How to Design a Competing System: Creating a Looping-out Knowledge Cycle Model of the US Pharmaceutical Industry

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Abstract--**Governments across the globe establish systems to maintain diversity in specific industries and avoid the formation of oligopolistic market structures. The U.S. government has made special provisions for the country's pharmaceutical industry; namely, the Orange Book, Abbreviated New Drug Application (ANDA), and the Bolar Act. These three provisions combine into a special competing system that offers "Product-Patent Linkage" (PPL), accelerating generic products, and research and development free space to establish a level playing field between generic and brand drug companies. We construct a looping-out knowledge cycle model to examine the relationship between knowledge resources, competing system and oligopoly, and find that the "Knowledge conversion" point determines if knowledge can loop away from private proprietary and avoid oligopolistic tendencies. We believe that competing system should be designed to enable the formation of the knowledge conversion point, which prompts knowledge flow from private proprietary into the public domain. On the other hand, the importance of accelerating imitation and free space for research and development is also important for designing a competing system.**

I. INTRODUCTION

Okuguchi and Szidarovszky described oligopoly as "a state of industry where a small number of firms produce homogeneous goods or close substitutes, competitively [1]." Further, Severová *et al*. pointed out that oligopoly can be problematic as it significantly affects the product prices based on the relative market share [2].

Price control is an important aspect of industrial development that relates to economic problems and social welfare. Especially, the price of medicine is a key factor that affects consumer access and treatment outcomes, and providing inexpensive and quality medication is important for governments [3] [4]. To achieve this, governments such as those in China, India, and Norway decide the maximum price of medicines [5]. Another method is to maintain a state of high competitiveness in the industry to thwart monopolistic or oligopolistic tendencies. The United States chose this second method to maintain competitiveness in its pharmaceutical industry [3], allowing the market to accommodate various companies. The market share of the top 20 corporations in the U.S. pharmaceutical industry is 63.4%, and the top four companies only occupy 21.7% of the market share [6]. Market competition has granted both growth and dynamism to the U.S. pharmaceutical industry. This study uses the U.S. pharmaceutical industry as a reference and analyzes the systems needed to incentivize new entrants in the industry. The analysis uses our model to examine the relationship between systems and oligopoly, and observes the changes to market dynamics in the absence of these systems.

II. LITERATURE REVIEW

This study considers the following themes in research literature: (1) Branded drugs, generic drugs, intellectual property, and (2) The Drug Price Competition and Patent Term Restoration Act.

A. Branded drugs, generic drugs, and intellectual property

Kaplan *et al*. pointed out that competition in the U.S. pharmaceutical industry is primarily between large generic drug companies and large brand drug companies [3]. For the latter, developing new drugs requires long-term investment in both time and money with lower success ratios [7]; therefore, protecting technical knowledge and new products is crucial. Large brands use the patent system to protect intellectual property and ensure return on investment. The primary function of the patent system is to enable inventors or patent owners to obtain exclusive right of their intellectual property and thereby promote industrial development (e.g., the patent system protects intellectual property in a knowledge-based field such as biotechnology) [8]. Simultaneously, new technology and products are released to the public and third parties are allowed access to intellectual property after expiry of the related patents. Offering incentives (e.g., exclusive rights) to inventors and sharing intellectual property are two methods of promoting invention and innovation.

However, this exclusive right ends after the expiry of the patent and brand drug companies cede their advantage to imitators [9]. In the pharmaceutical industry, a majority of imitators are generic drug companies. The latter release generic drugs that imitate the original but at a much lower price; consequently, a balanced market share and stable drug prices ensue. However, brand drug companies collect and privatize knowledge because they are first movers and prevent new entrants from establishing a foothold. Therefore, both brand drug companies and generic drug companies have their own advantages, and the challenge is to maintain a diverse market through competitive balance between brands and generic drug manufacturers [4]. To maintain competitiveness the regulations or systems must be impartial for all stakeholders. The patent system, offers the investor a possibility of recovering the investment; however, it also asks the patent applicant to publish their findings. However, only a patent system is insufficient for balancing the market power and maintaining diversity. We observe this in some

bio-related industries where oligopoly co-exists with a patent system [10] [11]. How does the U.S. pharmaceutical industry avoid high market concentration? Moreover, what are the special requirements of designing a competing system?

