Assessment of Drugs Approved by Public Knowledge-Based Applications (*Kouchi-shinsei*) During the Last Two Decades in Japan

Hideki Maeda[1,*], Yuka Fukuda[1] and Marika Uchida[1]

Public knowledge-based application ("*Kouchi-shinsei*" in Japanese) is unique to Japan, implemented to eliminate the off-label use of unapproved indications, dosages, and administrations because of drug lag. The guidance for public knowledge-based application was issued in 1999. This study comprehensively investigated the trends of items approved by public knowledge-based application in Japan during the last 2 decades. Prescription drugs approved from January 2000 to December 2019 were surveyed. In Japan, 1,855 drugs were approved within the target survey period. Among them, 219 (11.8%) were approved by public knowledge-based application. Considering the changes in the number of items approved by public knowledge-based application over the years, the number of items approved in 2000 was 7, reaching a maximum of 34 items in 2011, and decreased after that, 8 items were approved in 2019. The regulatory characteristics of drugs approved by public knowledge-based application and those of other drugs were compared. By public knowledge-based application, more anticancer and pediatric drugs were approved (*P* < 0.001), and only one drug for orphan diseases was approved (*P* < 0.001). In addition, the review time of public knowledge-based applications was significantly shorter than that of normal applications regardless of time point. The approval system using public knowledge-based application began in 2000, following issuance of the "Guidance for off-label use of prescription drugs." Furthermore, the approved items were mostly drugs for cancer, infectious diseases, and pediatric drugs. We anticipate the promotion of public knowledge-based application to accommodate the approval of drugs for orphan diseases.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Many drugs have been approved using public knowledge-based applications in Japan, but the details reported are limited due to the absence of a long-term comprehensive study on them. Moreover, the public knowledge-based application process itself is unique to Japan with little recognition overseas.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ This study comprehensively investigated the trends of items approved by public knowledge-based application against drug lag and off-label use in Japan during the last 2 decades.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ Many public knowledge-based applications exist for anticancer drugs, infectious diseases, and pediatric drugs, and very few public knowledge-based applications for orphan diseases.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ This study clarifies the details of the drugs approved in the last 20 years since public knowledge-based application was started in Japan and can suggest areas suitable for approval by public knowledge-based application in the future, trends, and similar drug approval methods in other countries where drug lag is an issue.

Prescription drugs are approved by regional regulatory agencies and should be properly used within the range of their approved indications, dosages, and administration methods.[1] However, in some countries, doctors may perform off-label use under their own responsibilities according to the condition of individual patients based on the evaluation of actual use overseas and in actual clinical practice and on clinical trials and pharmacological actions.[2,3] In Japan, off-label drug use is publicly recognized and covered by insurance under two occasions, namely (i) for drugs corresponding to the 1980 "Handling of prescription drugs in insurance medical care" guidance[4] and (ii) drugs determined as possible for public knowledge-based application by the Investigational Committee on Medically Necessary Unapproved Drugs and Off-Label Use Drugs.[5] The former are drugs for which the patent term has expired after a certain period following pharmaceutical approval, and regardless of whether there is scientific evidence for

the intended indications or dosages and administrations, in the case when they are unapproved in Japan, the off-label use of these drugs at the discretion of doctors is recognized. Meanwhile, for the latter, off-label use is determined as medically necessary at investigational meetings of the regulatory agency following requests for off-label use by related institutions and patient groups. This situation may arise when the drug has been approved or is in actual use in foreign countries with the same medical standards and approval system as Japan or when there are supporting clinical trials. As a result, they are recognized as publicly known medically and pharmaceutically, and because the application type of public knowledge-based application is generally recognized without any additional clinical trials, early approval is granted. In the case of public knowledge-based application, off-label use is publicly recognized until approval is granted by the investigational committee. In addition, when a drug is evaluated as not corresponding to public knowledge-based application, the regulatory agency encourages related industries to conduct clinical trials or draft development plans to acquire additional indications. Alternatively, when drug lag was serious in Japan,[6–9] the use of drugs outside their authorized indications as well as their dosages and administrations due to drug lag was sometimes problematic.[10] In fact, public knowledge-based application was initiated in 2000 to rectify off-label use and eliminate drug lag.[11] Public knowledge-based application is a type of supplemental new drug application (sNDA), which is unique to Japan.[12] Public knowledge-based application allows the approval of the use of drugs for unapproved indications without having to conduct the entire or part of a clinical trial again. Meanwhile, since 1979, clinical trial outcomes have been necessary for drug approvals in principle in Japan, and clinical trial outcomes for new drugs, additional indications, new routes of administration, and new dosages should be attached at the time of application.[13] Public knowledge-based application is not well-known overseas; however, after 2 decades since the start of the system, to date, many drugs have been approved using the system of public knowledge-based application in Japan. However, data on the process and details remain limited, and existing reports are only available in Japanese.[12,14] In addition, public knowledge-based application is an approval application system that is unique to Japan and, until this point, has been hardly implemented in other countries. Therefore, this study was conducted to retrospectively and comprehensively survey drugs approved by public knowledge-based application in Japan in the last 2 decades, examine the details, and investigate the trends. Then, by reviewing the results and clarifying the actual state of this system, this study examined how this system should exist in the future and found ways to expand its use globally.

MATERIALS AND METHODS

Data construction

In this study, prescription drugs approved in Japan from January 2000 to December 2019 were surveyed. Not only the initial NDAs (iNDAs) as new molecular entities but also sNDAs for additional indications were included in the survey. This study was prepared according to the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines[15] for cross-sectional studies.

