value larger than 1.5 interquartile range below the first quartile.

Table 6. Approval lag for pediatric indications by ATC classification.

ATC classification*	Total		2007-2010		2011-2014		2015-2018	
	n	Approval lag, days	n	Approval lag, days	n	Approval lag, days	n	Approval lag, days
A	15	269	6	532	4	272	5	213
B	17	140	2	3335	6	36	9	140
J	17	897	4	1090	7	1745	6	427
L	14	850	6	869	4	1140	4	40
R	8	1939	2	2765	2	1871	4	1371

*Categories of n=3 or less excluded.

ATC classification: A, Alimentary tract and metabolism; B, Blood and blood-forming organs; J, Anti-infectives for systemic use; L, Antineoplastic and immunomodulating agents; R, Respiratory system.

Examination of factors affecting approval lag

The investigation of the factors affecting approval lag showed that the approval lag (140 days) for drugs developed with a global clinical trial was significantly shorter compared to drugs without it (1235 days) (p=0.0002) (Table 7). Other factors did not show significant differences, but the approval lag for orphan drugs and the drugs developed by the Japanese company was less than one year. In addition, the lag for drugs approved using foreign clinical data was more than 2 years shorter than those without it.

Table 7. Examination of factors affecting approval lag.

Variable	n	Approval lag, days	*p* value*
Formulation			
Injections	58	543	.2972
Oral and external agents	24	809	-
New formulations for children			
Yes	6	1033	.2229
No	76	663	-
Orphan drugs			
Yes	33	301	.2796
No	49	945	-
Company nationality			
Japanese	14	222	.1251
Foreign affiliated	68	793	-
Foreign clinical data			
Yes	71	659	.3655
No	11	1621	-
Global clinical trial			
Yes	27	140	.0002
No	55	1235	-

*Mann-Whitney U test.

Characteristics of drugs approved based on global clinical trial data

The approval lag for the drugs that were developed with a global study was significantly shorter than the lag for the other drugs, thus, the characteristics of these drugs were analyzed. There was a total of 27 drugs approved based on global clinical trial data. The annual number of approvals was revealed prominently in 2014 and it has been generally constant since then (Figure 4). In terms of analysis by ATC classification, the number for category B was 13, and the ratio within category B accounted for 76% (13/17) (Table 8).

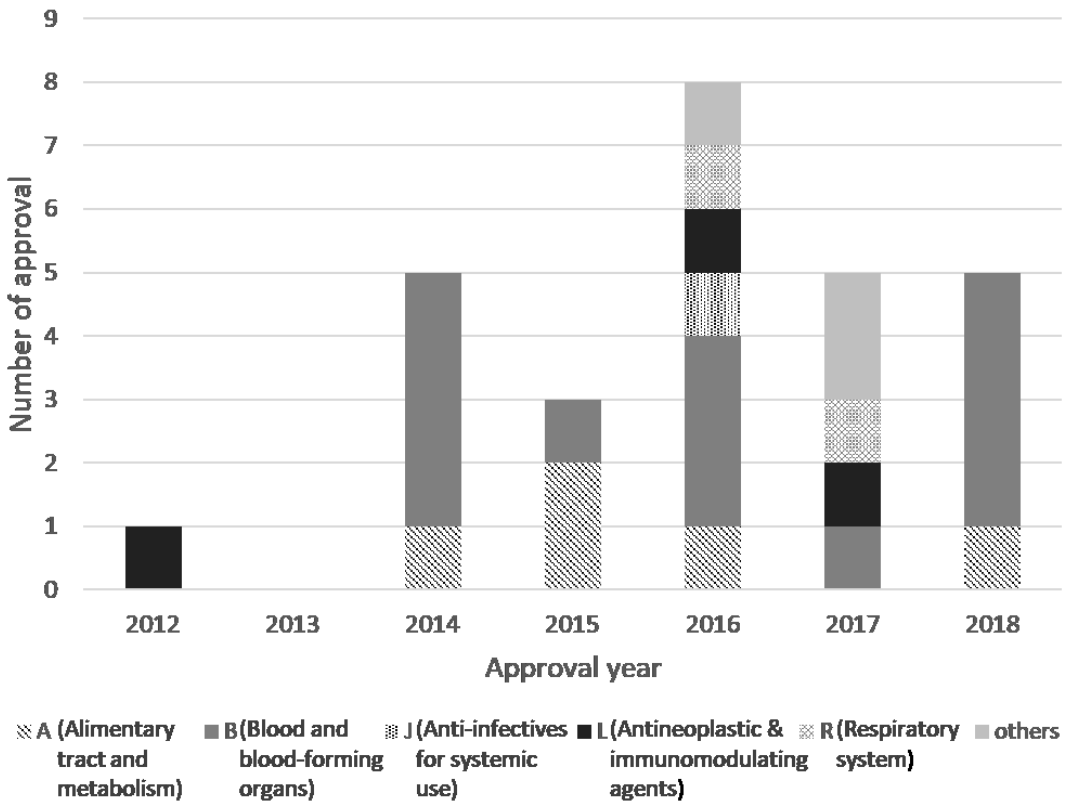

Figure 4. Transition of the number of drugs approved for pediatric indications based on global clinical trial data.

