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What Factors Lead to Prolonged Regulatory Review Times for New Drugs in Japan?

Shigetomo Yoneda[1], **Ryuta Asada**[1,2,3*], **Shinobu Shimizu**[4], **Shunsuke Ono**[5] **and Takuhiro Yamaguchi**[1]

[1]*Department of Biostatistics, Tohoku University Graduate School of Medicine, Sendai, Japan*

[2]*Innovative and Clinical Research Promotion Center, Gifu University Hospital, Gifu, Japan*

[3]*Clinical Research Center, National Hospital Organization Nagoya Medical Center, Japan*

[4]*Center for Advanced Medicine and Clinical Research, Nagoya University Hospital, Nagoya, Japan*

[5]*Laboratory of Pharmaceutical Regulatory Science, Graduate School of Pharmaceutical Sciences, University of Tokyo, Tokyo, Japan*

[*]**Corresponding author:** Ryuta Asada, 1-1 Yanagido, Gifu City, 501-1194 Japan, Tel: 81-58-230-6650; Fax: 81-58-230-6651; E-mail: rasada@gifu-u.ac.jp

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Abstract

Objective: Among all the new drugs approved in Japan, the regulatory review time for some greatly exceeds the median each year. However, to our knowledge, no reports have detailed why the review times were prolonged in these instances. In this study, we examined new applications (NDAs) whose review times were more than twice as long as the median each year in order to pinpoint the cause of delayed approval.

Methods: We analyzed 564 NDAs that were approved in Japan between 2005 and 2011.

Results: Thirty-eight NDAs were found to have prolonged review times. Of the 38 NDAs, the most popular therapeutic categories were oncology drugs and vaccines, and 28 of the drugs had already been approved in foreign countries when approval was granted in Japan, some with lag times of more than 36 months. This observation suggests that prolonged regulatory review time further worsens lags in drug approval. "Problem related to clinical data" was cited as the most common reason for prolonged review time. For most of the NDAs categorized into this group, additional clinical trials were conducted during the same review time without NDA withdrawal because the clinical study design was inappropriate, a deficiency in the evidence of a dosage regimen was observed, or efficacy was not confirmed in a confirmatory study trial.

Conclusion: Our analyses of these trial details indicate the importance of determining the optimal dosage regimen carefully and utilizing objective endpoints in clinical trials.

Keywords: Regulatory review; Drug development; Clinical trial; Drug lag; New drug applications; Regulatory review times; Access gap

Objective

In Japan, approval of a new drug abroad that is not approved for use in Japan has become a major issue [1-8]. This problem has been termed drug lag, and its direct cause includes delays in the start of clinical development, the progress of clinical trials, and in the regulatory review. In order to minimize these delays, the Japanese regulatory authorities, the Ministry of Health, Labour and Welfare (MHLW), and the Pharmaceuticals and Medical Devices Agency (PMDA), have conducted several projects [9]. As a result, the PMDA has shortened the average review time to a length that is comparable to what was observed in the United States (US) in 2011 [10]. However, the review time of each new drug varied from 1 to 192 months, and for some new drugs, the review time largely exceeded the median review time each year. It is important to reduce the number of these drugs in order to eliminate an access gap of new drugs.

To date, several studies have compared the review times in Japan to those in the US or Europe Union (EU), or investigated the relationship between review times, components of new drug applications (NDAs), regulatory agencies, and features of pharmaceutical companies in Japan [2,3,5,6,8]. However, to our knowledge, no studies have focused on new drugs that had exceptionally prolonged review times or closely examined the reasons for the prolonged review times in these cases.

In this study, we investigated all the NDAs approved in Japan between 2005 and 2011 on the basis of their review reports and summaries of registration documents, which could be accessed from the official PMDA website. Of all the NDAs, we focused on those for which the review time was more than twice as long as the median review time each year.

The purpose of this study was to analyze the information about these drugs in detail and to identify considerations during some stages of drug development or regulatory review that may contribute to delayed approval.

Methods

We gathered information about 630 NDAs approved in Japan between January 2005 and December 2011 from the official PMDA and MHLW websites. For 2 of the 630 NDAs, special approval was granted in response to a state emergency caused by a new strain of influenza. For 10 of the NDAs, prior assessment was performed before

the NDA because they were anti-HIV agents. For 54 of the NDAs, prior assessment before the NDA was performed in the council for pediatric pharmacotherapy or for combination anti-cancer agent therapy at the Japanese MHLW. Therefore, for these 66 NDAs, the review times were extremely short; hence, we removed them from the research targets and examined the other 564 NDAs.

We calculated the review time of each NDA from the date of application to approval. For standard review and priority review products, we picked the NDAs for which the review time was more than twice as long as the median review time each year.

For these NDAs, we checked the status of overseas approval, drug lag period, therapeutic category, and reasons why the review times were long. We categorized the reasons into 5 groups: "submission of additional data related to chemistry, manufacturing, and control (CMC)," "submission of additional non-clinical data," "problem related to clinical data," "revision of submitted documents," and "unknown."