Definition of public knowledge-based application

Regarding the definition of public knowledge-based application, items approved by public knowledge-based application were defined as items applied based on the "Guidance for off-label use of prescription drugs notified by two directors" (February 1, 1999),[16] those that underwent approval application or expedited review[17] based on the "Guidance for approval review of drugs pre-evaluated by the Pharmaceutical Affairs and Food Sanitation Council,"[5] and those that underwent approval application according to these standards. In addition, items with the description of "prescription drugs pertaining to off-label use" or "approval application based on pre-evaluation/expedited review based on pre-evaluation" in the column of Special Notes for Review in review reports[18] were also target items of public knowledge-based application.

Data collection and regulatory characteristics

Data were collected from publicly available databases in the Pharmaceuticals and Medical Devices Agency (PMDA) website (http://www.pmda.go.jp/english/index.html). When surveying, prescription drugs approved in Japan from January 2000 to December 2019 were first specified. Then, drugs approved by public knowledge-based application were identified. Last, survey items about the following drug background and regulatory characteristics of each drug were investigated, and an independent database was created. Information on application, application type (new/additional indication/additional dosage, etc.), disease classification, therapeutic indication classification, regulatory review field (PMDA Review Department), review time, indication, special notes for review (expedited review/priority review/pre-review, etc.) applicant (Japanese company/foreign company), type of clinical trial data, and the presence or absence of international joint trials and information on approval were obtained and analyzed. For pediatric drugs, package inserts[19] were investigated, and those with descriptions, such as "children" and "newborn," in the column of "dosage and administration" or "indication" were surveyed, whereas for drugs for orphan diseases—drugs that had undergone an orphan disease application[20]—were surveyed. In terms of the regulatory review field, classification was performed according to the regulatory review fields of PMDA[21]; in terms of therapeutic indication, classification was performed according to the Japan Standard Commodity Classification numbers[22]; and disease classification was performed according to the International Statistical Classification of Diseases and Related Health Problems (ICD) classification.[23] Evidence supporting public knowledge-based application was classified into three according to the "Guidance for off-label use of prescription drugs notified by two directors,"[16] namely, (i) items approved in developed foreign countries and information used in the approval application with foreign review agencies is available; (ii) those approved in developed foreign countries, which were described in reliable textbooks and guidelines; and (iii) those with reliable clinical trial results published in top journals.[16] If there was an overlap in the classification of individual drugs, the drugs were classified as "other evidence (combined evidence)."

Statistical analysis

We used descriptive statistics to characterize the new drugs and their indications. We used the χ^2 test for trend comparisons of regulatory characteristics between public knowledge-based application and other applications. All statistical tests were two-tailed, and P values of < 0.05 were used to denote statistical significance. All analyses were conducted using analytical tools of Microsoft Excel 2019.

RESULTS

Drugs surveyed

In Japan, 1,855 prescription drugs were approved from January 2000 to December 2019, and among them, 219 (11.8%) were approved by public knowledge-based application. Then, 663

drugs were approved as new molecular entities or iNDAs, and none of them was approved by public knowledge-based application, but by nonpublic knowledge-based application, that is, normal application. **Table 1** shows a list of approvals by public knowledge-based application and normal application. For public knowledge-based application, the most common application category was additional indications and dosage changes (114 items; 52.1%; $P < 0.001$).

Relationship between changes in the number of approvals over time, drug lag, and policies

Considering the changes in the number of items approved by public knowledge-based application over the years, the number of approved items in 2000 was 7, reaching a maximum of 34 items in 2011, and decreased after that; however, 8 items were approved in 2019 (**Figure 1**). The time and frequency of investigational meetings of the regulatory agencies for eliminating off-label use were added to the bottom of **Figure 1**. The investigational meetings of the Working Group on Anti-cancer Drug Combination Therapies were held 8 times from May 2004 to September 2005, and from January 2005 to October 2009, whereas those of the Investigational Committee for Usage of Unapproved Drugs were held 22 times. Since 2010, drugs requiring public knowledge-based application have been investigated at the Investigational Committee on Medically Necessary Unapproved Drugs and Off-Label Use Drugs, and 43 meetings had been held by December 2020.

Background of target drugs of public knowledge-based application and difference in background with normal items of nonpublic knowledge-based application

The backgrounds and regulatory characteristics of the targeted 219 public knowledge-based application items and 1,636 normal application (nonpublic knowledge-based application) items were investigated and compared. The results are shown in **Table 2**. In terms of drug background and regulatory characteristics, therapeutic indications, regulatory review fields, special notes for review, applicants (Japanese/foreign companies), types of clinical trial data, the presence or absence or international joint trials, pediatric drugs, and orphan drugs were investigated. Based on the results, for public knowledge-based application, more drugs for cancer and cardiovascular and infectious diseases, radiopharmaceuticals, and blood derivatives were approved in the regulatory review fields, whereas only a small number of drugs for central nervous system, respiratory, and metabolic diseases and acquired immune deficiency disease syndrome were approved. In terms of therapeutic indications, more drugs for cancer and infectious diseases were approved by public knowledge-based application, and significantly fewer blood derivatives, drugs for metabolic diseases, and narcotic drugs were approved by public knowledge-based application. In addition, pediatric drugs were significantly commonly approved by public knowledge-based application ($P < 0.001$), and only one drug for orphan diseases was approved by public knowledge-based application ($P < 0.001$). There were 330 items approved by normal application for drugs of orphan diseases, of which 173 items were iNDAs and 157 items were sNDAs. As for the data package regarding NDA for orphan drugs, 234 items were based on clinical trials conducted in foreign countries and 49 on domestic clinical trials. For public knowledge-based application, no new clinical trials were conducted for 171 of 219 items (78.1%), whereas some kind of clinical trial was conducted for 48 items (21.9%). Moreover, among the items approved by nonpublic knowledge-based applications, 27 items (1.7%) were without clinical trials. This breakdown did not use the application type of public knowledge-based application; however, these items were approved by applications based on treatise information and real-world data upon the requests of institutions or were specially approved for emergency use.