B. The Drug Price Competition and Patent Term Restoration Act

There is a long history of pharmaceutical regulation in the United States; however, the old regulations were proving a poor fit for the rapid developments of the modern age and a new system was deemed necessary. It would have to solve various problems such as market entry barriers for generic drugs, and incentivizing new entrants to produce low-priced generic drugs [5]. To promote generic drugs the government can consider several strategies, such as reducing barriers of entry into the generic drugs market; providing incentives to encourage new entrants producing lower-priced generic drugs; and improving public confidence in generic drugs [12]. Under these premises, in 1984, a federal law known as the The Drug Price Competition and Patent Term Restoration Act, also known as the Hatch-Waxman Act, was introduced and included the following components. It revised the Abbreviated New Drug Application (ANDA), which offers generic drugs an easier and faster way to gain Food and Drug Administration (FDA) approval; research exception before expiry of patent; and 180-Day marketing exclusivity for the first successful challenger. For brand drug companies, the Hatch-Waxman Act offers the extension of patent protection and 30 months of market exclusivity [4] [13]. Therefore, the Act attempts to balance the brand power of drug companies with the benefits offered by generic drugs [4].

III. ANALYSIS

To maintain diversity and avoid oligopoly in the pharmaceutical industry, the US government established some rules and regulations. In this study, we define such checks-and-balances as a "competing system." The ultimate objective of a competing system is to provide equal opportunities to both generic and brand drug companies in the market. Here, we analyze three parts of the special competing systems of the U.S. pharmaceutical industry, and discuss how these systems create new space or change the inferior image of generic drug companies.

A. The Orange Book

The FDA publishes the "Approved Drug Products with Therapeutic Equivalence Evaluations," also known as the "Orange Book." It discloses patents for drug ingredients, product formulation, composition, and usage methods [14]. This data is obtained from the New Drug Application (NDA) that must be submitted to the FDA. The most important information in the Orange Book is the relationship between drugs and patent information. Patent strategies differ for every drug and a single could be supported by several patents and vice versa [14] [16], making it difficult to understand patent portfolios. We define this relationship between patents and products as "product-patent linkage" (PPL), and as PPL is difficult to assess in the short term, new entrants in the pharmaceutical industry face high risks of patent infringement. However, the Orange Book enables the collection and disclosure of PPL information, allowing new entrants to assess intellectual property portfolios, confirm possible patent infringement, and save time and money for fresh research in case of clashes with the patented range.

B. The Abbreviated New Drug Application (ANDA)

The ANDA is a system revised by the U.S. government based on the Hatch-Waxman Act. Enforced by Hatch-Waxman Act, the ANDA system allows a generic drug company, under certain conditions, to shorten the evaluation period and obtain FDA approval for marketing before the expiration of the brand drug patent. The generic drug company must satisfy the following conditions: first, the "paragraph IV certification" that certifies the patent in question as invalid or otherwise not infringed by the generic product; and second, notifying the patent holder of ANDA submission [17]. If the patent holder does not respond within 45 days of the ANDA notification, the FDA will approve the launch of the generic drug. Further, release timings will significantly affect the profit generation from new drug launches. The Institute for Policy Innovation (IPI) noted that eventually, drug companies would engage in price competition to gain market share [18]; therefore, the ANDA system offers a way to facilitate the launch of generic drugs and reduce the time between the expiration of a branded drug patent and profit recovery for the generic one. This is a crucial for the survival of generic drug companies in this highly competitive industry.

