Drug Development Abandonment Stage for Japanese Pharmaceutical Companies

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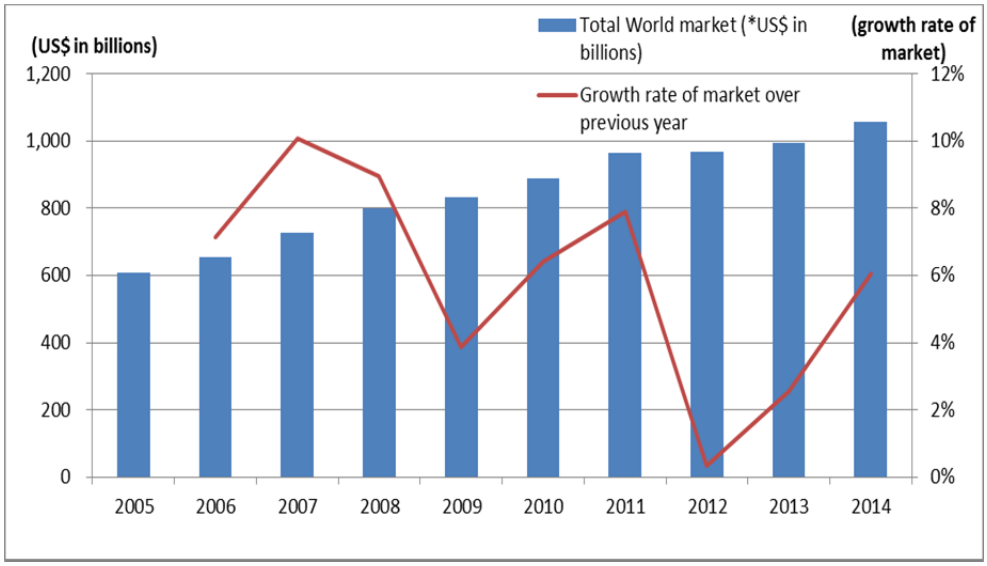
***Abstract*--With a focus on Japan, this paper empirically examines the stage in which drug development is abandoned. The time-consuming approval process for new drugs involves many stages and has low certainty. Based on pipeline data, we examine the stage in which drug development is completely abandoned or is "dead." Using pipeline data on Japanese pharmaceutical companies, we investigate whether the abandonment of drug development depends on the drugs' characteristics. Through a review of the data, we find differences in the timing of drug development abandonment and the number of such abandonment by the disease and technology.**

I. INTRODUCTION

While the average world population has been aging since the 2000s, Japan's aging speed has been particularly fast, and the need for health care services has thus been increasing. Therefore, the improvement in the health industry of Japan would contribute to not only this domestic need but also the welfare of the world in terms of welfare and improving the quality of life of the aging. The pharmaceutical market is spreading globally behind aging society.

Figure 1 shows the transition of scale of the global pharmaceutical market. The bar chart shows the scale of the global pharmaceutical market, while the line chart compares the growth rate of the market from two consecutive fiscal years. The growth rate substantially decreased in 2009 and 2012. The former was caused by the effect of the Lehman shock, while the latter was caused by the pharmaceutical problem in 2010 problem, where the patents of blockbuster drugs expired and were transferred to generic drugs in 2010. However, subsequently these growth rates improved substantively despite the occurrence of these exogenous shocks. Therefore, the global pharmaceutical market is currently in a growth phase.

While the US tops the list of number of drug discoveries, Japan is one of the few regions that can discover drugs independently. Developing the pharmaceutical industry is accordingly regarded as one of the important policy agendas in Japan. The "Japan reconstruction strategy" regarded healthy life expectancy as a strategic field in 2012, and the pharmaceutical industry is considered to play a central role in this. We expect that developing the pharmaceutical industry would substantially contribute to economic growth because its products have high added value and are resistant to economic trends in [1]. This would increase intellectual property, which regions as valuable as rare natural resources to a region; hence, the region would benefit from creating more scientific knowledge through drug development. Enhancing the pharmaceutical industry for establishing and extending competitive power in the world is an important aspect of globalization.



Source：Data from IMS Health.
http://www.imshealth.com/files/web/Corporate/News/Top-Line%20Market%20Data/2014/World%20figures%202014.pdf
（2016/03/11accessible)
Note: All current information is as of May 2015. US$ figures use actual quarterly exchange rates.

Figure 1 Transition of scale of the global pharmaceutical market

However, the number of drug discoveries in Japan is not so high and shows a large excess of imports over exports [5]. There are various problems on drug discoveries in Japan. However, they are often talked as actual feelings and do not necessarily bring validation based on evidence.

We focus on the drug development processes of Japanese pharmaceutical companies. We examine the stage in which Japanese pharmaceutical companies abandon drug discovery. Moreover, we need to determine whether drug discovery is specific to regions, because it may be affected by the regulations or policies of different regions. We also examine how the environment around drug discovery affects it by reviewing the nature of drug discovery of Japanese pharmaceutical companies in each region. If there are differences in drug discovery among different regions, environment is likely to affect if, similar to regulations. Otherwise, Japanese pharmaceutical companies make similar decisions across regions. Then, regulation levels do not affect drug development. To examine whether the Japanese regulation environment affects drug discovery, it is better to compare it with the environment of the US and EU, because these developed regions are similar in terms of point of aging society and maturity of market. Therefore, we investigate drug discovery by Japanese pharmaceutical companies in not only Japan, but also the US and the EU. We examine how Japanese pharmaceutical companies develop new drugs in each of the regions considered

Further, we suppose that differences in drug type or disease area would affect differences in the timing of drug discovery. Thus, we examine whether drug development is abandoned by drug type or disease area.