Table 1 Number of approvals by public knowledge-based and normal applications between 2000 and 2019 in Japan

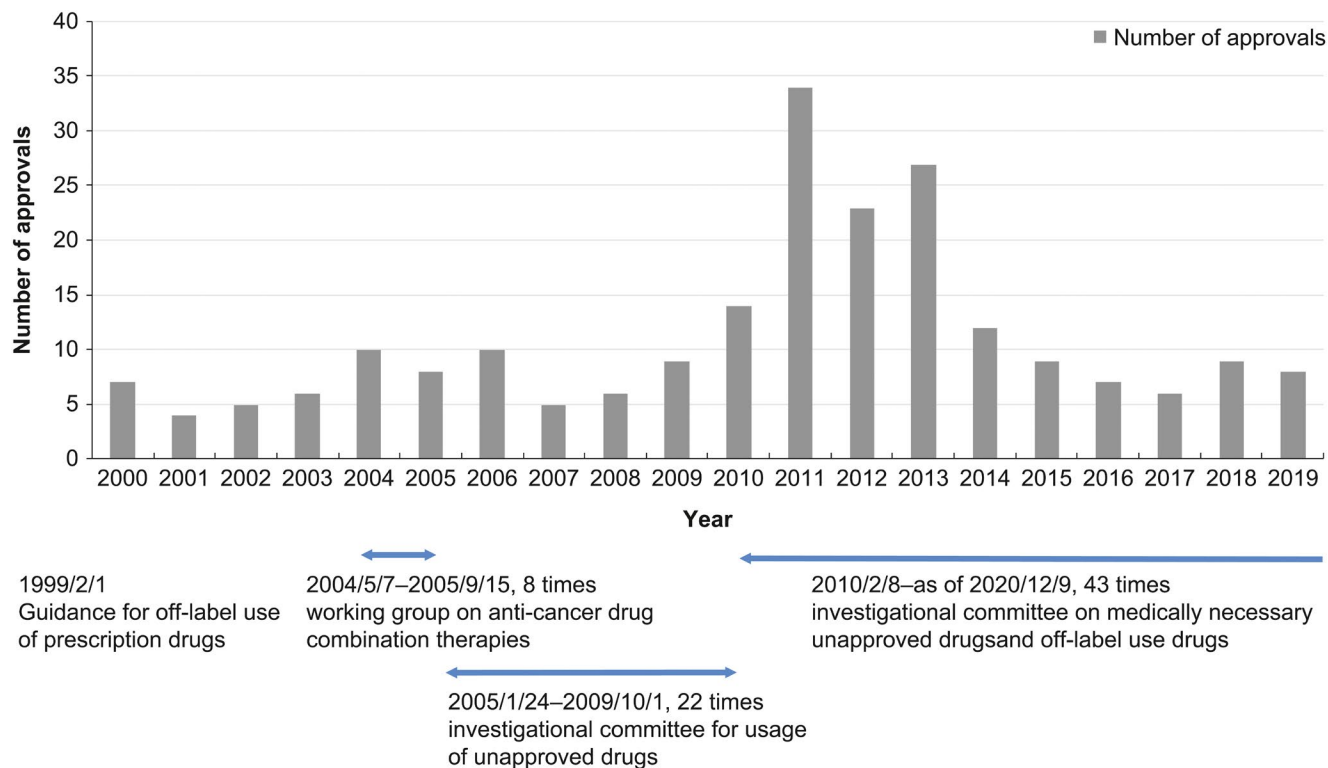|	Public knowledge-based applications	Normal applications	Total	P value (χ^2 test)
Number of approvals	219 (11.8%)	1,636 (88.2%)	1,855 (100.0%)	—
Initial NDA (new molecular entities)	0 (0%)	663 (40.5%)	663 (35.7%)	< 0.001
Supplemental NDA	219 (100%)	973 (59.5%)	1192 (64.3%)	
Type of supplemental NDA				
Additional indications	45 (20.5%)	207 (12.7%)	252 (13.6%)	0.138
Dosage changes	41 (18.7%)	120 (7.3%)	161 (8.7%)	0.017
Change in administrations	6 (2.7%)	73 (4.5%)	79 (4.3%)	0.494
Change in dosage form	0 (0%)	29 (1.8%)	29 (1.6%)	0.178
Fixed-dose combination	0 (0%)	69 (4.2%)	69 (3.7%)	0.038
Additional indications and dosage changes	114 (52.1%)	271 (16.6%)	385 (20.8%)	< 0.001
Dosage changes and change in dosage form	1 (0.46%)	40 (2.4%)	41 (2.2%)	0.248
Others	12 (5.5%)	164 (10.0%)	176 (9.5%)	0.234

NDA, new drug application.

Figure 1 Changes in numbers of approved drugs by public knowledge-based applications from 2000 to 2019 in Japan. [Colour figure can be viewed at wileyonlinelibrary.com]

Data supporting approval, evidence level, and approval countries

Data supporting approvals were divided into three groups: group 1 = approvals in other regions and application documents in foreign countries; group 2 = approvals in other regions, which are described in textbooks/guidelines; and group 3 = reliable results of clinical trials in top journals—and then investigated. Based on the results, group 2 supported the most approvals (141 drugs; 64.4%; **Table 3**). In addition, in terms of countries that had approved drugs at the time of public knowledge-based application in Japan, Europe had the most approvals (144 drugs; 65.8%), followed by the United States (109 drugs; 49.8%). Furthermore, 39 drugs (17.8%) had not been approved in other countries (**Table 4**).