Further, we checked if additional clinical trials were performed during the same review time for the NDAs classified under the category of "Problem related to clinical data" and examined the characteristics of these NDAs in detail.

Results

Selecting the NDAs of interest

The number of NDAs approved in Japan between 2005 and 2011 and the median review times are shown in Table 1. For 39 of the 564 NDAs, the review time was over twice the median each year. We excluded Liovel combination tablets (Alogliptin benzoate/Pioglitazone hydrochloride) because the time to reach market approval was obtained after the PMDA's review was completed.

	Overall				Over twice as long	
	Standard review		Priority review		Standard	Priority
	N	Time (months)	N	Time (months)	N	N
2005	33	24	12	23.5	3	0
2006	58	26	12	14.5	6	3
2007	59	22	21	15	8	2
2008	47	21	27	15	2	1
2009	81	19	12	15.5	3	0
2010	90	17	13	11	2	2
2011	84	11.5	15	9	7	0
	452		112		31	8

Table 1: Median review time and number of NDAs approved in Japan for which the review time was long.

Therapeutic category	Number of total NDAs in the target therapeutic category (%)	Number of NDAs for which the review time was over twice the median time (%)	Ratio of NDAs for which the review time was over twice that of the total NDAs in the target therapeutic category
Oncology drugs	78 (13.8)	5 (13.2)	6.4% (5/78)
Vaccines	9 (1.5)	5 (13.2)	55.6% (5/9)
Central nervous system drugs	36 (6.4)	4 (10.5)	11.1% (4/36)
Blood products	13 (2.1)	4 (10.5)	30.8% (4/13)
Sensory organ drugs (excluding drugs for inflammatory diseases)	31 (5.5)	4 (10.5)	12.9% (4/31)
Cardiovascular drugs	35 (6.2)	3 (7.9)	8.6% (3/35)
In vivo diagnostics	15 (2.4)	3 (7.9)	20.0% (3/15)
Other	347 (61.5)	10 (26.3)	2.9% (10/347)
Total	564 (100.0)	38 (100)	6.7% (38/564)

Table 2: Therapeutic categories for NDAs.

Therefore, we examined the 38 NDAs (standard review products: 30, priority review products: 8) in detail.

The therapeutic categories for the 38 NDAs are shown in Table 2. Oncology drugs and vaccines were the most common, followed by central nervous system agents, blood products, and sensory organ drugs (excluding drugs for inflammatory diseases). For vaccines, blood products, and *in vivo* diagnostics, the ratios of the NDAs for which the review time was prolonged to the total NDAs of the target therapeutic category were 55.6%, 30.8%, and 20.0%, respectively, which were higher than that of other therapeutic categories.

Current situation of drug lag for NDAs for which the review time was prolonged

We examined the approval situations of the 38 NDAs in the US, Canada, and EU when the NDAs were approved in Japan. The duration of drug lag was calculated as the difference between the approval date in Japan and the US, Canada, or EU for the same indication. The 10 NDAs described below were excluded because it was difficult to calculate the drug lag:

- 2 NDAs: The category of application was a new additional dosage
- 1 NDA: The category of application was a new additional form
- 1 NDA: Indicated for use in patch tests
- 4 Vaccines: The same active ingredient had been approved in Japan
- 2 NDAs: Public knowledge-based application

Therefore, we examined 28 NDAs in detail. The approval condition in foreign countries and the duration of drug lag for these NDAs were compared to 409 NDAs, which excluded 155 of them from the 564 in a similar way as above. These results are shown in Table 3.

	Approval in foreign countries: No	Approval in foreign countries: Yes				
		Drug lag (months)				
Total		36<	36<, ≤ 60	60<, ≤ 120	120<, ≤ 180	≤ 180
28 (100)	6 (21.4)	0	3 (10.7)	6 (21.4)	8 (28.6)	5 (17.9)
409 (100)	101 (24.7)	66 (16.1)	59 (14.4)	106 (25.9)	52 (12.7)	25 (6.1)

Table 3: Approval condition in foreign countries and the duration of drug lag for 28 NDAs.

The proportion of NDAs that were not approved in foreign countries was similar. (21.4% vs. 24.7%) For the NDAs that had much longer review times, the proportion for which the duration of drug lag was more than 120 and within 180 months or more than 180 months was higher than that of total the NDAs. (28.6% and 17.9% vs. 12.7% and 6.1%, respectively) These results suggest that the drug lag of the NDAs for which the review time was prolonged were long. However, evaluating drug lag in terms of duration alone is inappropriate because it is affected by various factors, such as differences in the number of patients between Japan and other countries. Therefore, this study was limited by the fact that it was impossible to include other factors.

Factors related to prolonged review time

The 38 NDAs for which the review time was over twice as long as the median review time each year were classified into 5 groups, according to the reasons why the review time was long. These results are shown in Table 4. We attributed the prolongation of review time to one factor. However, for Cetrorelix acetate, we came up with 2 factors because it was difficult to choose a main factor for the following reason: It was necessary to correct the submitted data because the study was found to deviate greatly from the protocol upon the PMDA's GCP on-site inspection. In addition, reproductive and developmental toxicity studies were conducted after the application was submitted.