II. CURRENT LITERATURE

It is reviewed drug development worldwide based on the current pipeline data in [3]. It is also examined the process of research and development in the global pharmaceutical industry using data in [5][6][7]. They tried to review and forecast about the pharmaceutical industry based on a new index to provide evidence, for which the research institute selects fields and themes, and decides policies[1]. As one of them, they analyze the pipeline compounds in the research and development of pharmaceutical companies. The pipeline compound in drug development is a candidate that can be used to develop new drugs. It is tried to capture the capacity of research and development in each region by comparing the development of the pipeline compound in each region by considering small molecule drugs based on technologies or bio drugs based on new technologies in [5]. It is compared the sales in the market by technology and pipeline compound among regions, particularly for bio drugs in [6]. It is analyzed the status of research and development of drugs by disease area in [7]. Further, a series of studies by [5][6][7] focus on the “alive” pipeline.

While the studies by [5][6][7] consider the pipelines of pharmaceutical companies around the world, we focus on the pipelines of Japanese pharmaceutical companies in the world. That is, we analyze drug development by Japanese pharmaceutical companies in Japan, the US, and the EU. While the studies by [5][6][7] focus on the “alive” pipeline in progress, we are interested in the bottleneck of pipeline. Therefore, we focus on the stage in which drug development is abandoned, making this study complementary to previous works. Further, by using data on pharmaceutical companies in Japan, we consider whether the abandonment depends on the characteristics of drugs.

III. DATA

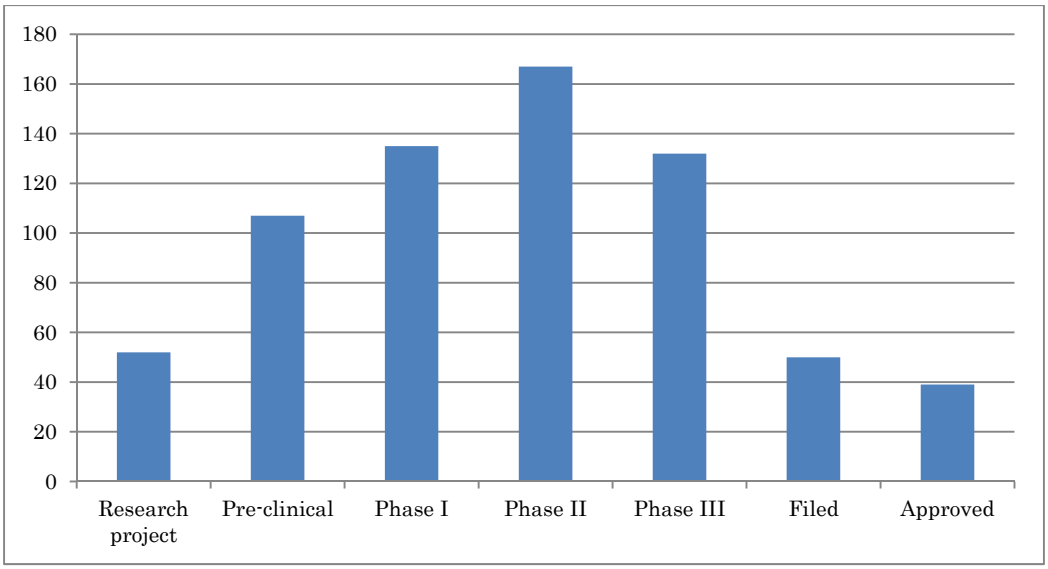
Similar to [5][6], we use the database EvaluatePharma, created by Evaluate. This database follows financial and pipeline data for pharmaceutical companies and bio pharmaceutical companies in the world. It is constructed by collecting data that the companies report, and thus, the data of companies that are not assigned to report depend on voluntary reporting. Therefore, it is not necessary for all pipelines to be listed on this database. Our data were collected until March 7, 2014.

We collected data from pipelines that Japanese pharmaceutical companies have developed in Japan and other regions. The number of pipelines is 7,392 here. We can capture the drug development status based on the database. This provides information on not only the stage of development and the number of pipelines but also the stage when the drug development was abandoned.

IV. CONSIDERATIONS ON DRUG DEVELOPMENT IN JAPAN

We examine the stage in which the Japanese pharmaceutical companies develop drugs in each region. First, we show the distribution of the pipelines that Japanese pharmaceutical companies are developing in Japan.

[1] Japan Agency for Medical Research and Development (AMED) was founded in 2015 to assist research through ministries, providing funds for enhance consistent research and development from basic research to applied research, to apply their outcomes, and to arrange environment.
One of its important roles is to choose the research field and themes that should be assisted. Then, evidence is needed for decision making. Therefore, it is intended to develop the index to capture not only past research and development capacity and industrial competitive force but also future trends in [5][6][7].



Unit: number of cases

Figure 2 Drug development by Japanese pharmaceutical companies in Japan

While the above figures show the number of pipelines in the research and development stage at a point in time, they do not depict that each pipeline transfers in the development process. However, we assume that pipelines pass through each stage with a certain probability [5].

This distribution has one peak, where Phase II is at the highest. We confirm that the pipeline of Phase II is the most common. Subsequently, the pipelines of Phases I and III are also common. The number of pipelines increases until Phase II, but it decreases over Phase II. We suppose that the reason for this is that the pipeline decreases as the development stage progresses [5].