C. The Bolar Act

The Roche *v. Bolar* patent lawsuit is an important case in the pharmaceutical industry. Both Roche and Bolar are pharmaceutical companies; however, Bolar began their experiments before expiration of Roche's drug patent. Roche claimed that Bolar infringed on their patented technology, and after multiple appeals, the court finally ruled that generic companies have developmental freedom if their experiments are for obtaining approval for a new drug [19]. This act is a landmark for generic drug companies because it permits them to develop drugs that have existing patents, under certain conditions, and promotes R&D activities in generic companies [4].

The Bolar Act contributes in creating free space for generic companies to use patented technology for drugs approval examination; however, there are many controversial cases of patent infringement in academic research [20]. Here, we consider research freedom related to academics, for example, non-profit research at universities could use patented technology before existing patents expire. Under the Bolar Act, after product finalization, the period of evaluating and designing marketing strategies falls under the

development stage; however, the Act fails to provide clear regulations that protect the academic field's right to research. U.S. case law recognizes that experimentation or non-profit use is not included under infringement, however, this doctrine is unclear, and there have been contrary judgments [21]. At least, the free developmental space will reduce time wastage and has the potential to protect research freedom.

Table 1 shows the relationship between these three parts in the left column. The right column details the corresponding requirement of new entrants when they enter the industry. Large pioneering companies can raise massive obstacles to thwart new competitors, forcing them to rely on coercive techniques such as government systems or policies. The Orange Book, ANDA, and the Bolar Act together create a competing system to find a balance between brand and generic drug companies.

TABLE 1. ANALYTICAL FRAMEWORK

Components of the competing system	Requirement
Orange Book	Product-patent linkage disclosure
Abbreviated New Drug Application (ANDA)	Accelerating generic products
Bolar Act	Research and development free space

Table 1 contains our analytical framework based on the existing system in the U.S. pharmaceutical industry.

However, understanding each part is insufficient in answering how the competing system prevents situations of oligopoly/monopoly. Therefore, in the next section, we combine all systems in a model that examines how the competing system affects market situation.

IV. MODEL

Prior studies show that the development in the pharmaceutical industry is closely linked with the field of biology, which is a knowledge intensive subject [22] [23]. This is evident from the relationship between the industry and the patent system. Grootendorst *et al.* and Biddle both state that patenting is common in the pharmaceutical industry and indicate that intellectual property is an important factor [20] [22]. Therefore, we construct the model from the perspective of knowledge flow considering the status of the industry.

Figure 1 shows the looping-out knowledge cycle in the U.S. pharmaceutical industry. The grey line represents the flow of knowledge, the green route indicates life cycle management by brand drug companies, and the red line denotes the active generic drug companies. Here we use blue boxes to denote the competing system designed by the government.

Fig. 1 shows our looping-out knowledge cycle in the U.S. pharmaceutical industry. We assume all knowledge and natural resources are initially in the public domain. The industry gains shape when corporations apply public knowledge and create marketable products. In Fig. 1, companies or research institutions begin to explore natural resources, defined as "knowledge exploration." If corporations discovered something valuable at this stage, they would evaluate its market potential and develop the product, which is defined as "exploitation" state. Many public research institutions might release their findings for open access and use. However, private institutions and corporations form an exclusive knowledge circle. Therefore, knowledge resources or natural resources would move from the public domain into a private proprietary cycle, such as the brand drug proprietary cycle in Fig. 1. As this proprietary cycle is a profit source, its maintenance, and expansion is crucial for private companies or institutions. They can use techniques of life cycle management (green route in Fig. 1), such as patent or licensing strategies, to close the knowledge loop in the brand cycle and contain the feedback. Thus, if there is no other regulation to force companies (or institutions) to release more knowledge from the proprietary cycle, the majority of extracted knowledge will be unable to return to the public domain.

