Asian Journal of Innovation and Policy (2019) 8.2:180-207
DOI: http//dx.doi.org/10.7545/ajip.2019.8.2.180

Creation of System Dynamics in an Uncertain and Complex Market: The Case of Korea's Evolving Biopharmaceutical Industry

Jeong Hyop Lee [*], Jaewon Kim [**], Byung-Hwan Hyeon [***]

Abstract This article explores the historical evolutionary process of the bio-pharmaceutical industry of Korea, and how intentional and unintentional policy interventions have triggered the creation of the industry's system dynamics and paved the way for the generation of a few global leading products, including biosimilar, as well as next-generation therapeutics of gene and cell. The policies cover the simple technology transfer of API synthesis to overcome the endemic parasitic disease, new substance patent adoption and new drug development consortia, human resource development, various national initiatives influenced by the Human Genome Project, and venture promotion schemes. The scope and implementation tools under these policies have been aligned and refined to transform traditional fine chemical-based pharmaceuticals, to stimulate large companies' participation and to create technology-based venture companies in the biopharma business of Korea.

Keywords Biopharmaceutical industry, policy interventions, system dynamics, uncertainty and complexity, industrial evolution

I. Introduction

Bio-industry[1] and associated biotechnology have commanded worldwide attention over the past decade. Ever-increasing concerns over the dependence

Submitted, May 1, 2019; Accepted, June 11, 2019
[*] Innovation Development and Partners, Seoul, Korea; jeonghyoplee@gmail.com
[**] Science Technology and Innovation Policy Institute (STIPI) at King Mongkut's University of Technology Thonburi (KMUTT), Thailand; jaewon.kim@mail.kmutt.ac.th
[***] Daejeon University, Korea; hyunvv@gmail.com

[1] Bio-industry is where goods and services are produced by applying science and technology to the use of biological systems, living organisms or its derivatives. Bio-industry can be segmented into namely bio-pharmaceuticals, bio-agriculture, bio-services, and bio-industrial on the basis of applications. Benefits of accelerating progress of biotechnology include: better therapeutic and diagnostic approaches and solutions; supplies of potentially safer products at reduced health care costs; enhanced crop productivity; or reduced environmental hazards caused by chemicals (Falket et al., 2002; Zika et al., 2007).

on fast-depleting conventional sources of energy, climate change and the ever-increasing need for better cure for cancer or rare diseases have ignited interest in developing biotechnology. So much so that many governments have increasingly emphasized the promotion of bio-industry as an important means of achieving green and sustainable economic growth. The demand for biopharmaceuticals, in particular, has continued to rise exponentially due to the prevalence of chronic diseases and other life-threatening diseases for which there is no available or affordable treatments. The biopharmaceutical industry has attracted huge R&D investments, as it is, in nature, particularly critical for the players to stay ahead of the latest innovations.

However, technical and regulatory hurdles in the new bio drug development, production and delivery are often too high, and its R&D is notoriously time consuming and costly. The biopharmaceutical industry, by nature, represents a high level of risk and uncertainty, and is also fraught with high complexity that associates not only technology and stakeholder networks, but also complex social issues such as public awareness, human rights, culture and religion. The elimination of the high market access and reimbursement hurdles is extremely challenging, but newly set regulations or policies to overcome those challenges may be also fraught with unwanted consequences within the rapidly changing biopharma ecosystem.

Under such uncertainty and complexity, only a few advanced countries have led the biopharmaceutical industry. It inherently takes a long time to conceive a sophisticated biopharmaceutical system and trigger its industrial dynamics. It also requires networked and combined actors with cognitive, organizational and strategic proximity, which are mostly embedded in a specific territory and social system (Depret and Hamdouch, 2010). The Korean experience of nurturing the biopharmaceutical industry, however, is quite distinctive. It does not have a long history of development, thus had hardly accumulated scientific and industrial skills and knowledge, networks, and financial assets. Regardless of its weak foundation, intentional and unintentional policy interventions have triggered the industry's system dynamics in a short period of time. Korea has managed to successfully register a dynamic growth in biopharmaceuticals in both quantitative and qualitative terms over a few decades. The biopharmaceutical industry is currently one of the fastest evolving and strategically important industries in Korea and has attracted extensive regulatory and financial supports. Based on robust R&D and a growing pool of highly-skilled human resources, not only large leading firms and chaebols, but also bioventure firms and start-ups have become competitive on the global arena, and the pace of growth of the biopharmaceutical industry ranks among the top among emerging players. Aggressive investment and achievements in biosimilar and stem cell therapy products, for example, are further strengthening the competitive position of the Korean biopharma market. Considering its status, only several decades ago, as

a foreign aid recipient who heavily relied on imported drugs for parasitic diseases, the development process of the biopharmaceutical industry of Korea is quite distinctive.

Against this backdrop, the purpose of this paper is to shed light on how Korea has successfully created system dynamics in the hardly predictable and complex biopharmaceutical market from virtually a nonexistent status only a few decades ago (Figure 1). The analysis of evolving government policies and programs aligned through multi-ministerial coordination, engagement of large firms, innovative ventures and research body, and development of professional human resource, is expected to provide some insights for other emerging economies who set biopharmaceuticals or other related bio-industry as a national priority to overcome middle-income trap and achieve sustainable economic growth. In particular, Korea's strategic response to internal and external threats or unexpected events faced in the development process may provide critical implications.