Transition of review time

The transition of review time was examined (**Figure 2**). Recent review time of items approved by public knowledge-based application between 2015 and 2019 was, on average, 186.1 ± 84.7 days, which was significantly shorter than that of items approved by normal application (308.3 ± 103.1 days) ($P < 0.001$). In addition, the transition of changes every 5 years was examined, and the review times of items approved by both public knowledge-based and normal applications shortened over the years. Moreover, the review times approved by public knowledge-based and normal applications were compared every 5 years, and they were significantly shorter for items approved by public knowledge-based application than those for items approved by normal applications at all time points ($P < 0.001$).

DISCUSSION

Public knowledge-based application in Japan is not well-known internationally; few studies have focused on this topic; and no recent study results are available.[24,25] In addition, the target areas of surveys and the survey periods of previous studies are limited, and no other long-term comprehensive study exists. Moreover, the results of these studies were mostly published in Japanese.[12,14] In the only comprehensive study, Shimazawa *et al.* have comprehensively investigated 80 items approved by public knowledge-based application from 1999 to 2009 and reported that the number of approvals and applications per year showed no consistent trend. The variety and quantity of literature evidence provided in the application showed no consistent trend in terms of international approval status.[25] However, this study showed that the number of approvals by public knowledge-based application reached its peak in 2011. In addition, in this study, countries that had approved at the time of submitting public knowledge-based applications in Japan were investigated, and we found that 39 drugs had not been approved in any other countries and that there were drugs for which off-label use was approved overseas, including approvals based on results conforming with the Pediatric Written Request Letter of the United States. In terms of evidence used for public knowledge-based application, many items were approved with reliable evidence (**Table 3**).

In Japan, almost all drugs are reimbursed by insurance after receiving pharmaceutical approval[26]; however, this is not necessarily the same in other countries. For example, in the field of oncology, in the United States, the National Comprehensive Cancer Network frequently recommends beyond the US Food

Table 2 Therapeutic indication and regulatory characteristics of drugs approved by public knowledge-based and normal applications

	Public knowledge-based applications (n = 219)		Normal applications (n = 1,636)		
	n	%	n	%	P value
Regulatory review field					
Oncology	50	22.8	281	17.2	0.04
Field 1 (gastroenterology)	19	8.7	207	12.7	0.091
Field 2 (cardiovascular disease)	39	17.8	201	12.3	0.022
Field 3 (central nervous system)	17	7.8	204	12.5	0.044
Field 4 (infectious disease)	40	18.3	171	10.5	< 0.001
Field 5 (urology)	8	3.7	72	4.4	0.608
Field 6 (respiratory diseases, metabolic diseases)	19	8.7	333	20.4	< 0.001
Field of diagnostic drugs	5	2.3	27	1.7	0.499
Field of radiopharmaceuticals	5	2.3	7	0.4	0.001
Field of AIDS	0	0.0	33	2.0	0.034
Field of vaccines	2	0.9	20	1.2	0.691
Field of blood derivatives	15	6.8	33	2.0	< 0.001
Field of biologics	0	0.0	23	1.4	0.009
Therapeutic indication classification					
Central nerve system disease	20	9.1	225	13.8	0.058
Cardiovascular disease, hormone, gastroenterology	51	23.3	376	23.0	0.920
Blood derivatives, metabolic disease	25	11.4	299	18.3	0.012
Oncology, radiopharmaceuticals	56	25.6	325	19.9	0.05
Infectious disease	59	26.9	335	20.5	0.028
Topical use drugs	6	2.7	41	2.5	0.836
Narcotic drugs	2	0.9	26	1.6	0.441
Special notes for review					
Normal review	7	3.2	1221	74.6	< 0.001
Pre-evaluation	126	57.5	58	3.5	< 0.001
Expedited review/priority review	135	61.6	179	10.9	< 0.001
Other	0	0.0	14	0.9	0.169
Type of applicants					
Japanese companies	112	51.1	743	45.4	< 0.001
Foreign companies	75	34.2	841	51.4	
Combination	32	14.6	52	3.2	
Others					
Pediatric drugs	74	33.8	259	15.8	< 0.001
Orphan drugs	1	0.5	330	20.2	< 0.001
Applications without clinical trials	171	78.1	27	1.7	< 0.001

and Drug Administration (FDA)-approved indications even for newer, branded drugs.[27,28] In addition, even though unapproved in countries, such as the United States, off-label use of some drugs is practiced based on evidence.[29,30] During drug approval, some Asian countries, other than Japan, do not require new clinical trial outcomes if the drug has been approved in developed countries.[31,32] However, in Japan, clinical trial outcomes are required in principle. Japan has been a member of the International Council on Harmonization since its establishment, and the regulatory agency of Japan is capable of approving drugs.[33] However, Japan has also been troubled by the issue of "drug lag" in the past, and the regulatory approval procedure and regulatory agencies have implemented several countermeasures to eliminate this. In addition, the system of public knowledge-based application to rectify off-label use can be considered one of the countermeasures. In fact, as clarified in this study, the review time by

Table 3 Evidence type for supporting approval by public knowledge-based application

