

Is the total review time of new medical devices related to the size of the company?: Medical devices development and its related factors in Japan

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Abstract

Japan has one of the largest medical device markets in the world, but most devices used in Japan are pioneered by foreign medical device companies. On the other hand, medical device companies in Japan have significant potential to develop innovative medical devices. Through this research, we aim to elucidate the factors related to the total review time of new medical devices so that innovative medical devices would be developed sooner. Using the lists of approved medical devices disclosed by the Pharmaceuticals and Medical Devices Agency (PMDA), we chose all the new medical devices that were approved in Japan between Fiscal Year (FY) 2009 and 2015. We conducted two main types of analyses based on the total review time after submission and sales of the companies. The total review time tends to decrease with “Year of approval by the PMDA” in FY 2009 to 2015 ($p < 0.001$). Moreover, the total review time of small and medium-sized companies is greater than that of large companies ($p = 0.004$). In conclusion, the total review time of new medical devices in Japan appears to be related to the following two factors: (1) year of approval, and (2) size of the enterprise.

Keywords: medical device, device development, PMDA, Japan

Author’s Note: All of the abbreviations in this article are names of variables in the dataset. Detailed definitions of the variables are provided in Table 1.

1. Introduction

Japan has one of the largest medical device markets in the world, but most devices used in Japan are pioneered by foreign medical device companies. In 2014, the country’s imports amounted to 1,369 billion yen, whereas exports only amounted to 572 billion yen [2]. It is especially noticeable that the imports exceed the exports in the area of therapeutic devices [6, 8]. Moreover, medical device companies in the United States have strong development power, not only in the area of therapeutic devices, but also in that of diagnostic devices [13]. On the other hand, it can be said that Japan is one of the most developed countries in the world in regards to science and technology, and that it exports high quality engineering products and precision instruments. Therefore, it is natural to assume that medical device companies in Japan have significant potential to develop innovative medical devices.

Nakano et al. defined and measured “device lag”, reporting the review time of 30 cases of new innovative medical devices in the United States and Japan between April 2001 and March 2008 [9]. The authors also found that the lag of review time

between the United States and Japan was 1.70 years, and that the lag of filing between the United States and Japan was 2.42 years. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan have enacted many policy changes recently to promote patient access to innovative medical devices; thus, it is reported that the device lag is relatively improved. Ikeno et al. pointed out that the MHLW and PDMA’s review time for new innovative medical devices has been improving each year, with an average review time of 9.5 months [3]. The total time from the PMDA filing to introduction of the device to patients in Japan was found to be similar to that of the United States and four European countries: Germany, France, Italy, and the United Kingdom.

Medical devices are generally developed based on unmet needs in the medical field, rather than in the laboratory, and generally have shorter lifecycles and more heavily depend on the user’s technique and/or adaptation, when compared with pharmaceutical drugs [13]. In addition, most companies are small and medium-sized enterprises (SMEs), which have remarkably small development budgets compared to the large pharmaceut-

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Variable	Short Name	Description
Approved Year	AppYear	Year of medical device approval
Product Name	ProductNM	Name of medical device
Company Name	CompanyNM	Name of company that developed medical device
Total Review Time (Days)	TotalRevTime	Total review time is the time that the authority and company took to review the medical device from submission to approval. These data are captured from the PMDA List of Approved Products (New & Improved Medical Devices). [10]
Category of Pivotal Study	StudyCateg	The category of the pivotal study in the submission package to the PMDA, such as A: foreign study only, B: foreign and domestic study, C: no clinical study was conducted, D: domestic study only, and E: international clinical trial.
Global Harmonization Task Force (GHTF) Classification [13]	Class	GHTF Classification is a series of rules that allow a medical device to be assigned to one of four classes based on its intended use. Class A: low hazard (e.g., bandages/tongue depressors); class B: low-moderate hazard (e.g., hypodermic needles/suction equipment); class C: moderate-high hazard (e.g., lung ventilator/bone fixation plate); and class D: high hazard (e.g., heart valves/implantable defibrillator). GHTF has been replaced by the International Medical Device Regulators Forum.
Number of Approved Devices	AppDevices	The number of approved devices in the company from FY 2009 to 2015, counted based on the PMDA List of Approved Products.[11] For example, when two devices were developed by company A in FY 2009 to 2015, both of these devices were given values of “1-3.” Therefore, “1-3” represents that a group of devices was developed by companies that developed 1-3 devices from FY 2009 to 2015. The other two categories, “4-6” and “7-,” represent companies in the same manner.
Device Category	DeviceCateg	The devices are divided into ‘therapeutic and surgical devices’, ‘diagnostic devices’ and ‘others’ according to the categorization by Kakudo [5]. Other devices include ‘Ophthalmic goods and related product’, ‘Dental material’, ‘Medical apparatus for home use’, ‘Dental equipment’ and ‘Surgical dressing and hygienic product’. There is no diagnostic device in the new medical devices from 2009 - 2015.
Company Sales (Mil. Yen)	Sales	These data are the sales of the company that developed the medical devices. In case that one company gets approval for more than two medical devices from FY 2009 to 2015, the latest sales of the company were selected from Teikoku Databank.
Foreign or Domestic Companies	ForeignDomestic	Companies are divided into ‘foreign companies’ and ‘domestic companies’.
Binary Review Time	BinRevTime	Binary Review Time is derived data divided into short (0) and long (1) review time based on the median of Total Review Time.
Binary Sales	BinSales	Binary Sales is derived data divided into small (0) and large (1) enterprises based on the median of Sales.