Factor	Number of NDAs
Submission of additional data related to chemistry, manufacturing and control (CMC)	4 (10.3)
Submission of additional non-clinical data	1 (2.6)
Problem related to clinical data	24 (61.5)
Completion of an additional clinical trial	16 (41.0)
Correction of submitted data	5 (12.8)
Unknown	5 (12.8)
Total	39 (100)

Table 4: Classification of the factors contributing to a prolonged review time.

For the 5 NDAs categorized into the "correction of submitted data" group, the reason for the prolonged review time was mostly due to the poor quality of applicant's correspondences, such as the presence of errors and unclear statements in submitted documents and delayed replies to the PMDA's questions.

Among the 24 NDAs categorized into the "problem related to clinical data" group, 16 of them were also categorized into the "completion of additional clinical trials" group, to examine in detail the reasons why PMDA required additional clinical trials. In the other 8 drugs, the review times were prolonged for the following reasons:

- Situations of approval and regulatory review in foreign countries
- The incidence of serious adverse events in foreign countries
- Unclear efficacy for the same indication in adults as for infants at the time of application
- Corrections in submitted documents and secondary analysis of submitted data
- Inappropriate correspondence with the applicant
- Insufficient consensus about the disease concept among experts in Japan at the time of application

Reasons for classifying drugs requiring additional clinical study

Of 16 NDAs, Epoetin Beta (genetical recombination) and Letrozole were counted as 2 NDAs because the regulatory agencies required that additional clinical trials be conducted twice and the applicants were implementing the trials. Sertraline hydrochloride was also counted as 2 NDAs because additional double-blind clinical trials were conducted for depression and panic disorder. Therefore, we closely examined the 19 NDAs.

The detailed reasons for classifying drugs requiring additional clinical study are shown in Table 5. We further examined the group "the clinical study design was inappropriate" and "deficiency in the evidence of a dosage regimen" in detail. For the 7 NDAs categorized into the "The clinical study design was inappropriate" group, the endpoints, inclusion/exclusion criteria, dosage and administration, and dose of concomitant/previous medication were inappropriate. These results indicate that it is necessary to carefully determine the endpoint and inclusion/exclusion criteria when a clinical study is planned.

Causes	Number (%)
The clinical study design was inappropriate	7 (31.8)
Deficiency in the evidence of a dosage regimen	6 (27.3)
Efficacy was not confirmed in a confirmatory study	4 (18.2)
The clinical data package was inappropriate	3 (13.6)
The reliability of the data in the clinical study was not ensured	2 (9.1)
Total	22 (100)

Table 5: Detailed reasons for classifying drugs requiring additional clinical study.

The details of NDAs classified under the "deficiency in the evidence of a dosage regimen" group were as follows. For Letrozole, the PMDA required additional clinical trials to be conducted twice because there was lack of evidence for a dosage regimen. In the first situation, PMDA required the use of a 2.5 mg dose in a Japanese trial because the efficacy of 2.5 mg was indicated in a few confirmatory trials in foreign countries. Therefore, the applicant conducted the unblended trail to evaluate the efficacy of 2.5 mg Letrozole. However, in the second situation, the PMDA judged the Japanese data at 2.5 mg to be insufficient because the sample size was small.

For two freeze-dried, cell culture-derived Japanese encephalitis vaccines in Phase 3 trials, the only dose referenced in the approved vaccine was analyzed without examination of an optimal dosage. Therefore, additional clinical trials were performed to examine the dose response at lower doses.

For sertraline hydrochloride and Zonisamide, the trials establishing dosage were conducted, but the former did not indicate efficacy in a confirmatory trial using the determined dosage from the trial, and the latter drug did not indicate the dose response.

For 3 of the 4 NDAs categorized into the "efficacy was not confirmed in a confirmatory study" group, the examination dose in Phase 3 trials was low. Therefore, the dose in additional clinical studies was higher than before.

These results reveal the importance of dose-finding studies when a development strategy is established, and the necessity of determining the dosage group and examination dose carefully when a clinical study is planned. In the descriptive study [11] on failed clinical development cases, it also reports the importance of carefully determining the optimal dosage regimen.

Conclusion

Vaccines, blood products, and diagnostics have been found to be the most common NDAs with prolonged regulatory review times. For NDAs with prolonged regulatory review times, the length of drug lag was also prolonged, and this time tends to worsen the drug lag further.

Many drugs showed long regulatory review times because of "Problem[s] related to clinical data" that occurred during the process of regulatory review. The most common factor was that additional clinical studies had to be conducted.

Detailed investigation of the reasons why the PMDA judged that NDAs require additional clinical studies revealed the importance of clinical study design and evidence of dosage and administration.

Although the regulatory review time in Japan has been reduced recently [10], applicants should consider these factors as critical to ensuring a smooth drug development process, so that patients can gain

access to new drugs as soon as possible. To avoid a prolonged regulatory review time, it is important to consult with the PMDA about the construction of a clinical data package, the design of a clinical study, evidence of dosage and administration, endpoint determination, choice of subjects, and examination dose.

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