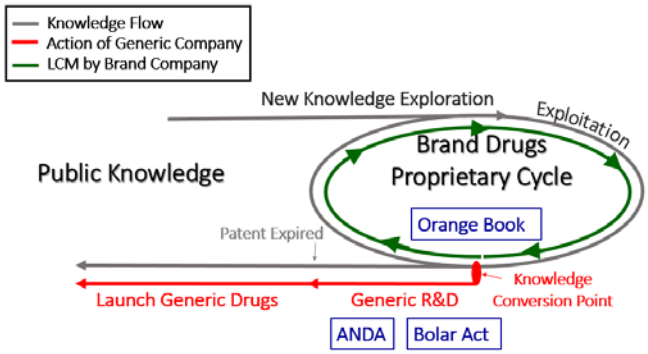

Figure 1. The looping-out knowledge cycle in the U.S. pharmaceutical industry.

New comers find it difficult to enter the market without access to knowledge. However, this situation did not occur in the U.S. pharmaceutical industry. When we incorporate the competing system (here, Orange Book, the Bolar Act, and the ANDA) into the model, we observe that the PPL acts as a push to generic drug companies. As mentioned in the literature review, the drug patent strategies are always complicated [15] [16], and it is difficult to understand the entire patent portfolio of one drug through a patent searching system or other fragmentary data. After PPL disclosure (by the Orange Book), the companies easily and quickly asses the patent-product portfolio of the industry, and start their business domain or product R&D into this industry, as the red arrow shows in Fig. 1. Therefore, the disclosure of PPL is the point where knowledge begins to flow to the public domain again, and can be used by third parties (generic drug companies) and we call this "knowledge conversion." This also signifies that the generic drug companies can enter the market with lower risk of patent infringement.

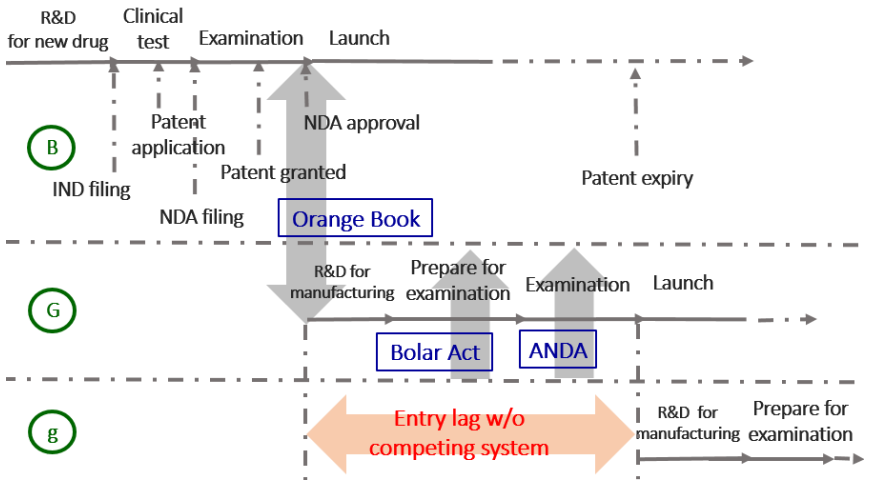

Figure2. The entry lag without competing system.

Figure 2 shows the entry lag for a generic drug company without the presence of a competing system. The zone with marked B indicates the situation of brand drug companies, the G zone is the situation of generic drug companies with a competing system (shown by blue boxes and grey arrows), and the g zone is the situation of generic drug companies without a competing system. The red arrow indicates the lag period of generic drugs entry without a competing system.

However, only PPL disclosure is not enough to create incentives and attract generic drug companies to join the market. Without free space for R&D which is protected by the Bolar Act, and although the other potential entrants know the current patent portfolio, it is still difficult to complete their R&D process before the patent expires. On the other hand, the ANDA system shortens the examination period of product launch. Both systems can facilitate the R&D process and give new entrants the confidence to recapture their investment. Figure 2 shows the launch timeline combination of three drugs: B zone shows the activities of the brand drug company; G zone shows the situation of the generic drug company; and finally, the g zone shows the situation of generic drug companies without the competing system. Without an Orange book to disclose the PPL, it will be very difficult to help new entrants distinguish which types of technologies they can use to start a new business without patent infringement. However, as Figure 2 reveals, only the Orange book is insufficient in increasing incentives for gathering generic players. Without the Bolar Act and the ANDA system, all the experiments and filing procedure would wait until the related patent/s expired. This entry lag will reduce the return of generic drugs, because the second generation of brand drugs may be prepared for release during this time. Therefore, PPL is just the first step in creating a competing system; however, it still needs other components to improve the overall procedure and ensure the survival of generic drug companies.