Table 1: Definitions of database variables.

ical drug companies. Often, SMEs of medical devices do not have development divisions, which may lead to insufficient scientific discussion with authorities and to a longer review time prior to approval. Even if innovative devices were originated in Japan, many may have been spoilt before approval or even filing [8]. In this situation, innovative medical devices cannot be efficiently brought to patients.

We posed the research question, “what factors are related to the efficient development of new medical devices in Japan?” For the first step in addressing this question, we focused on total review time by the MHLW and PMDA for new medical devices. This study was carried out to elucidate the factors related to the total review time of new medical devices so that innovative medical devices could be developed sooner. The result of this study will contribute to the more efficient development infrastructure for innovative medical devices.

2. Materials and Methods

2.1. Identification of Target Medical Devices

Using the lists of approved medical devices disclosed by the PMDA, we chose all the new medical devices that were approved in Japan between FY 2009 and 2015. The following new medical devices were excluded: (1) devices of partial changes, because this research focused on new medical devices; (2) appurtenant devices of the main device, because we needed to avoid double-counting for those devices which are used with the main device and are reviewed at the same time; (3) devices developed by conglomerate companies, because their businesses are not concerned solely with medical devices, which may affect the analysis related to company size; and (4) devices of the same product but with a different brand name, because we needed to avoid duplication of data due to identical devices.

2.2. Variables and Source of Original Database

In this research, we developed an original database of the new medical devices approved between FY 2009 and 2015. The database has twelve variables. The data on the following six variables were collected from the List of Approved Products (New & Improved Medical Devices) by the PMDA: Approved Year (AppYear), Product Name (ProductNM), Company Name (CompanyNM), Total Review Time (TotalRevTime), Category of Pivotal Study (StudyCateg), and Number of the Approved Devices in the Company in the Period (AppDevices) [11]. The Global Harmonization Task Force (GHTF) Classification [5] (Class) for each device was investigated based on the classification on the List of Approved Products (New & Improved Medical Devices) [11] by the PMDA. The GHTF was an organization conceived in 1992 in an effort to achieve greater uniformity between national medical-device regulatory systems, and it was permanently replaced by the International Medical Device Regulators Forum in 2011 [4]. The devices were divided into therapeutic and surgical devices, diagnostic devices, and others (DeviceCateg) according to the categorization by Kakudo [6]. Moreover, company financial data, specifically

Company Sales (Sales), were collected from the Teikoku Data-bank. We divided those companies into foreign companies and domestic companies (ForeignDomestic).

In addition, we created the following two variables: Binary Review Time (BinRevTime), short (0) and long (1) review time, is a variable derived from the categorization of TotalRevTime based on the median of Total Review Time; and Binary Sales (BinSales), small and medium-sized (0) and large (1) enterprises, is a variable derived from the categorization of company sales data based on the median of Sales. Detailed definitions of these twelve variables are provided in Table 1.

2.3. Statistical Analysis

Using our database, we conducted two main types of analyses, based on TotalRevTime and Sales. Prior to conducting such analyses, we counted the number of new medical devices and computed descriptive statistics of TotalRevTime and Sales. All statistical analyses were performed with EZR version 1.27 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [7].

2.4. Analyses on TotalRevTime

Bivariate analyses of TotalRevTime and other variables were performed for (1) TotalRevTime and AppYear, (2) TotalRevTime and BinSales, (3) TotalRevTime and AppDevices, (4) TotalRevTime and StudyCateg, (5) TotalRevTime and ForeignDomestic, and (6) TotalRevTime and DeviceCateg. For analyses (1), (3) and (4) statistical significance was determined using the KruskalWallis (KW) test, and for analysis (2), (5) and (6), the MannWhitney U (MW-U) test was used. Values of $p < 0.05$ were considered significant. For analysis (5), odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using logistic regression, setting BinRevTime as a dependent variable and other variables as explanatory variables.

2.5. Analyses on Sales

Bivariate analyses of Sales and other variables were performed for (1) Sales and AppDevices and (2) Sales and StudyCateg. Statistical significance in these analyses was determined using the KW test. Values of $p < 0.05$ were considered significant.

3. Results

3.1. Analysis of Number of New Medical Devices

The total number of new medical devices approved from FY 2009 to 2015 was 176, as shown in Table 2. Some of the devices were excluded from the analysis for the following three reasons. First, 22 of the appurtenant devices of the main device were excluded to avoid double-counting because those devices are used with the main device, and they are reviewed at the same time. Second, 14 devices from conglomerate companies were also excluded from the database because their businesses are not concerned solely with medical devices, which may affect the analysis related to company size. Third, seven devices of

	2009	2010	2011	2012	2013	2014	2015	Total
Approved new medical devices	25	13	14	27	51	24	22	176
Included	18	12	12	20	36	23	12	133
Excluded	7	1	2	7	15	1	10	43
Appurtenant devices of the main device	5	0	1	4	7	0	5	22
Devices developed by conglomerate companies	0	0	1	3	4	1	5	14
Devices of the same product but with a different brand name	2	1	0	0	4	0	0	7

Table 2: Number of approved new medical devices by year.

the same product, but with different brand name applications, were also excluded from the database to avoid duplication of data due to identical devices. Thus, there were 133 new medical devices for analysis. Moreover, the sales data of 34 companies could not be collected, leaving 99 devices for our sales-related analysis.