However, we cannot explain why the number of pipeline increases from Phase I to Phase II. This is true in the case of pharmaceutical companies around the world as well [3]. While there are pipelines abandoned between Phase I and Phase II, there are more pipelines in Phase II than in Phase I. While this may be counterintuitive, this is because it describes the drug development status in time [3]. To examine drug development by Japanese pharmaceutical companies in other regions, we investigate how Japanese pharmaceutical companies develop drugs in the US and the EU.

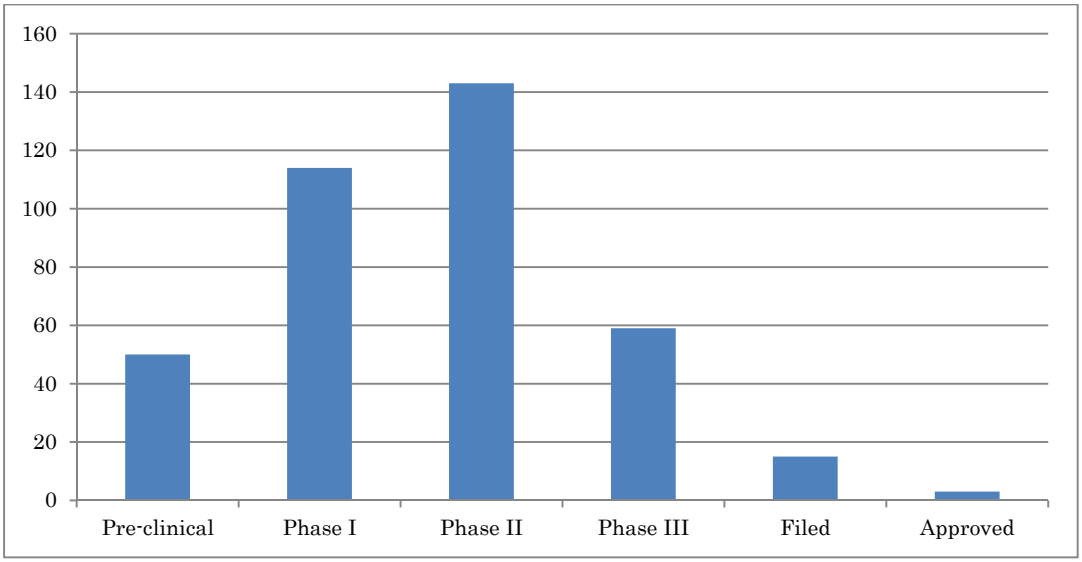


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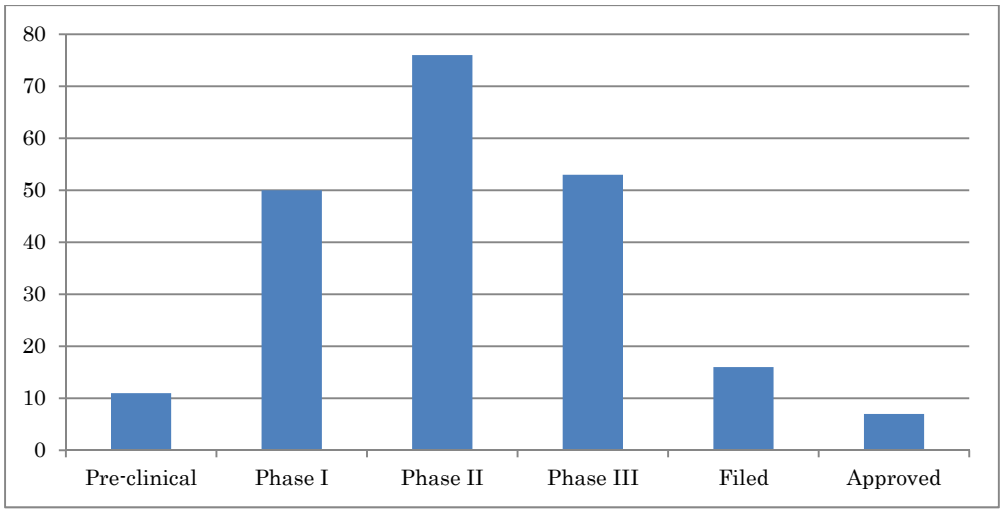
Figure 3. Drug development in the US by Japanese companies



Unit; Number of cases

Figure 4. Drug development in Europe by Japanese companies

The number of pipelines is the highest in Phase II in both the US and the EU, similar to Japan. This is true in the case of not only Japanese pharmaceutical companies but also pharmaceutical companies around the world [3][2].

Next, we determine the stage in which Japanese pharmaceutical companies abandon drug development in Japan, the US, and the EU.

The number of pipelines abandoned is also the highest in Phase II. The distribution takes a single peak in Phase II. As mentioned before, this shows the number of pipelines in each stage of research development at a time but does not show that each pipeline transfers across stages. However, when we assume that pipelines pass through each stage at a certain probability, the number of pipelines developing in progress and the number of pipelines abandoned are on an average the highest in Phase II. However, while many pipelines are developing, their number decreases in Phase III, suggesting that many pipelines are abandoned in Phase II. Thus, there is a site of abandoned pipelines between Phase II and Phase III.

Next, we examine how Japanese pharmaceutical companies abandon drug development in the US and the EU.