	Number	%	Chi-square test
Approvals in other regions and application documents in foreign countries	33	15.1	P < 0.001
Approvals in other region, which are described in textbooks/guidelines	141	64.4	
Reliable results of clinical trials in top journals	16	7.3	
Other evidence (combined evidence)	29	13.2	
Total	219	100	

regulatory agencies for item approved by public knowledge-based application is shorter than that for items approved by non-public knowledge-based application, and the average review time is also decreasing by year overall (**Figure 2**). The result that the review time for public knowledge-based applications has always been shorter than that for other items, which has become shorter over time can be inferred to have contributed to the elimination of drug lag. Here, we reviewed the initiatives of the regulatory agencies for off-label use of drugs in Japan. Initially, for off-label use due to drug lag, focus was put on anticancer drug combination therapies; the Working Group on Anti-cancer Drug Combination Therapies was organized by the Ministry of Health, Labour, and Welfare; and approvals by public knowledge-based application were promoted.[34] The next focused area is the pediatric area. The Council for Pediatric Pharmacotherapy of the Japanese Ministry of Health, Labour, and Welfare was held in 2006, and numerous conferences have subsequently been held promoting pediatric drug development in Japan.[34,35] In these conferences, the approval of additional dosages and administrations and indications for pediatric use by public knowledge-based application was promoted.[35] In Japan, incentive to the drug industry for pediatric drugs is little, and pediatric drug development is not legally supported in Japan, unlike in the United States and European countries.[36–38] Thus, the framework of public knowledge-based application should play an important role in pediatric drug development in the future. In addition, the name of the investigational committee of the Ministry of Health, Labour, and Welfare for the off-label use of drugs was changed to the Investigational Committee on Medically Necessary Unapproved Drugs and Off-Label Use Drugs in 2010, and the areas have been widely expanded, not only covering the target areas of anticancer and pediatric drugs but also performing development requests of off-label use of drugs and pre-evaluations of public knowledge-based applications.[39,40] In this study, approvals by public knowledge-based application reached their peak in 2011, which is assumed to be related to the investigational committee for off-label use by the regulatory agency (**Figure 1**). In addition, public knowledge-based application has been used for anticancer and pediatric drugs so far (**Table 2**), due to the

extensive unmet medical needs for serious diseases and the priority given to areas wherein knowledge on drugs for adult and other cancer types is available. The investigational committee for off-label use of drugs is estimated to have promoted public knowledge-based application. Moreover, drug lag has recently been eliminated in Japan,[41] and it is assumed that public knowledge-based application has been useful in eliminating drug lag.[6,7] Furthermore, although drug lag had previously been marked for anticancer drugs, it may occur for drugs for orphan diseases in the future.[42,43] Clearly, patient access to drugs for orphan diseases is a global issue.[44] Thus, in the future, when considering the direction of public knowledge-based application in Japan, we consider it necessary to apply this method of application to orphan diseases. As clarified in this study, almost no public knowledge-based application has been submitted for drugs for orphan diseases so far (**Table 2**). In terms of the development of orphan diseases, pharmaceutical companies around the world are reluctant to invest in orphan diseases because they are not commercially viable. For this reason, the governments of many countries prepare measures to support drug development for orphan diseases, but it has been reported that in Japan, pharmaceutical companies do not feel that Japan's economic incentives are of great benefit.[45,46] For instance, in the United States, approximately half of the drugs approved as new drugs are drugs for orphan diseases, whereas few drugs for orphan diseases exist in Japan, at only ~ 30% compared with that in the United States.[45] The number of patients in orphan diseases is limited, and it is difficult to collect enough cases to conduct clinical trials such as randomized controlled trials.[47] In particular, it is extremely difficult to conduct clinical trials in Japan alone.[46,48] In fact, in our investigation, of 330 items approved by normal application for drugs for orphan diseases during last 2 decades, 70.9% (234 items) were submitted NDAs using clinical trials data in foreign countries and only 14.8% (49 items) were submitted NDAs using data of domestic clinical trials. The implementation of clinical trials involving orphan diseases is difficult, and the approvals of drugs for orphan diseases are lesser in Japan than in the United States, so public knowledge-based application can be anticipated to become a useful approval procedure for drugs for orphan diseases in the future. Meanwhile, there are following limitations when considering the application of public knowledge-based application to orphan disease applications. First, the public knowledge-based application is a system for approving drugs that are approved overseas in Japan. Considering many orphan drugs are approved in the United States,[45] and > 70% of the drugs in

Table 4 Regions that have approved drugs at the time of application by public knowledge-based application in Japan

United States	Europe	Others	No country
109 (49.8%)	144 (65.8%)	69 (31.5%)	39 (17.8%)