3.2. Descriptive Analyses

A descriptive analysis of TotalRevTime and Sales was performed. The median of TotalRevTime is 418 (days), the minimum is 89 (days), and the maximum is 2,091 (days) ($n = 133$). The data of TotalRevTime do not follow a normal distribution. Regarding Sales, the median is 55,700 (mil. yen), the minimum is 55 (mil. yen), and the maximum is 402,294 (mil. yen) ($n = 99$). Further, Sales data also do not follow a normal distribution.

3.3. Analyses on TotalRevTime

We performed the following five analyses on TotalRevTime: In the analysis of TotalRevTime and AppYear, TotalRevTime tends to decrease with AppYear from FY 2009 to 2015 ($p < 0.001$), as shown in Figure 1. Median days (n) of TotalRevTime by AppYear are 586.5 (18), 577.5 (12), 498.5 (12), 460.5 (20), 418.0 (36), 209.0 (23), and 303.5 (12) in 2009 through 2015, respectively.

In the analysis of TotalRevTime and BinSales, TotalRevTime of group 0 (small and medium-sized companies) is longer than that of group 1 (large companies) ($p = 0.004$), as shown in Figure 2. Median days (n) of TotalRevTime are 509 (46) for group 0 and 396 (53) for group 1. Further, group 0 has a larger variance (416.3) than does group 1 (315.8).

In the analysis of TotalRevTime and AppDevices in 2009 to 2015, group “7-” has the shortest TotalRevTime ($p < 0.001$), as shown in Figure 3. The median days (n) of TotalRevTime by AppDevices are 498.5 (56), 459.0 (16), and 331.0 (61) for “1-3,” “4-6,” and “7-,” respectively.

In the analysis of TotalRevTime and StudyCateg, the TotalRevTime of group C (no clinical study was conducted) was the shortest in the foreign study only (A), foreign and domestic

study (B), domestic study only (D), and international clinical trial (E) ($p = 0.009$) groups, as shown in Figure 4. In addition, the TotalRevTime of group D (domestic study only) was the longest. The median days (n) of TotalRevTime by StudyCateg are 419.5 (42), 434.0 (17), 364.0 (41), 484.5 (28), and 375.0 (5) for A, B, C, D, and E, respectively.

In the analysis of TotalRevTime and ForeignDomestic, TotalRevTime of Domestic was longer than that of Foreign ($p = 0.064$), as shown in Figure 5. Median days (n) of TotalRevTime are 447 (27) for Domestic and 416 (106) for Foreign. We found only nine devices developed by big domestic companies.

In the analysis of TotalRevTime and DeviceCateg, TotalRevTime of Others was longer than that of Therapeutic and Surgical ($p = 0.009$), as shown in Figure 6. Median days (n) of TotalRevTime are 892 (8) for Others and 417 (125) for Therapeutic and Surgical. There were no diagnostic devices approved as new medical devices between 2009 and 2015.

When performing logistic regression, setting BinRevTime as a dependent variable, and AppYear, StudyCateg, Class, AppDevices, Foreign-Domestic, DeviceCateg and BinSales as explanatory variables, only AppYear (OR: 0.566, 95% CI: 0.428-0.749, $p < 0.001$) and BinSales (OR: 0.296, 95% CI: 0.117-0.748, $p = 0.010$) showed statistical significance. To evaluate the fit of the regression, we developed a plot of the receiver operating characteristic (ROC) curve. The area under the ROC curve is 0.84 (95% CI: 0.760 - 0.918), as shown in Figure 7.

3.4. Analyses on Sales

Additionally, we performed the following two analyses on Sales: First, in the analysis of Sales and AppDevices, the Company Sales (Sales) of group “7-” of AppDevices is the highest in the three groups ($p < 0.001$), as shown in Figure 8. The medians (n) of Sales by AppDevices are 15,800 (47), 55,700 (12), and 76,858 (40) (mil. Yen) for groups “1-3,” “4-6,” and “7-,” respectively. Group “4-6” has the biggest variance (163,473.1).

Second, in the analysis of Sales and StudyCateg, the Company Sales (Sales) of group B (foreign and domestic study) is the highest and Sales of group D (domestic study only) is the