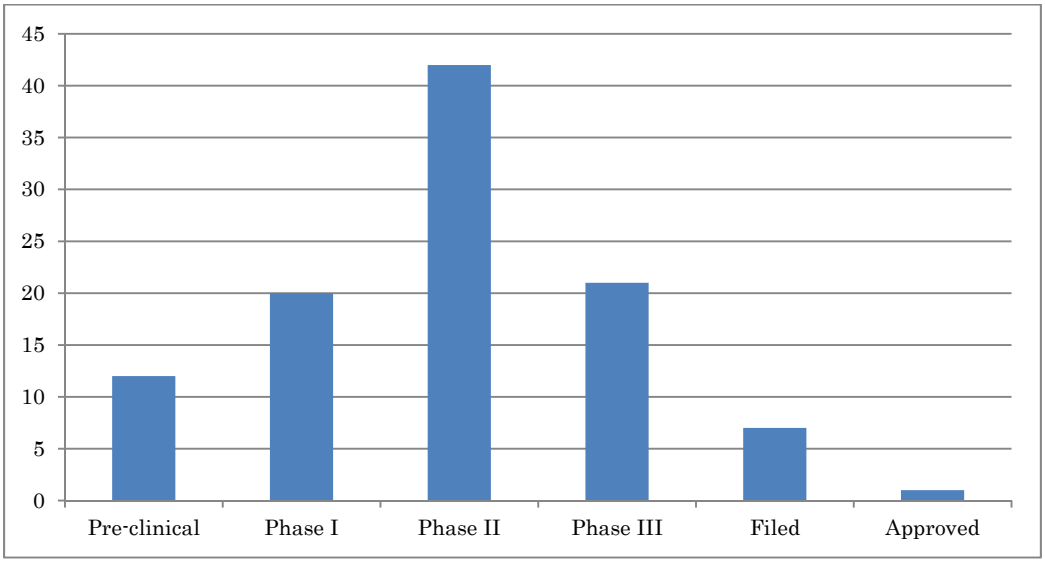


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Figure 5. Drug development abandoned in Japan by Japanese companies

[2] Refer to Figure 3 in [3].

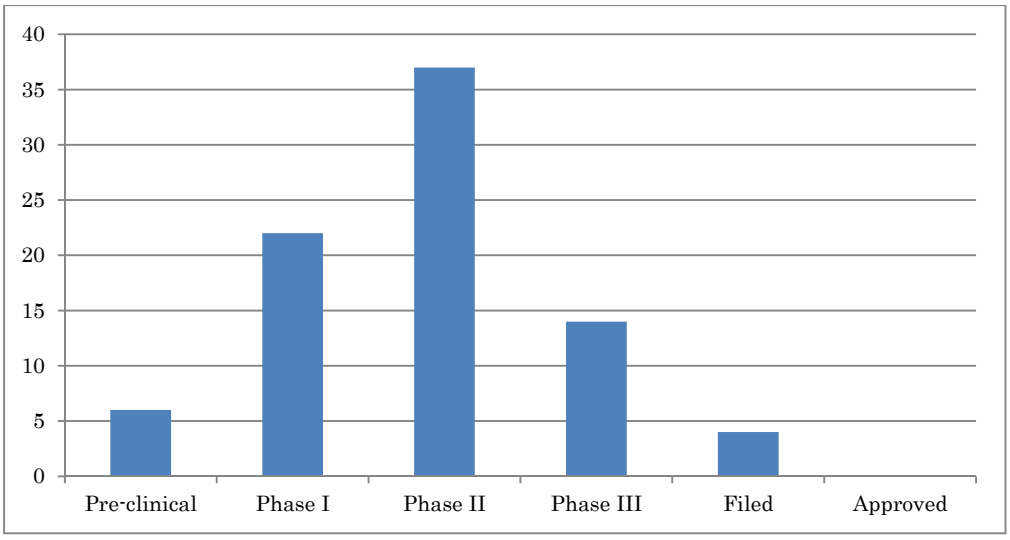

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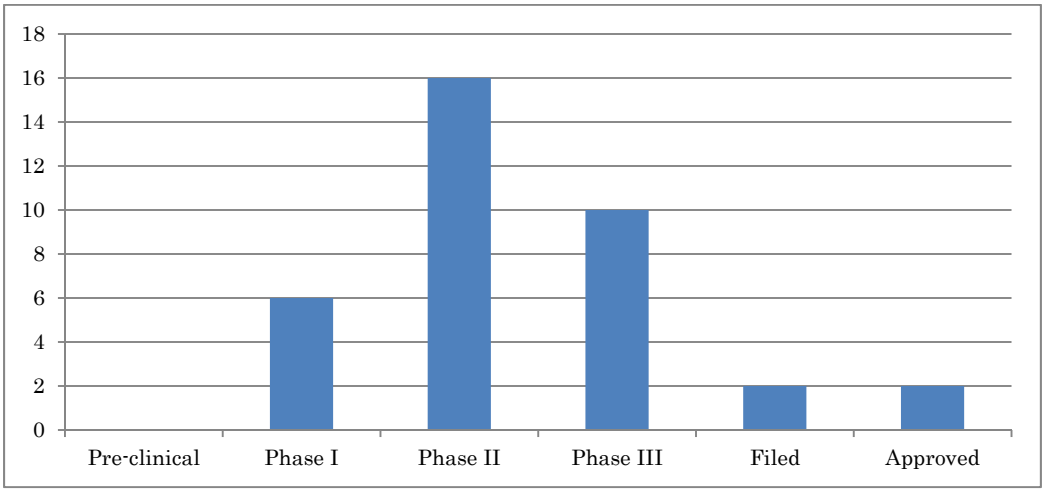
Figure 6. Drug development abandoned in the US by Japanese companies



Unit; Number of cases

Figure 7. Drug development abandoned in Europe by Japanese companies

There are many pipelines that cannot proceed from Phase II to Phase III. Therefore, the number of pipelines that Japanese pharmaceutical companies have abandoned is the highest in Phase II. This is true for Japan, the US, and the EU. That is, Japanese pharmaceutical companies often tend to abandon drug development in Phase II regardless of the regions in which they develop drugs. This suggests that the decision to abandon depends not on regulations or policies, but on the decision made within Japanese pharmaceutical companies. It is also true for pharmaceutical companies around the world that there are many pipelines that cannot proceed beyond Phase II [3]. There are more pipelines in Phase II than Phase I, because our data justly describe the status at a single point in time and it takes more time to develop in Phase II than in Phase I. Therefore, we propose that many pipelines remain in Phase II. Although it is not clear why many pipelines are abandoned in Phase II and cannot proceed to Phase III, we suppose that pharmaceutical companies make investment decisions based on cost effectiveness.