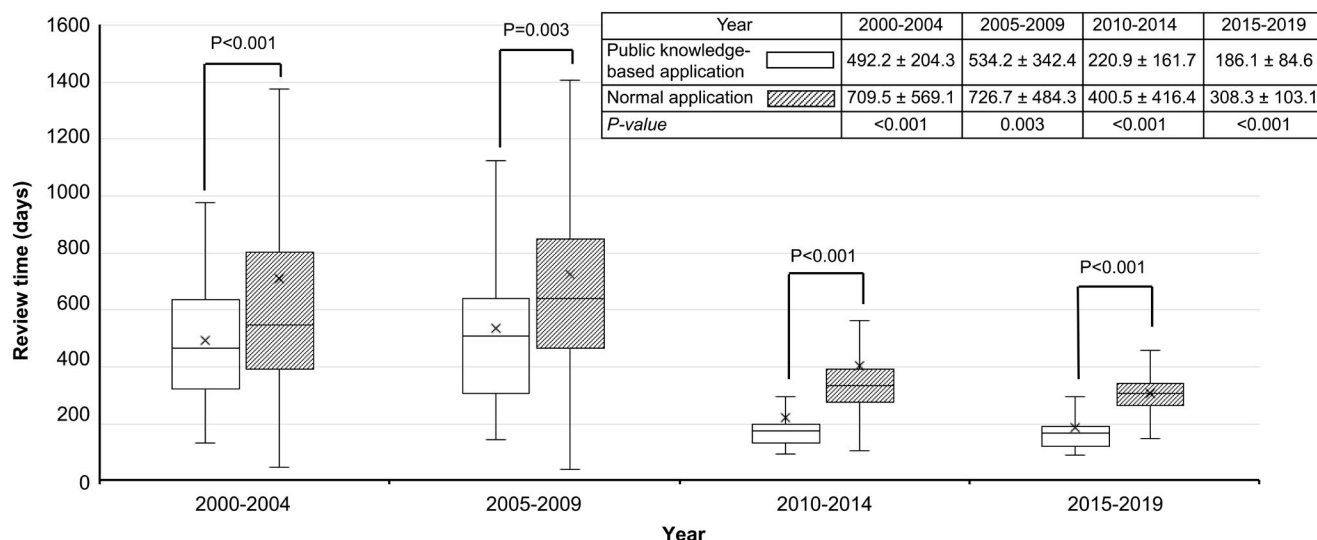| Year	2000-2004	2005-2009	2010-2014	2015-2019
Public knowledge-based application	492.2 ± 204.3	534.2 ± 342.4	220.9 ± 161.7	186.1 ± 84.6
Normal application	709.5 ± 569.1	726.7 ± 484.3	400.5 ± 416.4	308.3 ± 103.1
P-value	<0.001	0.003	<0.001	<0.001

Figure 2 Comparison of review time between public knowledge-based and normal applications (2000–2019).

our investigation of data for the past 20 years have been submitted using overseas data, we believe that it is worthwhile to apply the public knowledge-based application to rare diseases. Second, the level of evidence required for a public knowledge-based application is high. The guidance for public knowledge-based application is based on the requirements of data supporting approval, such as "described in textbooks/guidelines," "reliable results of clinical trials in top journals," or "application documents in foreign countries." It is reported that more than two randomized controlled trials were conducted for only 25% of the orphan drugs in NDA clinical data package in Japan.[46] Therefore, it is difficult to meet the above criteria for public knowledge-based application. Accordingly, when considering the application of orphan drugs to public knowledge-based applications, it may be necessary to review the requirement data supporting approval conditions to resolve issues of the level of evidence. In addition, it would be better to use of "application documents in foreign countries" as NDA data supporting approval efficiently. The last limitation is that public knowledge-based application is for sNDA. Indeed, public knowledge-based applications are not applicable to new molecular entities. For iNDA, global simultaneous developments may be useful for orphan diseases. In other words, one of the pros of public knowledge-based applications is that clinical trials can be waived, but one of the cons is that such drugs cannot be used for iNDA. We also believe that in countries where drug lag is an issue, it would be useful to adopt a system, such as public knowledge-based application that uses the results on approval and experience of the drugs of other countries. This study had the following limitations.

- It was a retrospective survey of published information, and was not a prospective study.
- Only approved drugs were targeted, whereas discontinued drugs and drugs that had not yet been approved were excluded.
- This study discusses public knowledge-based application from the perspective of improving patient access, and does not discuss economic aspects such as drug prices.

CONCLUSIONS

In conclusion, this was the first comprehensive study of public knowledge-based applications in Japan covering a long period of 20 years. In Japan, 1,855 drugs were approved during the study period, and among them, 219 (11.8%) were approved by public knowledge-based application, reaching a maximum number of approved items of 34 items in 2011. In 2019, a certain number of approvals by public knowledge-based application were also performed. In addition, the target areas of public knowledge-based application were mostly drugs for cancer and infectious diseases and pediatric drugs and few drugs for orphan diseases. Public knowledge-based application could be necessary as an approval system for anti-cancer and pediatric drugs in the future. Moreover, examining its utility value as a development method of drugs for orphan diseases in the future is necessary.

CONFLICTS OF INTEREST
The authors declared no competing interests to this work.

AUTHOR CONTRIBUTIONS
H.M. and Y.F. wrote the manuscript. H.M. and Y.F. designed the research. H.M., Y.F., and M.U. performed the research. H.M., Y.F., and M.U analyzed the data. H.M. contributed new reagents/analytical tools.

ETHICAL CONSIDERATIONS
This study did not require institutional review board approval or patient informed consent because it was based on publicly available information and involved no patient records.