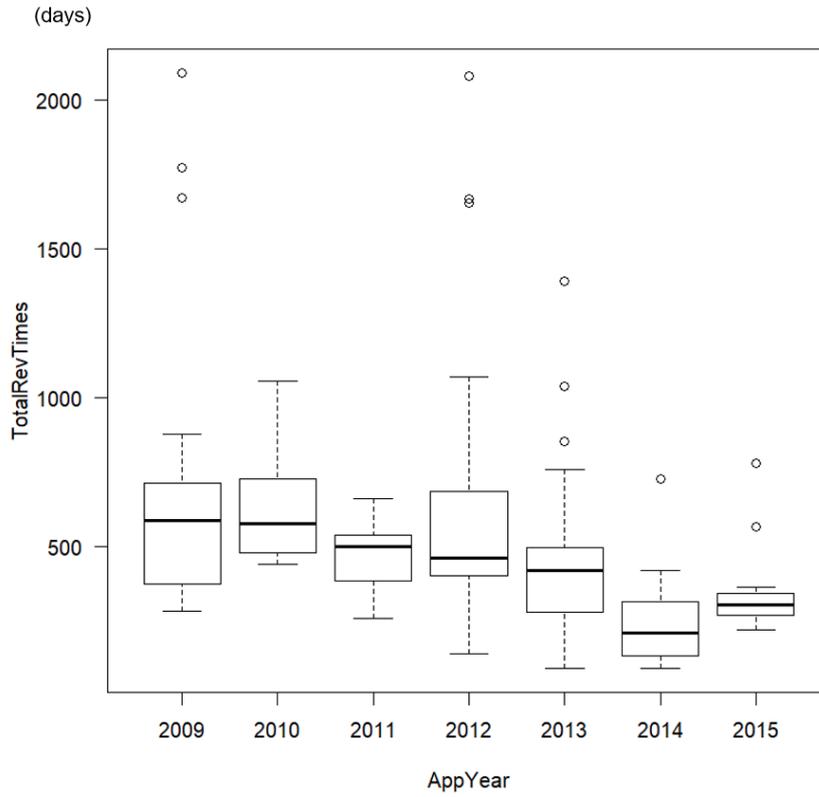


Figure 1: TotalRevTime by AppYear between FY 2009 and 2015.

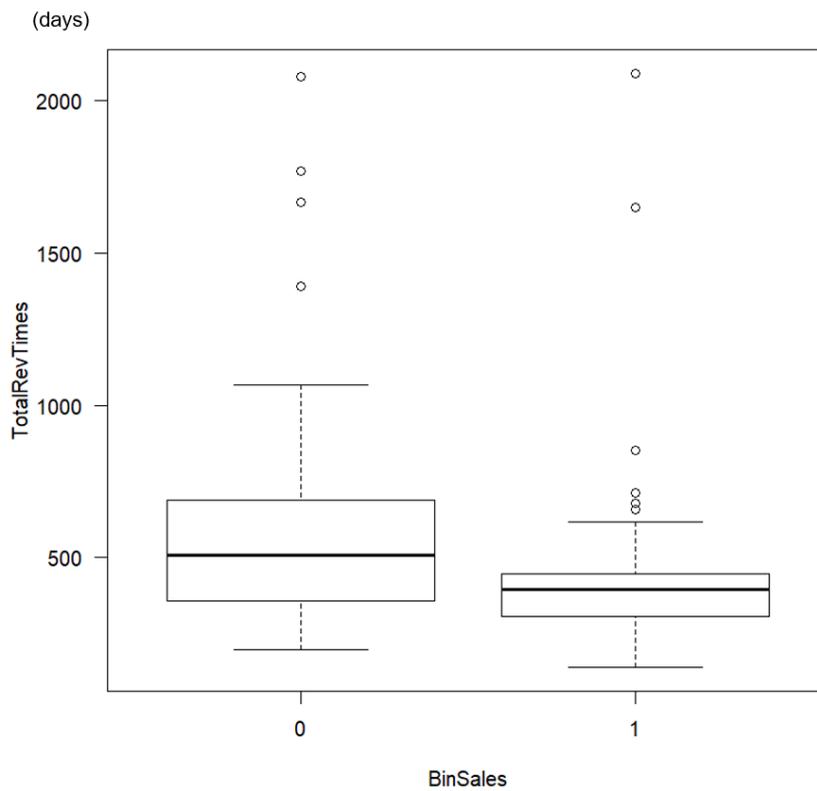


Figure 2: TotalRevTime by BinSales between FY 2009 and 2015. BinSales is derived data divided into small and large enterprises based on the median of sales. “0” represents enterprises below the median of sales (small companies) and “1” represents those above the median of sales (large companies).