V. THE DIFFERENCES IN DEVELOPMENT PROCESS BY TYPE OF DRUG.

We confirmed that Japanese pharmaceutical companies tend to abandon drug development in Phase II regardless of region. However, there are other aspects behind this decision. Therefore, we examine the different processes in which Japanese pharmaceutical companies abandon drug development from some other viewpoints. First, we review drug development process by small molecule drugs and bio medical drugs. We find that the development processes abandoned are different between small molecule drugs and bio medical drugs, which are new type.

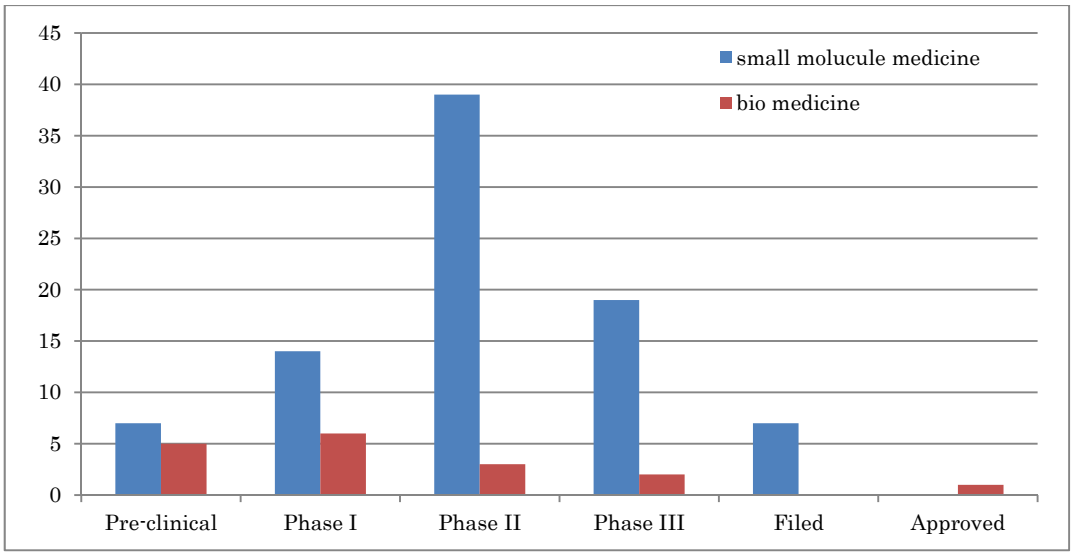


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Figure 8. Drug development which Japanese pharmaceutical companies abandoned in Japan by type (small molecule drugs and bio medical drugs)

Figure 8 shows the stage in which drug development was abandoned when Japanese pharmaceutical companies developed drugs in Japan by type of drug—small molecule drugs or bio medical drugs. The pipelines of small molecule drugs are overwhelmingly abandoned in Phase II. This distribution also has a single peak similar to figure 5. We suppose that the former distribution (figure 5) almost reflects small molecule drugs because these drugs still compose most drugs in the market. This is true not only for Japan but also for the US and the EU.

On the other hand, the pipelines of bio medical drugs exist most often in Phase I, although we cannot easily make a comparison because we have only a few cases. Surely, we cannot simply compare small molecule drugs and bio medical drugs because the latter are few in number. However, we can confirm that pharmaceutical companies decide whether they should abandon the development of bio medical drugs at stages earlier than that for small molecule drugs.

Next, we examine the stage in which drug development was abandoned when Japanese pharmaceutical companies developed drugs in the US and the EU by type of drug—small molecule drugs or bio medical drugs.