1. Kessler, D.A. Approval of new drugs in the United States. *JAMA*. **276**, 1826 (1996). http://doi.org/10.1001/jama.1996.03540 220050030.
2. Fukuzawa, M., Inoue, M. & Tsutani, K. Status of off-label use of drug and its regulations in the US and Japan since late 1990s. *Pharm. Med. Dev. Regul. Sci.* **42**, 346–356 (2011).
3. Abernethy, A.P. *et al*. Systematic review: reliability of compendia methods for off-label oncology indications. *Ann. Intern. Med.* **150**, 336–343 (2009).
4. Ministry of Health and Welfare, Japan. Handling of prescription drugs in insurance medical care <https://www.ganjoho.org/knowledge/reference/55.pdf> (in Japanese) (1980). Accessed March 14, 2021.
5. Pharmaceuticals and Medical Devices Agency, Japan. Prescription drugs for reimbursement by health insurance coverage after review of pre-evaluation on public knowledge-based applications by Pharmaceutical Affairs and Food Sanitation Council during non-approved period in Japan <https://www.pmda.go.jp/review-services/drug-reviews/review-information/p-drugs/0017.html> (in Japanese). Accessed March 14, 2021.
6. Maeda, H. & Kurokawa, T. Recent trends for drug lag in clinical development of oncology drugs in Japan: does the oncology drug lag still exist in Japan? *Int. J. Clin. Oncol.* **20**, 1072–1080 (2015). http://doi.org/10.1007/s10147-015-0825-4.
7. Maeda, H. & Kurokawa, T. Regulatory review time for approval of oncology drugs in Japan between 2001 and 2014. Considerations of changes, factors that affect review time, and difference with the United States. *J. Clin. Pharmacol.* **55**, 481–489 (2015). http://doi.org/10.1002/jcph.458.
8. Tsuji, K. Approval of new biopharmaceuticals 1999–2006: comparison of the US, EU and Japan situations. *Eur. J. Pharm. Biopharm.* **68**, 496–502 (2008). http://doi.org/10.1016/j.ejpb.2007.07.013.
9. Ishibashi, T., Yasuda, K., Kusama, M., Sugiyama, Y. & Ono, S. Clinical development and review times for new drugs in Japan: associated factors. *Clin. Pharmacol. Ther.* **88**, 487–491 (2010).
10. Yonemori, K. *et al*. The notorious "drug lag" for oncology drugs in Japan. *Invest. New Drugs* **29**, 706–712 (2011). http://doi.org/10.1007/s10637-011-9638-0.
11. Ministry of Health Labour and Welfare, Japan. Investigational Committee on Medically Necessary Unapproved Drugs and Off-Label Use Drugs <https://www.mhlw.go.jp/stf/shingi/other-iyaku_128701.html> (in Japanese) (1999). Accessed March 14, 2021.
12. Ito, T., Urushihara, H., Matsushima, Y., Nakajima, K. & Kurokawa, T. Mode of regulatory applications of drugs used off-label reviewed by the evaluation committee on unapproved or off-labeled drugs with high medical needs. *Jpn. J. Clin. Pharmacol. Ther.* **46**, 233–241 (2015). http://doi.org/10.3999/jscpt.46.233.
13. Ministry of Health, Labour and Welfare, Japan. Application category and attached documents <https://www.pmda.go.jp/review-services/drug-reviews/about-reviews/otc/0001.html> (in Japanese) (2014). Accessed March 14, 2021.
14. Furukawa, I. & Narukawa, M. Analysis of the situation of new indication approvals base on "Kouchi-shinsei" and consideration of measures for its effective utilization. *Jpn. J. Clin. Pharmacol. Ther.* **45**, 59–62 (2014).
15. Vandenbroucke, J.P. *et al*. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Int. J. Surg.* **12**, 1500–1524 (2014). http://doi.org/10.1016/j.ijsu.2014.07.014.
16. Director of Research and Development Promotion and Director of Drug Safety Control Bureau, Ministry of Health and Welfare, Japan. Guidance for off-label use of prescription drugs <https://www.mhlw.go.jp/web/t_doc?dataId=00ta7596&dataType=1&pageNo=1> (in Japanese) (1999). Accessed March 14, 2021.
17. Pharmaceuticals and Medical Devices Agency, Japan. Consultation on the applicability of priority/expedited review and conditional early approvals for new drugs <https://www.pmda.go.jp/review-services/f2f-pre/consultations/0009.html> (in Japanese). Accessed March 14, 2021.
18. Pharmaceuticals and Medical Devices Agency, Japan. Review reports: Drugs <https://www.pmda.go.jp/english/review-services/reviews/approved-information/drugs/0001.html>. Accessed March 14, 2021.
19. Pharmaceuticals and Medical Devices Agency/Ministry of Health and Labour Welfare, Japan. Package insert notification system <https://www.pmda.go.jp/files/000197910.pdf>. Accessed March 14, 2021.
20. Ministry of Health, Labour and Welfare, Japan. Handling of designation of drugs for rare diseases <https://www.pmda.go.jp/files/000236893.pdf> (in Japanese) (2020). Accessed March 14, 2021.
21. Pharmaceuticals and Medical Devices Agency, Japan. Department of PMDA in charge of new drugs, medical devices and regenerative medicine products <https://www.pmda.go.jp/files/000205048.pdf> (in Japanese). (2020). Accessed March 14, 2021.
22. Ministry of Internal Affairs and Communications, Japan. Significance of the Japan Standard Commodity Classification (revised in June 1990), revision policy and outline <https://www.soumu.go.jp/toukei_toukatsu/index/seido/syouhin/gaiyou.htm> (in Japanese) (2020). Accessed March 14, 2021.
23. World Health Organization. International Statistical Classification of Diseases and Related Health Problems (ICD) <https://www.who.int/classifications/classification-of-diseases>. Accessed March 14, 2021.
24. Ito, Y., Narimatsu, H., Fukui, T., Fukao, A. & Yoshioka, T. Critical review of 'Public domain application': a flexible drug approval system in Japan. *Jpn. Oncol.* **24**, 1297–1305 (2013).
25. Shimazawa, R. & Ikeda, M. Japanese regulatory system for approval of off-label drug use: evaluation of safety and effectiveness in literature-based applications. *Clin. Ther.* **34**, 2104–2116 (2012).
26. Reich, M.R. & Shibuya, K. The future of Japan's health system — Sustaining good health with equity at low cost. *N. Engl. J. Med.* **373**, 1793–1797 (2015). http://doi.org/10.1056/nejmp1410676.
27. Wagner, J. *et al*. Frequency and level of evidence used in recommendations by the National Comprehensive Cancer Network guidelines beyond approvals of the US Food and Drug Administration: retrospective observational study. *BMJ* **k668** (2018). http://doi.org/10.1136/bmj.k668.
28. Kurzrock, R. *et al*. Level of evidence used in recommendations by the National Comprehensive Cancer Network (NCCN) guidelines beyond Food and Drug Administration approvals. *Ann. Oncol.* **30**, 1647–1652 (2019).
29. Levêque, D. Off-label use of anticancer drugs. *Lancet. Oncol.* **9**, 1102–1107 (2008). http://doi.org/10.1016/s1470-2045(08)70280-8.
30. Bolislis, W.A. *et al*. Orphan medicines for pediatric use: a focus on the European Union. *Clin. Ther.* **41**, 2630–2642 (2019).
31. Venkatakrishnan, K. *et al*. Toward optimum benefit-risk and reduced access lag for cancer drugs in Asia: a global development framework guided by clinical pharmacology principles. *Clin. Transl. Sci.* **9**, 9–22 (2016).
32. Lee, S.-W. *et al*. Notable differences in drug lag between Korea and Japan of new drugs between 2009 and 2017. *Ther. Innov. Regul. Sci.* **54**, 418–423 (2020). http://doi.org/10.1007/s43441-019-00071-9.
33. Han, F.V. & Weiss, K. Regulatory trends in drug development in Asia Pacific. *Ther. Innov. Regul. Sci.* **53**, 497–501 (2019). http://doi.org/10.1177/2168479018791539.
34. Pharmaceuticals and Medical Devices Agency, Japan. Meeting materials for Working Group on Anti-cancer Combination Therapies <https://www.mhlw.go.jp/stf/shingi/other-iyaku_128731.html> (in Japanese) (2005). Accessed March 14, 2021.
35. Pharmaceuticals and Medical Devices Agency, Japan. Meeting materials for Investigational Committee on Pediatric Drug Therapies <https://www.mhlw.go.jp/stf/shingi/other-iyaku_128694.html> (in Japanese) (2009). Accessed March 14, 2021.
36. Saitou, H., Nakatani, D., Myoui, A., Kubota, T. & Ozono, K. Pediatric drug development in Japan: current issues and perspectives. *Clin. Pediatr. Endocrinol.* **29**, 1–7 (2020).