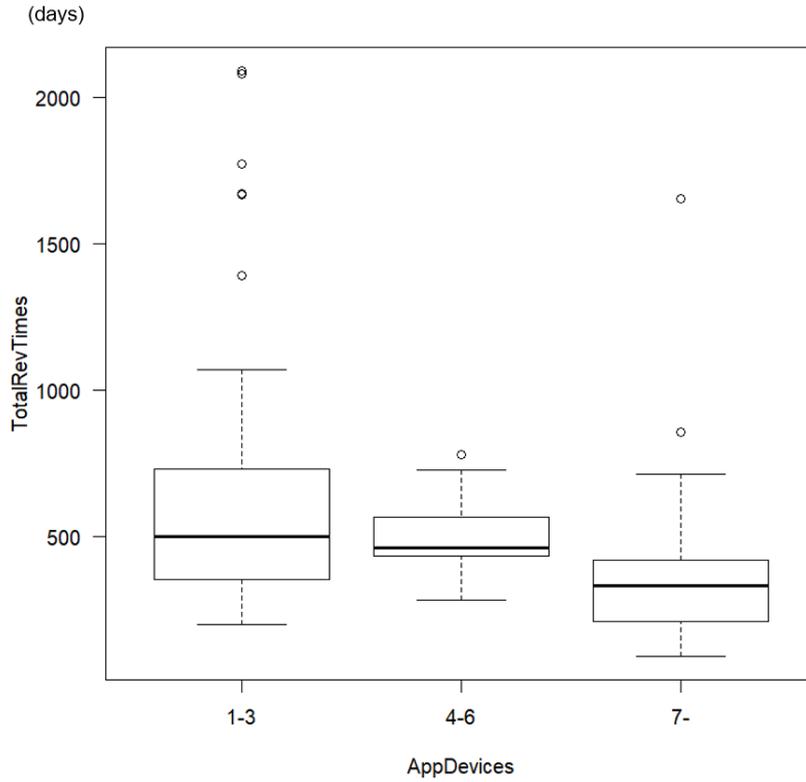


Figure 3: Total Review Time by AppDevices. “1-3” represents that a group of devices was developed by companies that developed 1-3 devices between FY 2009 to 2015. “4-6” and “7-” represent company devices in the same manner.

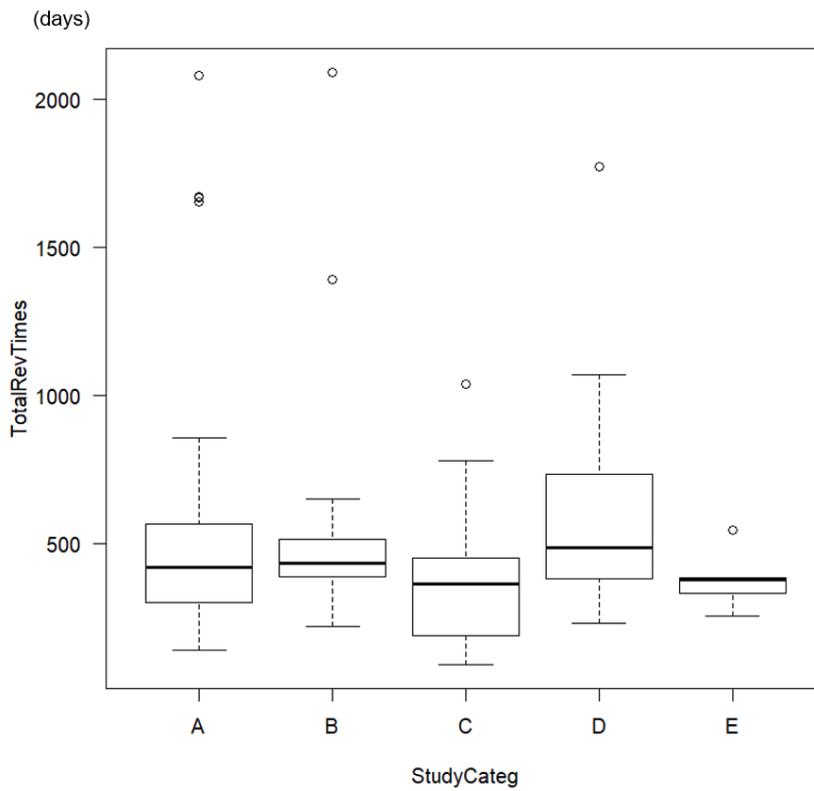


Figure 4: TotalRevTime by StudyCateg in FY 2009-2015. A represents: foreign study only, B represents foreign and domestic study, C represents no clinical study was conducted, D represents domestic study only and E represents international clinical trial.

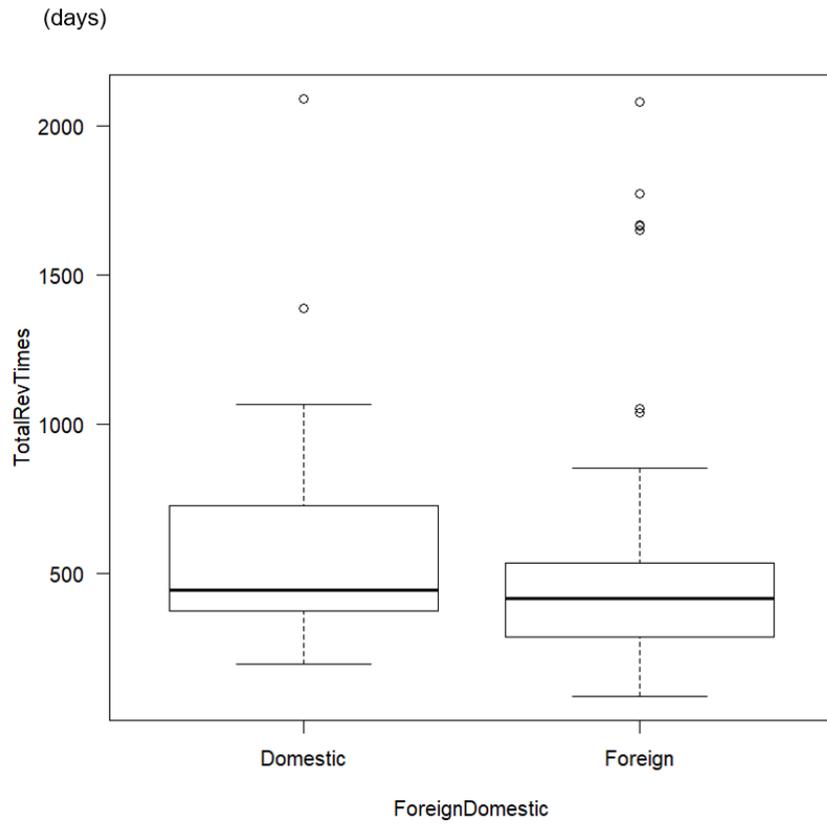


Figure 5: Total Review Time by Foreign Companies and Domestic Companies between FY 2009 and 2015.