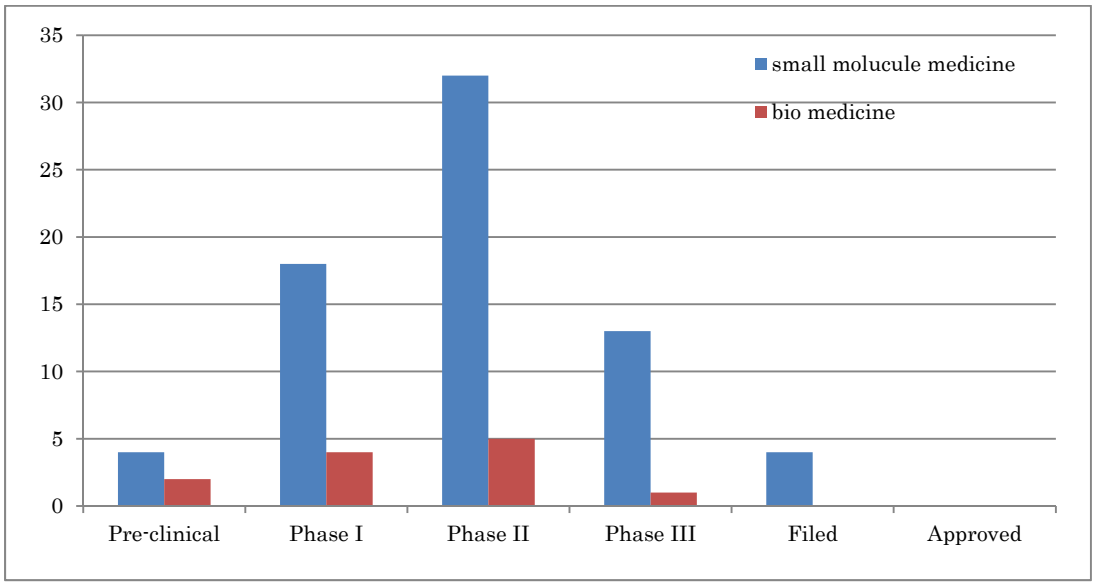

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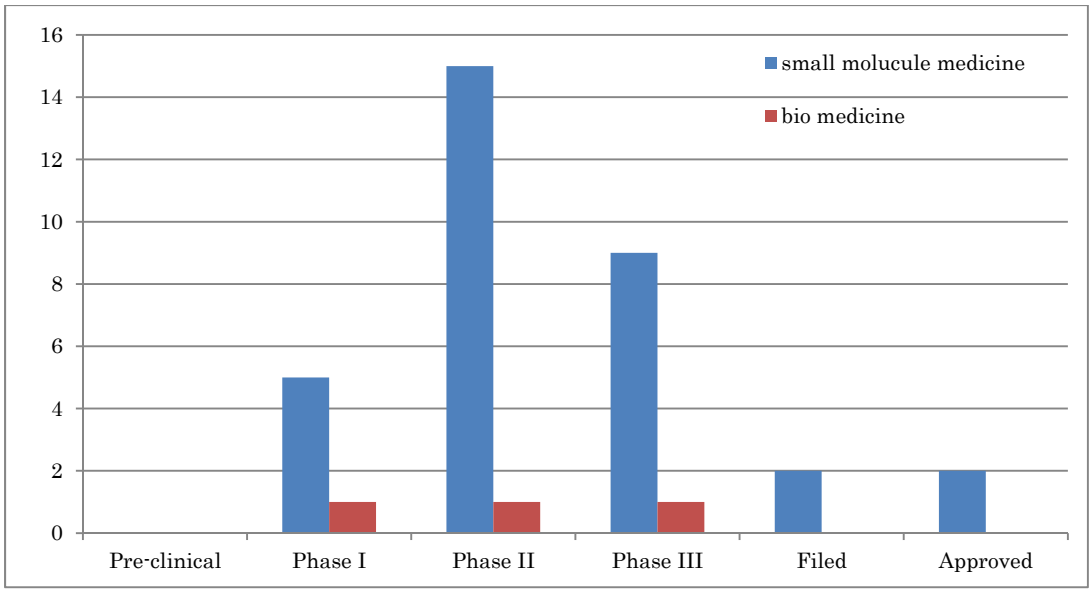
Figure 9. Drug development abandoned in the US by Japanese companies (small molecule and bio medical drugs)



Unit; Number of cases

Figure 10. Drug development abandoned in Europe by Japanese companies (small molecule and bio medical drugs)

The pipelines of small molecule drugs are also highest abandoned in Phase II even in the US and the EU. However, although the pipelines of bio medical drugs are highest on Phase I in the US and there are no differences among stage in the EU, this is not a considerable aspect of discussion, given the small number of bio medical drugs.

The pipelines of small molecule drugs are the highest abandoned among the given regions while those of bio medical drugs do not have common tendency among them.

The development of bio medical drugs takes higher productive cost than small molecule drugs because of their complexity of productive process and control tests. Further costs are involved in the product pipeline for clinical trial. Therefore, we suppose that abandonment of development of bio medical drugs is decided in earlier stages than that of small molecule drugs[3].

VI. STAGE IN WHICH DRUG DEVELOPMENT IS ABANDONED IN EACH DISEASE AREA

Next, we consider the stage in which Japanese pharmaceutical companies abandon drug development by each disease area.

The number of pipelines abandoned is not necessarily many as a whole. In addition, it is difficult to capture the trend when they are divided into stages at the time of abandonment by using figure A1 (Appendix). Therefore, we review the aggregate calculation of the abandoned pipeline by disease area and the share of pipeline developing or marketed regardless of development stage, to examine the stages of drug development abandonment by disease area.

[3] It is explained the difference between small molecule drugs and bio medical drugs as thus in [2]: "Bio medical drugs are made in production process where used living objects sensitive for change, compared with process of chemical synthesis used for making small molecule drugs. Therefore, final outputs depend on various factors in productive process. A small change in productive process might change final outputs because bio medical drugs are constituted of complex molecules with difficulty of analysis of characteristics. That is also very complex productive process. Therefore, they must meet product quality control standard (GMP) and given standard with high accuracy to keep safety and effectiveness of products. About 50 kinds of in-process control tests are conducted in small molecule drugs while about 250 kinds of in-process control tests are conducted in bio medical drugs." Manufacturing Industries Bureau in [4] says, "Drugs' paradigm largely is shifting from small molecule drugs to bio medical drugs with gen recombination technology in the world but Japanese pharmaceutical companies suffer from huge cost for bio drug development."