Based on this model, we conclude that the design of a competing system should facilitate the knowledge conversion point, as it is crucial in diverting the flow of knowledge from private proprietary to the public domain, and preventing oligopoly in a particular industry. Subsequently, to maintain the competitiveness of the new entrants, the regulations or policies for accelerating generic products, and creating free space for R&D free space, are also necessary for a competing system. Inclusion of these parts will enhance the confidence of generic drug companies to join the market with lower risks and higher profits, and prevent oligopolistic tendencies in the U.S. pharmaceutical industry.

V. DISCUSSION

A. Patent and PPL

In our looping-out knowledge cycle model, we mentioned that the formation of a knowledge conversion point is important for releasing knowledge back into the public domain. Even without a competing system, the proprietary knowledge can be released from the brand drugs proprietary cycle, for example, through a patent system. As a tool to promote industry development, the patent system requires the applicant to publish its finding publicly, thereby transferring this knowledge to the entire industry. However, when applicants file patents for exclusive rights to ensure profits, they also publish their knowhow to third parties. However, only a patent system is not enough to trigger knowledge flow in the pharmaceutical industry. The published documents in the patent system allows third parties to “know” how to apply this knowledge, but it does not allow third parties to know what “kind” of technology is usable (i.e., not patent protected). The reasons for this are as follows: first, defects in the long-term R&D and commercialization processes; and second, the complicated patent protection strategies.

We discuss the first point in the previous section. Bains mentions that whether a success or failure, launching a technically successful drug costs more than US$1 billion and takes 12.5 years [24]. Regulations in the United States require drug companies to apply for the IND (Investigational New

Drug) for clinical tests, and after the clinical test, they must apply to the NDA and await examination. Even for generic drugs, the development process and examination period requires a lot of time. If all the R&D procedures and examination processes waited until the related patent expires, while competing with other similar generic drugs or the next generation of brand drugs, generic drugs may not obtain reasonable returns from the market.

As for the second point, patent strategies for drugs always use the layer or duplication method to extend their virtual protected periods, and the relationship between products and patents is complex. For example, several different patents may support a single drug, and vice versa. Yamanaka and Kano constructed a model demonstrating how a brand drug company extends product marketability by filing patents with different objectives for a single drug. Further, the authors discussed the case of Atcand® and Atacand HTC®, which are angiotensin II receptor antagonists. In total, six patents cover these drugs, including three substance patents, one formulation patent, and two combination drugs patents. These six patents have five different expiration dates, and the days between earliest and latest date is 1145 days [16].

We can obtain data on the relationship between patents and products of the pharmaceutical industry easily because the Orange book records the PPL. However, without an Orange book, if the generic companies want to launch a new drug in the market, they will not know how to avoid the infringement risk from this layer-based patent protection strategy. Therefore, the disclosure of PPL is the first and most important step in the competing system, to facilitate and promote knowledge flow across the private and public domains.

If the U.S. pharmaceutical industry did not have this competing system to maintain the knowledge flow, it would be unable to form the knowledge conversion point. Without a system to disclose the PPL, new entrants would not achieve their business targets without the risk of infringement, which will be the first obstacle in reducing new entrants in the market. Without them, knowledge will be locked into the proprietary cycle, which will grow through feedback from exploration and exploitation and large, well-established companies will control the majority of knowledge resources. Therefore, even if new entrants attempt to enter the market, before they are hindered by the complicated PPL, they will have no access to applicable public knowledge to form their own proprietary cycles, eventually resulting in an oligopolistic market.