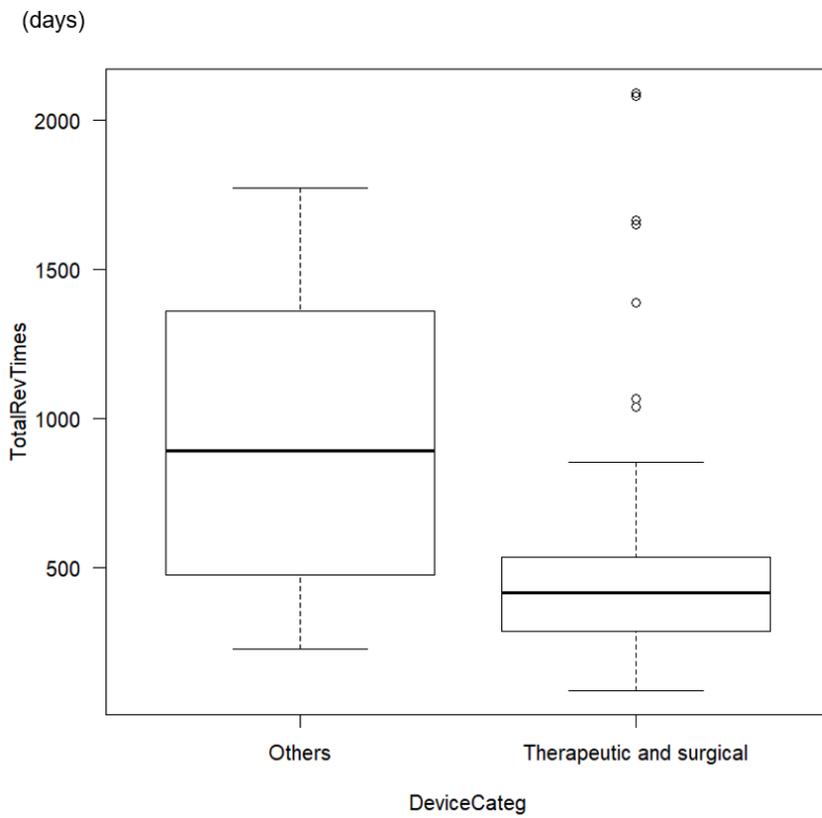


Figure 6: Total Review Time by ‘therapeutic and surgical devices’ and ‘other devices’ between FY 2009 and 2015.

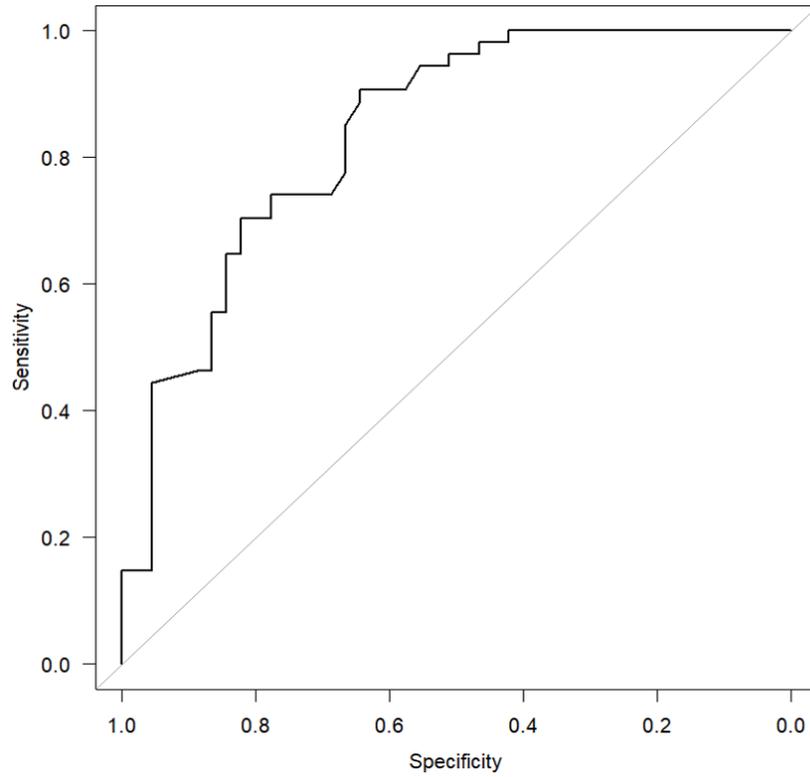


Figure 7: ROC curve for evaluation of logistic regression.