TABLE 1 THE RATIO OF ABANDONED PIPELINES FOR WHICH JAPANESE PHARMACEUTICAL COMPANIES ABANDON DRUG DEVELOPMENT IN JAPAN BY EACH DISEASE AREA

Disease area	Developing pipeline (excluding marketed) (a)	Marketed (b)	Abandoned pipeline (c)	(c)/(b)
Blood	21	154	9	5.8%
Musculoskeletal	33	290	9	3.1%
Oncology & Immunomodulators	210	219	24	11.0%
Various	22	82	1	1.2%
Respiratory	31	309	4	1.3%
Central Nervous System	76	355	11	3.1%
Dermatology	24	183	3	1.6%
Cardiovascular	42	407	11	2.7%
Genito-Urinary	23	159	9	5.7%
Gastro-Intestinal	40	462	5	1.1%
Endocrine	23	134	7	5.2%
Systemic Anti-infectives	61	352	9	2.6%
Sensory Organs	24	204	6	2.9%

Source: EvaluatePharma

The pipelines of Oncology & Immunomodulators were abandoned most often, but their developing pipelines (excluding the marketed pipeline) (a) were also abandoned most often. If the number of developing pipelines increases, the certainty of abandoned also increases. Therefore, we examine the ratio of Marketed pipelines (b), Abandoned pipelines (c), and Abandoned pipelines (c)/Marketed pipelines (b). By necessity, we show the number of pipelines in each developing stage at a time but do not show the way each pipeline reaches the market or is abandoned. Therefore, these ratios are different from the certainty with which each pipeline is abandoned. However, the pipeline passes through each stage with certainty [5]. Then, we can capture the average ratio of abandonment by disease area and finally review the results.

We review the ratio of abandoned pipelines to marketed drugs, (c)/(b). “Marketed” indicates that the pipeline survived the process of drug development. Therefore, this ratio indicates the percentage of abandoned pipelines to survived pipelines by disease area. The highest is Oncology & Immunomodulators at 11%. This result seems to contradict the result of the ratio of abandoned pipelines to developing pipelines. However, this might indicate that drug development for Oncology & Immunomodulators has recently been captured. Marketed drugs require accumulation for their sales. Therefore, they are more than the number of pipelines developing in progress. The number of marketed drugs is greater when the disease area has been focused for development. Moreover, some disease areas have corresponded not by drugs but by surgery. This might affect the number of marketed drugs that technology change from the way to correspond by surgery to by drugs. This should be interpreted with R&D data for each disease and presents scope for future research.

Next, we review the abandoned pipelines for which Japanese pharmaceutical companies abandon drug development in the US and the EU.

TABLE 2 THE RATIO OF ABANDONED PIPELINES FOR WHICH JAPANESE PHARMACEUTICAL COMPANIES ABANDON DRUG DEVELOPMENT IN THE US BY DISEASE AREA

Disease area	Developing pipeline (excluding marketed) (a)	Marketed (b)	Abandoned pipeline (c)	(c)/(b)
Blood	17	12	9	75.0%
Musculoskeletal	16	24	9	37.5%
Oncology & Immunomodulators	148	34	24	70.6%
Various	3	11	1	9.1%
Respiratory	13	30	4	13.3%
Central Nervous System	49	43	11	25.6%
Dermatology	15	10	3	30.0%
Cardiovascular	19	31	11	35.5%
Genito-Urinary	13	18	9	50.0%
Gastro-Intestinal	27	30	5	16.7%
Endocrine	13	16	7	43.8%
Systemic Anti-infectives	32	25	9	36.0%
Sensory Organs	19	23	6	26.1%

Source: EvaluatePharma

TABLE 3 THE RATIO OF ABANDONED PIPELINES FOR WHICH JAPANESE PHARMACEUTICAL COMPANIES ABANDON DRUG DEVELOPMENT IN THE EU BY DISEASE AREA

Disease area	Developing pipeline (excluding marketed) (a)	Marketed (b)	Abandoned pipeline (c)	(c)/(b)
Blood	15	12	2	16.7%
Musculoskeletal	10	22	3	13.6%
Oncology & Immunomodulators	80	43	9	20.9%
Various	3	6	0	0.0%
Respiratory	9	16	1	6.3%
Central Nervous System	17	34	3	8.8%
Dermatology	9	20	3	15.0%
Cardiovascular	12	32	2	6.3%
Genito-Urinary	11	21	3	14.3%
Gastro-Intestinal	17	27	3	11.1%
Endocrine	10	13	7	53.8%
Systemic Anti-infectives	12	20	0	0.0%
Sensory Organs	8	23	0	0.0%