B. The applicability of looping-out knowledge cycle model

Whether the competing system is attracts more generic players to the market can be known by examining the share of generic drugs in the market after the base year. The first edition of the Orange book was published in 1980; the ANDA system and the Bolar Act are related to the Hatch-Waxman Act, which was enacted in 1984. According to a report published by the Generic Pharmaceutical Association, the generic substitution rate in 1994, 2004, and 2014 reached to 42%, 50%, and 66%, respectively [25]. In 2014, 86% of all prescription medicines dispensed in the United States were of the generic kind, and more than 90% of approved drugs have a generic version [25] [26]. The Congressional Budget Office (CBO) also noted that the generic drugs market share in 1984 was only 19%, but had grown to 43% by 1996 [3] [27]. Based on this statistical data, we can judge that the competing system has a certain influence in raising the market share of generic drugs.

Alvin Toffler noted that we are now living in a "knowledge-based society" [28]. Nonaka also mentioned that innovation is the source of sustainable competitive advantage in society [29]. Cardinal and Powell *et al*. both emphasized the link between the R&D process for drugs and biological knowledge [23] [30]. The link between them can reveal why the patent system is so important in the pharmaceutical industry. There is a large volume of discussion on the knowledge model in industries; however, before 1990, most knowledge models focused on knowledge management and information gathering [31]. In recent times, studies have begun to focus on knowledge creation. Nonaka *et al*. mention that knowledge is dynamic, and present a SECI process to explain how knowledge is created. They created a four quadrants model: the first quadrant is externalization, in which the knowledge goes from tacit to explicit; the second quadrant is socialization, knowledge goes from tacit to tacit; the third quadrant is internalization, in which the knowledge goes from explicit to tacit, and the final quadrant is the combination, knowledge going from explicit to explicit. Therefore, in this model, knowledge creation spirals between these four quadrants [29].

Compared to our looping-out knowledge cycle model, the SECI model emphasizes that spiral knowledge process will become larger, and can trigger the generation of new spirals, similar to the feedback enlarging the knowledge cycle in our model. The basic concept of the knowledge between SECI model and our looping-out knowledge cycle model is similar; however, the SECI model focuses on how knowledge is created, and does not tackle the question of conflict in knowledge creation processes between competitors. In addition, although the SECI model discusses the interaction between organization and environment, it does not discuss the interaction between knowledge and public policy issues.

Amit and Schoemaker (1993) presented a resource-based model for the pharmaceutical industry. This model is for broadly discussed the sustainable strategies in the pharmaceutical industry and explains how resources transform the firm [32]. The cooperation between departments of a company is important; however, it still does not consider the issue of resource monopolization between competitors. In contrast, our looping-out knowledge cycle model considers the relationship between knowledge cycle and competitors, a new perspective in explaining how the competing system affects knowledge flow in an industry.

On the other hand, combining each part of competing

system with a systematic analysis of the oligopoly problem is the unique aspect of our study. The empirical data for each part of the competing system may be viewed in several prior studies [4] [14] [17] [25] [26]; however, this is the first time they have been combined from the knowledge cycle view. Prior studies have noted that when research is sequential, subsequent research may be discouraged by stronger patents [13] [20] [22], especially in the biotechnology industry [33]. However, through our looping-out knowledge cycle model, the problem could be solved even the strong patent system existed.

VI. CONCLUSION

Maintaining diversity and avoiding oligopolistic tendencies is important for industrial development. We analyzed three systems in the U.S. pharmaceutical industry; namely, the Orange Book, ANDA, and the Bolar Act, and examined the interaction between these systems and the flow of knowledge. The Orange book, ANDA and the Bolar Act represent PPL disclosure, growth in generic products, and research and development free space, respectively, and are important factors for new entrants in this industry. We combine them to form a competing system in the U.S. pharmaceutical industry that maintains diversity and competitiveness. Further, we construct a looping-out knowledge cycle model and find that PPL plays an important role in the formation of "Knowledge conversion" point, enabling the flow of knowledge between private proprietary and the public domain. Based on our model, new entrants cannot struggle to assess the patent portfolio of the industry in absence of the PPL, and find it difficult to conduct business.