(mil. Yen)

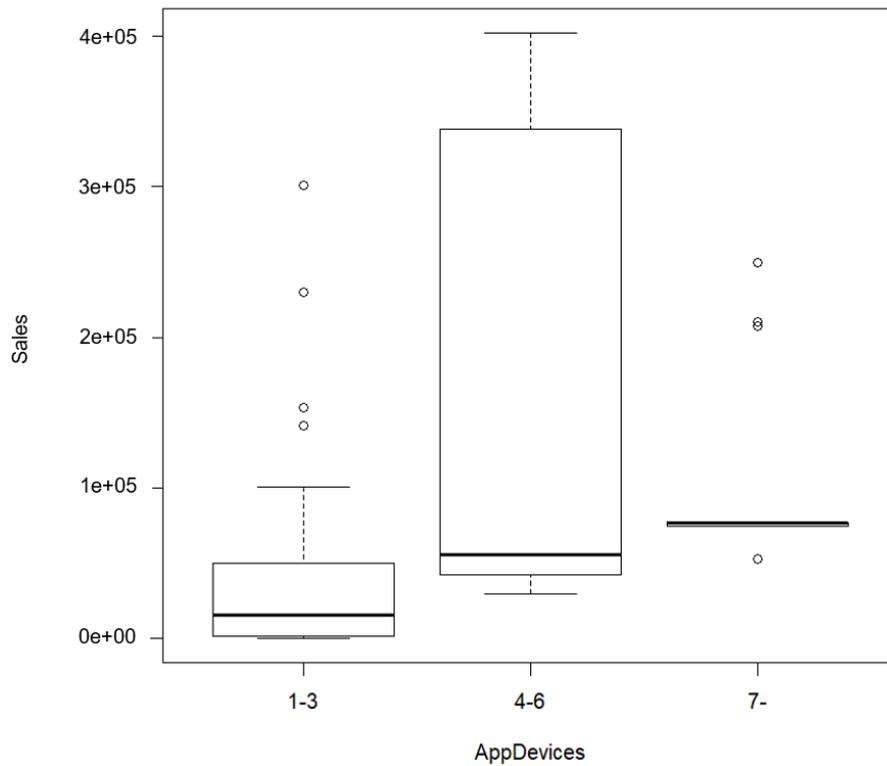


Figure 8: Sales by AppDevices between FY 2009 and 2015. “1-3” represents that a device was developed by a company that developed 1-3 devices in FY 2009 to 2015. “4-6” and “7-” represent company devices in the same manner.

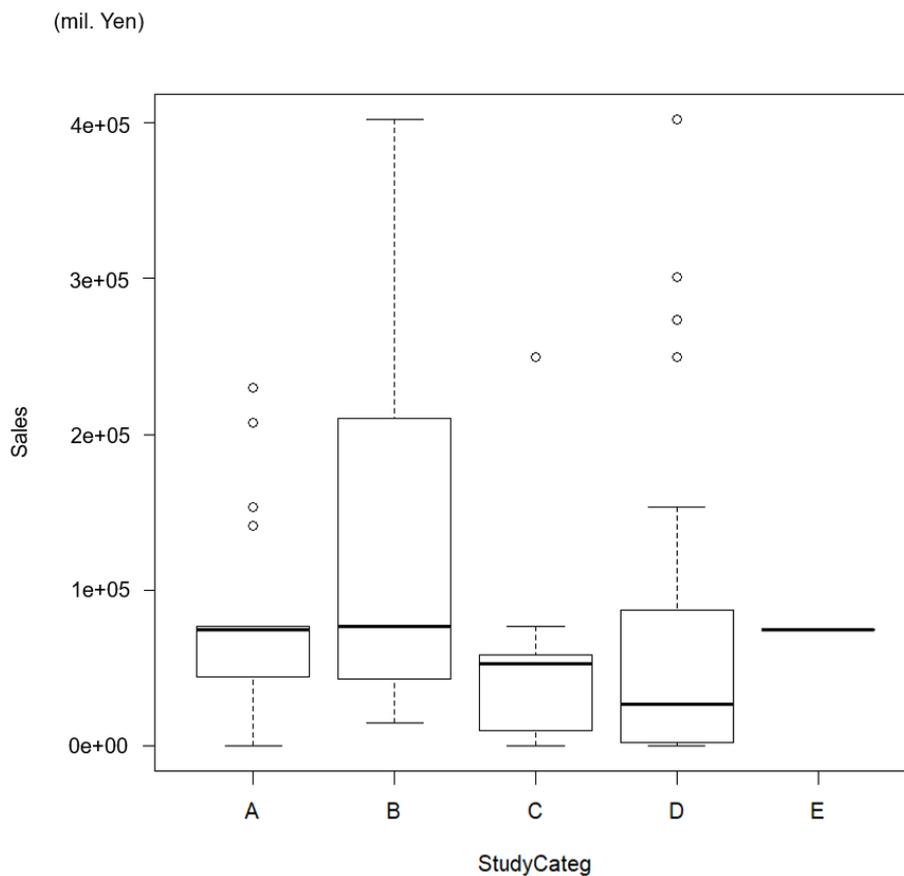


Figure 9: Sales by StudyCateg between FY 2009 and 2015. A represents foreign study only, B represents foreign and domestic study, C represents no clinical study was conducted, D represents domestic study only, and E represents international clinical trial.

lowest in the five category groups ($p = 0.059$), as shown in Figure 9. The medians (n) of Sales by StudyCateg are 75,000 (36), 76,858 (16), 53,000 (19), 26,802 (25), and 75,000 (3) (mil. yen) for A, B, C, D, and E, respectively. Group B has the largest variance (132,917.3) and group D has the second largest variance (112,081.8).