Table 8. Breakdown of pediatric drugs developed with global clinical trials by ATC classification.

ATC classification	Drugs with global clinical trial n=27	All drugs n=82
A	5 (33%)	15
B	13 (76%)	17
J	1 (6%)	17
L	3 (21%)	14
R	2 (25%)	8
Others	3 (27%)	11

ATC classification: A, Alimentary tract and metabolism; B, Blood and blood-forming organs; J, Anti-infectives for systemic use; L, Antineoplastic and immunomodulating agents; R, Respiratory system.

3.4 Discussion

A survey of the number of approvals for drugs that received pediatric indication in Japan from 2007 to 2018 revealed that the number clearly increased after the establishment of the Committee. However, the approval lag between Japan and Europe for the drugs that have obtained pediatric indications in Europe (EMA) was significantly longer for drugs developed after the Committee's request than those without the request. This suggests that although the establishment of the Committee contributed to the development of pediatric indications for drugs, it did not contribute to decreasing the approval lag because only the drugs that had been approved in Western countries were targeted in the Committee. The analysis of the approval lag by ATC classification showed that the pediatric development in "anti-neoplastic agents and immunomodulators" (category L) and "blood and hematopoietic agents" (category B) has been promoted more aggressively in recent years.

Examination of the factors that influence the approval lag for pediatric indication showed that the lag was shortened significantly when the development strategy involving global clinical trial was adopted. On the other hand, there was no significant difference in the study based on other factors. In the case of a drug owned by a Japanese company, previous research showed almost no drug lag,[21] thus we examined the impact of the company nationality (domestic or foreign affiliated). In addition, from the report stating that the use of foreign clinical data in the approval review shortened the lag,[22,23] we compared the case of using foreign data for drug approval and the case without it. No significant difference was found between the two groups in either case, but if the developer is a Japanese company and if foreign clinical data are utilized for drug approval,

the approval lag tends to be shorter. As mentioned above, some factors seem to improve the approval lag for pediatric drugs that have various limitations in conducting a clinical study compared to those in adults. However, only a global clinical trial significantly reduced the approval lag for pediatric drugs as already widely recognized in the drug development field, indicating that it is the most effective means of eliminating drug lag even for pediatric drugs.

Calculation of the implementation status of global clinical trials by ATC classification showed that “Blood and hematopoietic drugs” (category B) accounted for 76%. All these drugs are coagulation factor preparations for the treatment of hemophilia, and the influence of ethnic factors on drug evaluation is small. Therefore, the development using a global clinical trial is expected to be progressing. On the other hand, for drugs of other classes or categories with approval lag, it was suggested that clinical development plans participating in a global clinical trial should be discussed from the clinical development planning stage for adults in consideration of early acquisition of pediatric indication.

As mentioned above, global clinical trials are a powerful tool for eliminating the approval lag in pediatric drug development. Implementation of a global clinical trial takes a lot of preparation time such as the creation of study protocols and responding to the regulatory requirements of each country. Additionally, child-specific considerations in conducting clinical trials are required. Therefore, to further reduce the approval lag for pediatric drugs, development plans for children should be considered with the knowledge of pediatric development in early stages of clinical development for adults in Japan, as is done in Europe and the US, for drugs meant for diseases which do not have a cure yet. In addition, for early involvement on global development for pediatric drugs, measures and

systems for raising the awareness on pediatric development like in Europe and US might be necessary.

The present study on the approval lag considers only Europe and does not compare it with the US or other countries. Additionally, for the approvals in Europe, only centrally authorized products by the EMA were used for time lag calculations. In this regard, many nationally authorized medicinal products were approved in the 1980s and 1990s before the EMA was established, and we considered that the status of drug development including pediatric development in each European country would be different.