Analyzing both models, we concluded that the Knowledge conversion point is important when designing a competing system because it triggers the flow of knowledge to the public domain paving the way for new entrants, and we believe this model and concept could be applicable in other oligopolistic industries. However, this analysis is based on the perspective of knowledge cycles and intellectual property; therefore, the model has its limitations. First, the model is dependent on the intellectual property strategy. Therefore, the applicable industry should have a similar intellectual property protection strategy as the pharmaceutical industry, for example, the patent number of each product, and the dependence of the patent system. We anticipate that future studies will focus on finding other factors and include those factors in our knowledge cycle model. In addition, we only examine the knowledge flow between firms and do not comprehensively analyze the R&D activities of companies. This is our next step in creating a more robust theoretical framework.

REFERENCES

[1] Okuguchi, K. and F. Szidarovszky, *The Theory of Oligopoly with Multi-Product Firms.* NY: Springer-Verlag Berlin Heidelberg.

[2] Severová, L., L. Kopecká, R. Svoboda, and J. Brčák, "Oligopoly Competition in the Market with Food Products," *Agriculture Economics (Czech)*, vol. 57, 2011 (12), pp. 580–588, 2011.

[3] Kaplan, W. A., V. J. Wirtz, and P. Stephens, "The Market Dynamics of Generic Medicines in the Private Sector of 19 Low and Middle Income Countries between 2001 and 2011: A Descriptive Time Series Analysis," *PLoS ONE*, vol. 8(9): e74399. doi:10.1371/journal.pone.0074399, 2013.

[4] Chang, R. "Patent Linkage: Its History, Background, and Policy Function," *Intellectual Property Rights (Taiwan)*, vol. 196, pp. 5–19, 2015.

[5] World Health Organization; The World Medicines Situation 2011 (3rd ed.). Switzerland, World Health Organization. Retrieved 1/5/16 World Health Organization, http://apps.who.int/medicinedocs/documents/s20054en/s20054en.pdf?ua=1

[6] Statista. "Top 20 pharmaceutical companies worldwide based on prescription drug market share in 2014 and 2020," Retrieved 02/12/16 Statista, http://www.statista.com/statistics/309425/prescription-drugs-market-shares-by-top-companies-globally/

[7] Tanaka, K. *The Evaluation based on the Life Cycle Management of Medicine - Product-Generation Patent-Portfolio Map*. Kobe University, Japan, 2007.

[8] Moschini, G. "Competition Issues in the Seed Industry and the Role of Intellectual Property," *Choice*, vol. 25(2), Retrieved 10/30/15 Choice, http://www.choicesmagazine.org/magazine/article.php?article=120

[9] Lichtenberg, F. R. and T. J. Philipson, "The Dual Effects of Intellectual Property Regulations: Within- and between- Patent Competition in the U.S. Pharmaceuticals Industry," *The Journal of Law and Economics*, vol. 45(2), pp. 643–672, 2002.

[10] Tekgüç, H. "Oligopoly and Price Transmission in Turkey's Fluid Milk Market," *Agribusiness*, vol. 29, pp. 293–305, 2013.

[11] Balasubramaniam, K. V. and V. Sita, "Access to Vaccines and the Vaccine Industry - An Analysis," *Journal of Vaccines & Vaccination*, 5, 218. doi:10.4172/2157-7560.1000218, 2014

[12] World Health Organization (WHO).; "The World Medicines Situation 2011 (3rd ed.)," Switzerland, World Health Organization, 2011. Retrieved Jan 5, 2016, from http://apps.who.int/medicinedocs/documents/s20054en/s20054en.pdf?ua=1.

[13] Gallini, N. T. "The Economics of Patents: Lessons from Recent U.S. Patent Reform," *The Journal of Economic Perspectives*, vol. 16 (2), pp.131–154, 2002.

[14] Holovac, M. A. "A Balancing Act in the United States Drug Industry: Pioneer and Generic Drugs, the Orange Book, Marketing Protection and the US Consumer," *World Patent Information*, vol. 26, pp. 123–129, 2004.