Source: EvaluatePharma

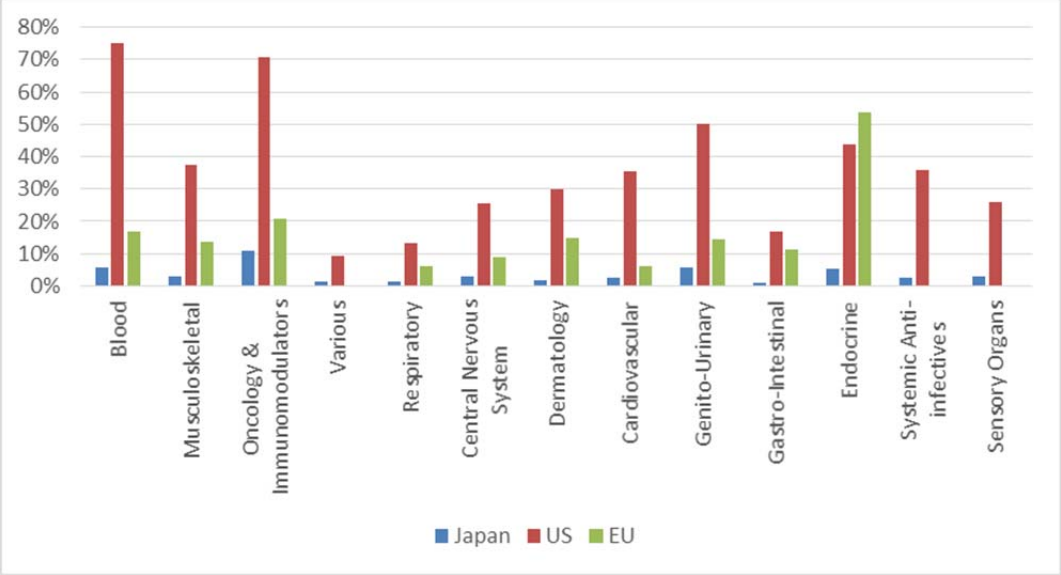


Figure 12 International comparison of the ratio of abandoned pipelines to marketed drugs by each disease area

First, we review the ratio of abandoned pipelines to marketed drugs by each disease area, (c)/(b), which Japanese pharmaceutical companies developed in the US (Table 2). The highest is Blood (75%), followed by Oncology & Immunomodulators (70.6%) and then Genito-urinary (50%).

Next, we review the case in the EU (Table 3). Excluding a part of the disease area (Various, Systemic Anti-infectives, Sensory Organs), the ratio of abandoned pipelines to marketed drugs, (c)/(b), is higher in most disease areas than in Japan.

Finally, for international comparison, we summarize the ratio of abandoned pipelines to marketed drugs, (c)/(b), in each disease area in Japan, the US, and the EU in Figure 12.

The ratios of abandoned pipelines to marketed drugs for any disease area are higher in the US than in Japan and the EU. This suggests that Japanese pharmaceutical companies tend to conduct clinical research with high risk of development failure in the US.

VII. CONCLUSION

We examined whether Japanese pharmaceutical companies develop drugs differently across Japan, the US, and the EU. We found that the timing of development abandonment is not largely different across these regions. They tend to abandon drug development in Phase II as a whole. This result suggests that the timing of abandonment does not depend on the regulations and policies in each region. We also examined whether the timing of abandonment is different across three regions by small molecule drugs and bio medical drugs. While the timing of abandonment of small molecule drugs is not different across the three regions, that of bio medical drugs is a little different across them. We also examined them by disease area. We

found that the ratio of abandoned pipelines to marketed drugs by disease area is higher in the US than in Japan and the EU.

We found some facts focused on the abandonment of drug development to search for bottlenecks when Japanese pharmaceutical companies develop drugs in Japan, the US, and the EU. Although we selected Japanese pharmaceutical companies that develop drugs in Japan, the US, and the EU, we should similarly analyze American or European companies to get universal results. To extend this research, we should follow the change in the need for drugs for a disease according to the change in the disease structure and technology developed according to it using time series.

ACKNOWLEDGEMENTS

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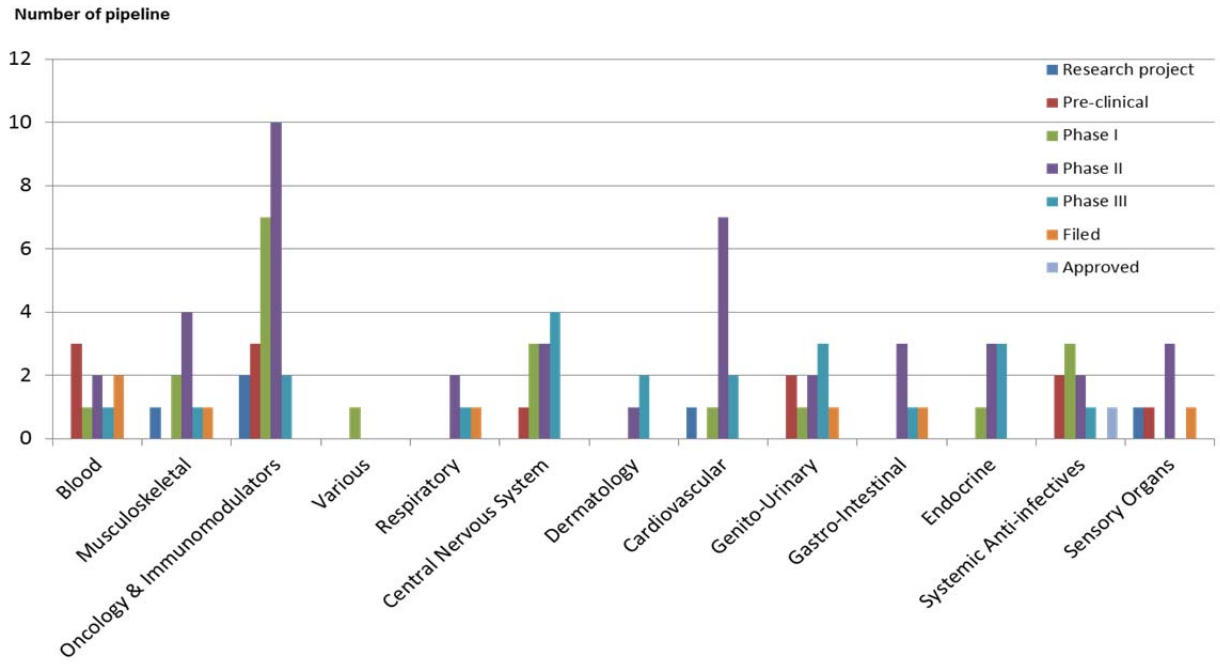
APPENDIX



Source: EvaluatePharma

Figure A1 Stage in which drug development is abandoned by disease area