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Mapping lifecycle management activities for blockbuster drugs in Japan based on drug approvals and patent term extensions

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Drug lifecycle management (LCM), which entails acquiring drug approvals and patent protections, contributes to maximizing drug discovery investment returns. In a previous survey, a comparative analysis between Japan and the USA indicated that a unique patent term extension system has an important role in Japanese drug LCM. Therefore, in this survey, we focused on drug approvals and patent term extensions, and found that the LCM for blockbuster drugs in Japan can be categorized into three types (drug approval-oriented LCM, patent term extension-oriented LCM, and inactive-type LCM), of which the first two have been implemented recently. Here, we suggest a strategy for selecting a suitable LCM approach among these three types based on the prospects for drug improvements.

Introduction

Over recent years, there has been a decline in the productivity of research and development (R&D) for new molecular entities (NME). Specifically, after peaking in 1996, the number of NMEs approved by the US Food and Drug Administration (FDA) has decreased, whereas the cost required to launch an NME has increased by 13.4% annually since the 1950s [1].

Under these circumstances, LCM has gained importance as a means to maximize revenue in return for investment in NME development. LCM approaches mainly comprise branding, product support, trade relations, manufacturing cost advantages, product improvements, and product-line extensions [2]. Product improvements and line extensions refer to the launch of enhanced products containing the same active ingredient (e.g., new indications, new formulations, and combination drugs) to add value to the entire product group and thereby maintain sales. Thus, these approaches contribute to increased product profitability [3,4].

Drug approval and patent protection are two key elements of drug LCM. Smith indicated that, based on an analysis of repositioning strategies for major drugs in the USA, drugs with new indications, or new formulations, can be exclusively sold for a long period by appropriately combining patent protection and market exclusivity based on drug approvals, even after expiration of the active ingredient patent [5]. Kapcynski analyzed secondary patents protecting NMEs that were approved in the USA from 1988 to 2005 and reported that formulation patents provided exclusivity periods of 6.5 years, whereas use patents had exclusivity periods of 7.4 years [6]. In addition, Dunn analyzed the timing of patent filing and market exclusivity, focusing on the NCEs approved in the USA from 2000 to 2010 [7]. Drug LCM in Japan has also been studied, with a focus on drug approvals and patent protections in some investigations. For example, a case analysis performed on 12 drugs in Japan noted that the patent protection of NMEs and improved products (e.g., new formulations), were crucial to the implementation of a successful drug LCM [8]. However, no quantitative analysis of drug LCM in Japan has been conducted from the perspective of those two key elements.

Before starting this survey, we carried out a comparative case analysis of drug LCM between Japan and the USA, focusing on the differences in patent term extension systems, in which a patent term can be extended based on a drug approval. In this comparative case analysis, we found that the unique patent term extension system has an important role in Japanese drug LCM. The key difference between the countries is the number of patents that could be extended with a single drug approval. In the USA, even if multiple drug approvals for the same active ingredient exist, only

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one patent can be extended based on the initial approval. By contrast, in Japan, if multiple drug approvals for the same active ingredient are obtained, then multiple patent term extensions can be obtained based on any of them. We also suggested some patent extension strategies in Japan and the USA based on this key difference, which represents a characteristic feature of Japanese drug LCM [9].

Therefore, in this survey, we quantitatively analyzed the LCM of 21 Japanese blockbuster drugs using a novel analytical framework that focuses on drug approval and patent term extension by taking this characteristic of Japanese drug LCM into consideration.

Background

Drug approval processes and re-examination systems in Japan

Drug companies need to obtain drug approvals from the Minister of Health, Labor, and Welfare when they launch drugs in Japan. Drug approvals are based on documents submitted to the Pharmaceuticals and Medical Devices Agency (PMDA); these documents include clinical trial results. The drug re-examination system performs a re-examination of the safety and efficacy of a 'new drug' after a certain post-marketing period, called the 'drug re-examination period' [10]. A 'new drug' is categorized into one of ten application divisions, including NMEs, drugs with new indications, new formulation drugs, new combination drugs, drugs with new routes of administration, and drugs with new doses. The drug re-examination period depends on these application types; for example, it is 8 years for an NME, 4 years for drugs with new indications, and 6 years for new combinations of drugs.