[15] Pearce II, J. A. "How Companies Can Preserve Market Dominance after Patent Expire," *Long Range Planning*, vol. 39, pp. 71–87, 2006.

[16] Yamanaka, T. and S. Kano, "Patent Term Extension Systems Differentiate Japanese and US Drug Lifecycle Management," *Druf Discovery Today*, vol. 21(1), pp.111–117, 2016.

[17] U.S. Food and Drug Administration; "*Paragraph IV Drug Product Applications: Generic Drug Patent Challenge Notifications"* (2014, Mar 27). Retrieved 1/5/2016 U.S. Food and Drug Administration, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm147166.htm

[18] Matthews, M. "Who's Afraid of Pharmaceutical Advertising? A Response to a Changing Health Care System," *Institute for Policy Innovation*, Policy Report 155, May 2001.

[19] Roche Products, Inc. v. *Bolar Pharmaceutical Co. Inc*., 733 F.2d 858 (Fed. Cir. 1984)

[20] Biddle, J. B. "Can Patents Prohibit Research? On the Social Epistemology of Patenting and Licensing in Science," *Studies in History and Philosophy of Science*, vol. 45, pp. 14–23, 2014.

[21] Pfizer, Inc. v. *International Rectifier Corp.*, 217 U.S.P.Q. (BNA) 157 (C.D. cal. 1982)

[22] Grootendorst, P., A. Hollis, D. K. Levine, T. Pogge, and A. M. Edwards,

"New Approaches to Rewarding Pharmaceutical Innovation," *Canadian Medical Association*, vol. 183(6), pp. 681–685, 2011.

[23] Cardinal, L. B. "Technological Innovation in the Pharmaceutical Industry: The Use of Organization Control in Managing Research and Development," *Organization Science*, vol. 12(1), pp. 19–36, 2001.

[24] Bains, W. "Failure Rates in Drug Discovery and Development: Will We Ever Get Any Better?" *Drug Discovery World*, vol. Fall 2004, pp. 9–18, 2016.

[25] Generic Pharmaceutical Association; "Hatch-Waxman: Driving Access, Savings & Innovation (Annual generic utilization and savings data compiled from IMS Health," the Generic Pharmaceutical Association, and the Congress Budget Office) Retrieved Mar 28, 2016, from http://www.gphaonline.org/media/cms/Hatch_Waxman_Driving_Access_Savings_and_Innovation.pdf

[26] Chu,S. "Introduction and Discussion on Patent Listing in U.S. 20 Patent Linkage System," *Intellectual Property Rights (Taiwan)*, vol. 96, pp. 20–33, 2015.

[27] US Congressional Budget Office (CBO); *How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry*. Washington, DC, US Congressional Budget Office, 1998.

[28] Toffler, A. *Powershift: Knowledge, Wealth and Violence at the Edge of the 21st Century*. Bantam Books, New York, 1990.

[29] Nonaka, I., R. Toyama, and N. Konno, "SECI, Ba and Leadership: a Unified Model of Dynamic Knowledge Creation," *Long Range Planning*, vol. 33, pp. 5–34, 2000.

[30] Powell, W., K. Koput, and L. Smith-Doerr, "Inter-organizational Collaboration and the Locus of Innovation: Networks of Learning in Biotechology," *Administrative Science Quarterly*, vol. 41, pp. 116–145, 1996.

[31] Bierly, P. and A. Chakrabarti, "Generic Knowledge Straategies in the U.S. Pharmaceutical Industry," *Strategic Management Journal*, vol. 17 (Winter Special Issue), pp. 123–135, 1996.

[32] Amit, R. and P. J. H. Schoemaker, "Strategic assets and organization rent," *Strategic Management Journal*, vol. 14(1), pp. 33–46, 1993.

[33] Oldham, P., S. Hall, and O. Forero, "Biological Diversity in the Patent System," *PLoS ONE*, vol. 8 (11): e78737. doi: 10.1371/journal.pone.0078737