4. Overall Discussion

In part 1 of the research, we found that the number of drugs approved for pediatric indications from 2007 to 2015 was greater in Japan than in Europe. The number in Japan increased from 2011 onward, while the number was numerically stable in Europe. This increase in Japan was generally consistent with the number of drugs for which development was initiated at the request of the Committee, suggesting the Committee exerted a substantial influence on the development and approval of drugs that had remained unapproved in Japan. Meanwhile, when we looked into the approval date of drugs with the same pediatric indication in both Europe (EMA) and Japan, the majority had been approved earlier in Europe than in Japan, indicating that access to medicine for pediatric patients in Japan is lagging behind that in Europe.

The proportion of drugs with pediatric indications in Japan among those approved for pediatric indications in Europe (EMA) for N (Nervous system) and J (Antiinfectives for systemic use) categories was less than 50% and lower than the respective proportions of such drugs with pediatric indications in Europe among those approved for pediatric indications in Japan, highlighting the potential need to close the gap for these specific categories. In addition, approval with the development of pediatric formulations was more frequent in Europe than in Japan, suggesting that drug development was likely conducted meticulously with consideration of the age of patients in Europe, where pediatric drug development is explicitly legislated. Furthermore, the period from adult to pediatric indication approval in Japan tended to be longer than that in Europe. Because the request by the Committee is based on the fact that the approval of the drug or the pediatric indication has been confirmed in other countries, current

regulations in Japan and efforts to establish an environment to facilitate pediatric drug development are not sufficient with respect to achieving timely access to medicine for pediatric patients.

In part 2 of the research, we found that, while the number of approvals for drugs that received pediatric indication from 2007 to 2018 clearly increased after the establishment of the Committee, the approval lag between Japan and Europe for the pediatric indications was significantly longer for drugs developed after the Committee's request than those without it. This supports that although the establishment of the Committee contributed to the development of pediatric indications for drugs, it did not contribute to decreasing the approval lag.

The analysis of the approval lag for pediatric indications between Japan and the EU by ATC classification showed that the pediatric development in "anti-neoplastic agents and immunomodulators" (category L) and "blood and hematopoietic agents" (category B) has been promoted more aggressively in recent years. Examination of the factors that influence the approval lag showed that the lag was shortened significantly when the development strategy involving global clinical trial was adopted, indicating that it is the most effective means of eliminating drug lag even for pediatric drugs. Calculation of the implementation status of global clinical trials by ATC classification showed that "Blood and hematopoietic drugs" (category B) accounted for 76%. All these drugs are coagulation factor preparations for the treatment of hemophilia, and the influence of ethnic factors on drug evaluation is small. Therefore, the development using a global clinical trial is expected to be progressing. For drugs of other classes or categories with approval lag, it was suggested that clinical development plans participating in a global clinical trial should be discussed from the clinical development planning stage for adults

in consideration of early acquisition of pediatric indication.

Based on our findings above, the introduction of measures such as the establishment of the Committee has promoted pediatric drug development in Japan. However, further improvement may yet be achieved in terms of the period from adult to pediatric indication approval and the development of pediatric drugs for certain diseases. The present study suggests the need for effective measures to promote and incentivize pediatric development, with an aim to achieve more timely access to medicine for pediatric patients. In addition, the present study showed that Japan had a significantly lower proportion of development of pediatric formulations, indicating the need to specifically promote the development of pediatric formulations in future regulatory initiatives.

Global clinical trials are a powerful tool for eliminating the approval lag in pediatric drug development. Implementation of a global clinical trial takes a lot of preparation time such as the creation of study protocols and responding to the regulatory requirements of each country. Additionally, child-specific considerations in conducting clinical trials are required. Therefore, to further reduce the approval lag for pediatric drugs, development plans for children should be considered with the knowledge of pediatric development in early stages of clinical development for adults in Japan, as is done in Europe and the US, for drugs meant for diseases which do not have a cure yet. In addition, for early involvement on global development for pediatric drugs, measures and systems for raising the awareness on pediatric development like in Europe and US would be worth considering.

5. Conclusion

The present study compared the current situation of pediatric drug approvals and their characteristics in Japan with those in Europe. We also analyzed the factors influencing the approval lag between Japan and Europe for the drugs that received pediatric indication. Our findings suggested that, owing mainly to the establishment of the Committee, pediatric development has indeed been promoted even in Japan, where no laws or regulations mandating pediatric development have yet been established. However, the period from adult to pediatric indication approval was longer in Japan than in Europe and the development of pediatric drugs for certain diseases has not been very active in Japan, indicating room for further improvement in the future.

This study also showed global clinical trial to be the most effective means of shortening the approval lag in pediatric drug development. In recent years, global development is becoming the mainstream for many adult diseases, thus creating an environment for proactive participation in global clinical trials even for pediatrics drugs. For further improvement in the pediatric drug lag, more active drug development for pediatric indications is required in tandem with the US and Europe.

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