Generic drugs can be approved by submitting fewer clinical data to the requisite authority, under the condition that equivalent bioavailability with the brand drug has been proven in human trials. However, when the approval application for a generic drug is submitted during the drug re-examination period of a brand drug, equivalent detailed documents are required. As a result, the launch of generic drugs is restricted during the drug re-examination period, and companies manufacturing brand drugs obtain market exclusivity during this period [10].

Patent term extensions in Japan

Drug companies can build a long-lasting and robust entry barrier and maximize the profitability of a drug by obtaining drug patents (e.g., substance patents, use patents, and formulation patents) and further extending their terms. The patent term extension system is a system in which a patent term, which typically expires 20 years after the filing date, can be extended based on a drug approval, if certain requirements are satisfied. Multiple drug patents can be extended based on a single drug approval. If multiple drug approvals exist for the same active ingredient, then patent terms can be individually extended based on any of these drug approvals [9]. The patent term can be extended by a period from the start date of clinical trials or the date of registration of establishment of a patent right (whichever is later), until the day before the arrival of drug approval, which can be up to 5 years. The scope of patent protection during the extension period is limited to the drug product and use(s) that have received approval. Thus, during the extension period, patents do not cover drugs that have different active ingredients or indications from those of approved drugs.

Model of drug LCM in Japan

Fig. 1 shows the drug LCM model in Japan, based on product improvements and product line extensions. In this model, a drug company acquires drug approval for an NME with indication X. Subsequently, this company obtains drug approval for a new indication (indication Y) for the same active ingredient, ingredient A.

Previous to those drug approvals, the company acquires a substance patent and two use patents for the new active ingredient A, indication X, and indication Y, respectively.

In Japan, multiple drug patents can be extended based on a single drug approval. For example, the terms of a substance patent (active ingredient A) and a use patent (indication X) can both be extended based on the drug approval of an NME (indication X). Moreover, because patent terms can be individually extended based on any drug approvals in Japan if multiple drug approvals exist, the terms of the substance patent (active ingredient A) and use patent (indication Y) can also be extended based on the drug approval for a new indication (indication Y). However, the patent does not protect a drug with an indication other than indication X during the extension period based on the drug approval of an NME, or a drug with indications other than indication Y during the extension period, based on the drug approval of new indication Y.

Implementing such a drug LCM prevents generic drug companies from launching a generic drug for indication X at least until the end of the market exclusivity period for NMEs, and the expiration of any patent term extensions. By contrast, launching a generic drug for indication X is possible if the extended patent term based on drug approval of the NMEs has expired, even though the extension period based on drug approval for new indication Y has not yet been completed. However, launching a generic drug for indication Y is not possible before expiry of the extended patent term based on drug approval for the new indication Y. Therefore, drug companies can sustain a certain level of sales of drugs containing the active ingredient A after launch of generic drugs for indication X by generic drug companies, because the company manufacturing the brand drug can exclusively sell drugs for indication Y.

Data and analysis framework

Drug selection

In this survey, we chose 21 drugs that had been ranked in the top ten at least once in the drug sales rankings in Japan between 2004 and 2013; we refer to these drugs as 'blockbusters' (Table 1). We limited our survey to 21 blockbuster drugs because drug LCM, especially product improvements and product line extensions, is an expensive practice that pharmaceutical companies would not implement for drugs with low sales.

Moreover, the growth, maturity, and decline stages of each drug were identified for further analysis based on sales in Japan for further analysis (Table 1). The growth stage was defined as the period from drug approval to marked peak sales (years), the maturity stage was the period during which 60% or more of peak sales was sustained, and the decline stage was the period in which sales decreased to <60%. Sales of drug combinations containing any of the 21 drugs were included in the calculations.

Tamiflu was excluded from the analysis by stage because the growth, maturity, and declines could not be identified because of wide fluctuations in its sales. Nu-lotan was also excluded from the maturity and the decline-stage analyses because sales data were

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