37. Ueyama, E., Kaneko, M. & Narukawa, M. Analysis of pediatric drug approval lag in Japan. *Ther. Innov. Regul. Sci.* **55**, 336–345 (2020).

38. Hirota, S. & Yamaguchi, T. Timing of pediatric drug approval and clinical evidence submitted to regulatory authorities: International comparison among Japan, the United States, and the European Union. *Clin. Pharmacol. Ther.* **108**(5), 985–994 (2020). http://doi.org/10.1002/cpt.1757.

39. Pharmaceuticals and Medical Devices Agency, Japan. The pharmaceuticals and medical devices agency annual report FY2009 <https://www.pmda.go.jp/files/000152147.pdf> (2010). Accessed March 14, 2021.

40. Sakiyama, M. Current research situation and challenges of pediatric clinical studies in Japan <https://www.pmda.go.jp/files/000153085.pdf> (2013). Accessed March 14, 2021.

41. Fujiwara, Y. & Ono, S. Regulatory review of new therapeutic agents. *N. Engl. J. Med.* **376**, 2598 (2017). http://doi.org/10.1056/nejmc1705868.

42. Murakami, M. & Narukawa, M. Matched analysis on orphan drug designations and approvals: cross regional analysis in the United States, the European Union, and Japan. *Drug Discov. Today* **21**, 544–549 (2016). http://doi.org/10.1016/j.drudis.2016.02.016.

43. Nakayama, H., Matsumaru, N. & Tsukamoto, K. The drug lag and associated factors for orphan anticancer drugs in Japan compared to the United States. *Invest. New Drugs* **37**, 1086–1093 (2019). http://doi.org/10.1007/s10637-018-0612-y.

44. Fonseca, D.A., Amaral, I., Pinto, A.C. & Cotrim, M.D. Orphan drugs: major development challenges at the clinical stage. *Drug Discov. Today* **24**, 867–872 (2019). http://doi.org/10.1016/j.drudis.2019.01.005.

45. Office of Pharmaceutical Industry Research, Japan Pharmaceutical Manufacturers Association. Development trend of orphan drugs. Analysis of the development status of orphan drugs approved by the FDA in Japan. <http://www.jpma.or.jp/opir/news/059/pdf/no59_p19.pdf> (2020). Accessed March 14, 2021.

46. Maeda, K., Kaneko, M., Narukawa, M. & Arato, T. Points to consider: efficacy and safety evaluations in the clinical development of ultra-orphan drugs. *Orphanet. J. Rare Dis.* 23;**12**, (2017). http://doi.org/10.1186/s13023-017-0690-5.

47. Field, M.J. & Boat, T.F. *Rare Diseases and Orphan Products: Accelerating Research and Development*. (National Academies Press, Washington, DC, 2010). <https://pubmed.ncbi.nlm.nih.gov/21796826/>.

48. Mizoguchi, H., Yamanaka, T. & Kano, S. Research and drug development activities in rare diseases: differences between Japan and Europe regarding influence of prevalence. *Drug Discov. Today* **21**, 1681–1689 (2016). http://doi.org/10.1016/j.drudis.2016.06.014.