4. Discussion

Our research has five major findings. First, we can reconfirm that TotalRevTime reduced with AppYear. The PMDA has operated based on the “Action Program to Accelerate Reviews of Medical Devices” in 2008 and “Mid-Term Plan of the Pharmaceuticals and Medical Devices Agency” in 2009 [12]. This result indicates that the PMDA’s efforts have been successful and that the recent review periods in Japan are comparable to those of the United States [3]. However, this trend is only for the review time of new medical devices in Japan. Further investigation is needed with regard to improved and generic medical devices.

Second, the TotalRevTime of enterprises with larger sales is shorter than that of those with smaller sales. In other words, large enterprises might obtain faster approvals than SMEs, and

most of the medical device companies in Japan are SMEs. Many SMEs do not have experienced development divisions or regulatory affairs departments, which can be a huge disadvantage for discussion of regulatory science issues on new medical devices with the PMDA. Moreover, the size of enterprises might be related to their experience and whether they have sufficient personnel for development. Large enterprises can choose more effective ways to shorten review time, and from a wider range of options, due to larger budgets than those of SMEs. In regard to foreign companies or domestic companies, we found only nine devices developed by big domestic companies. Analysis of the relationship between TotalRevTime and the ForeignDomestic did not show statistical significance.

Third, the results regarding the relationship between TotalRevTime and AppDevices in 2009 to 2015 indicate that experienced companies might obtain faster approval because they have more efficient methods of development, more sufficient human resources, or higher capabilities based on their accumulated knowledge. Because large enterprises have more development experience than SMEs, this supports the view that the size of enterprises may also affect the efficiency of their strategies for development.

Our fourth major finding concerns the relationship between

TotalRevTime and StudyCateg. It is natural that group C (no clinical study was conducted) has the shortest review time because the PMDA and companies usually discuss the plan sufficiently before submission when their applications are submitted without clinical study data. In such a case, the PMDA does not need time to review the results of the studies' data. However, generally speaking, to submit without clinical study results, the companies must gather necessary and sufficient information to claim validity for filing. On the contrary, group D (domestic study only) has the longest time among them, except for group E (international clinical trial). It is assumed that the devices of group D consist of those developed by Japanese domestic companies, most of which are SMEs. Therefore, it is reasonable that the review time of group D is the longest, except for group E, which has only five devices.

Finally, the logistic regression reveals that only AppYear and BinSales contribute to BinRevTime. Because the area under the ROC curve is 0.83, prediction accuracy of the regression is good. This result leads us to conclude that TotalRevTime decreases with AppYear, and large enterprises could obtain faster approvals. TotalRevTime and Sales do not follow a normal distribution, which is why BinRevTime and BinSales are used in the regression instead of TotalRevTime and Sales.

Several studies on review time for medical devices have been published [1, 3, 9]; however, little has been reported on streamlining in the development of medical devices, especially the factors contributing to review time. Our research has important value, as it is the first study aimed at finding the factors contributing to review time. We found two such contributing factors. Our results are compatible with the past report [3] that review time has improved each year. Our hypothesis that large enterprises could develop medical devices more efficiently and obtain approval in shorter review times than SMEs was supported by our results. However, further studies on the efficient development of medical devices are needed as our research focuses only on total review time after submission. The time before submission is another important issue to be considered.

Needless to say, we hope to consistently bring innovative medical devices to patients. However, the finding that large enterprises obtain approval faster shows the need to promote the development of medical devices, no matter the size of the enterprise.

In the United States, startup companies play central roles in the development of innovative medical devices, and take on more risk than large companies do [10, 14]. The medical device industry in the United States has an ecosystem that allows for the active creation of innovative medical devices [10]. This ecosystem is one of the efficient ways to develop innovative medical devices; large enterprises and SMEs produce complementary effects by diversifying risks.

The findings of this research suggests that the medical device industry in Japan needs to rebuild a new system that is not influenced by the size of the enterprise, by drawing on the system of investment and education in the United States. However, it is difficult to say whether the United States' method is the best way for the Japanese medical device industry to efficiently develop innovative devices, as business customs are quite dif-

ferent between the two countries. In recent decades, Japan has been suffering not only in the medical device industry, but also in the electronics industry and many other high-tech industries, despite having adequate technology and high capacity for manufacturing. Thus, this research suggests a structural weakness in the Japanese economy. This begs the question of how Japan should change itself to actively introduce innovative medical devices. Japan has many issues to resolve before it can realize its potential. More efficient ways to develop new medical devices in Japan must be found as soon as possible.

5. Conclusion

The total review time of new medical devices in Japan appears to be related to the following two factors: (1) year of approval and (2) size of the enterprise.

6. Declaration of Conflicting Interest

The authors have no potential conflicts of interest to declare with respect to research, authorship, and/or publication of this article.

7. Disclaimer

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9. Article Information

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