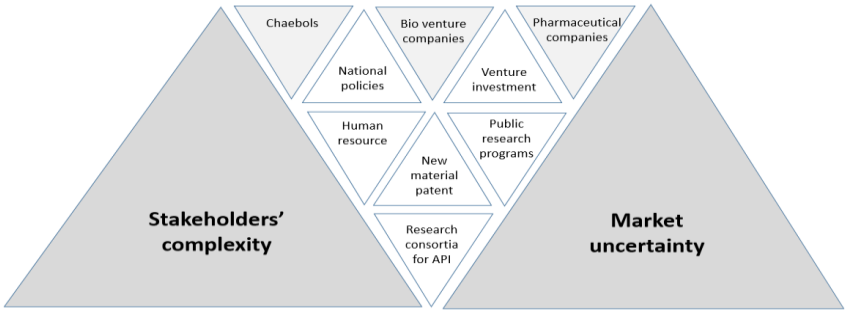


Figure 1 Major components to build system dynamics in Korean biopharmaceutical industry

II. Uncertainty and Complexity of Biopharmaceutical Industry

The demand for biopharmaceuticals has continued to rise exponentially due to the prevalence of chronic diseases such as metabolic, diabetes, neurological, cancer, and other life-threatening diseases for which there is no available or affordable treatments. The biopharmaceutical industry is at a stage where it is particularly critical to stay ahead of the latest innovation; hence it requires huge R&D investments. Worldwide R&D in pharmaceutical and biotechnology is expected to grow 2.4% per year to 2022, with total estimated R&D spending reaching $181 billion in 2022 compared to $156.7 billion in 2016 (Evaluate Pharma, 2017). However, a successful pathway for the biopharmaceutical sector

is fraught with complexity, and its R&D is notoriously time consuming, costly, and mired in uncertainty. The R&D efficiency of biopharmaceutical, which is described as the spending on R&D per successful approval and launch of new drugs, is much lower than R&D in many other industries, and constantly falling. According to Deloitte (2017), while the total cost for the top 12 largest biopharmaceutical companies to bring a new drug to market reached almost $2 billion, the overall rate of return on R&D remained at just 3.2% in 2017, which is a huge drop from 10.1% in 2010.

The biopharmaceutical industry, by nature, represents a high level of risk and uncertainty, intensified by strongly competitive and crowded market dynamics (Shah, 2004; Lückeet et al., 2012; Schuhmacheret et al., 2016). Among others, uncertain factors surrounding the risk and reward of R&D in biopharmaceuticals can be categorized as (Deloitte, 2014, p.2):

- Scientific uncertainty: Addressing the novel areas of unmet medical need requires innovators to tackle challenging therapeutic areas or emerging biologics modalities.
- Regulatory uncertainty: The FDA approval process is associated with a high degree of uncertainty that complicates an innovator's ability to predict review times, pre-approval requirements and post-approval requirements.
- Coverage uncertainty: In response to market trends as well as the Affordable Care Act (ACA), health plans have tightened coverage policies and formulary placements, causing significant uncertainty in patient access to new treatments.
- Policy and implementation uncertainty: Innovators have to account for future competition from biosimilars, biologic medicines that are developed to be similar to innovator biologics. The ACA created an abbreviated FDA approval pathway for biosimilars; however, the law created a lot of uncertainties and leaves many important areas open to interpretation.

Amidst these uncertainties, investment projections get more volatile when they face uncertainty of demand planning and forecasting. Even if the level of such uncertainties is reduced, it is decades long and a grueling process that awaits companies seeking to recoup R&D investments. The biosimilar market, which recently captures the particular attention of the global pharmaceutical industry, is also riddled with paramount uncertainties. Biosimilar medicines, which are cheaper, near-replicas of complex biologic drugs whose patent protection expired, have been forecast to aggressively expand with prospective lower cost for patients. However, in addition to high development costs estimated to be $100-$200 million per biosimilar, there are considerable

uncertainties associated with the development process (Brill and Robinson, 2018). Added to uncertainties stemming from intellectual property (IP) and regulatory approval that are still in flux is the immaturity of the biosimilar market. Many players in this nascent market lack the capability to recalibrate market expectations, biosimilar interchangeability, level and intensity of competition and public perception of biosimilar.

Another critical characteristic of the biopharmaceutical industry is its complexity, which is inherent in the pharmaceutical industry as a whole. The complexity of biopharmaceutical operations and the supply chain involves not only sophisticated technologies and applications, but also evolving regulatory requirements and interests of diverse groups of stakeholders that often severely conflict. Biopharmaceuticals require highly sophisticated manufacturing processes that come at great costs to reproduce large complex molecules reliably and consistently on an industrial scale, and each key component along the manufacturing process requires multiplex and time-consuming regulatory approval (Jagschies et al., 2014; Otto et al., 2014). The management of all potential risks along compound biopharmaceutical drug supply chains is also challenging as it covers many tiers including manufacturing, clinical trials and distribution that stretch to multiple geographic regions.

The biopharmaceutical industry, or more broadly, the pharmaceutical industry, is deemed uniquely complex as it operates in a highly sensitive environment where the impacts of mutually interacting social, political and ethical factors are enormous. Governments tend to strictly regulate the industry in price control, IP protection, insurance, material imports, etc., hence the hurdles for companies to enter the global market is high as each country has markedly differing regulatory environments. It also often requires political momentum to champion bold reforms to create a more favorable environment for the industry to be competitive in the global market. Therefore, it is necessary for decision makers to possess a high level of political will, and particularly in the case of biopharmaceuticals that requires clear understanding of the nature of the industry, as it is relatively new.

There are also several ethical issues that make the biopharmaceutical sector more complicated. Generally, it involves the complex issues of ethical principles and high standards applied along the overall process of R&D, approval and actual use for patients. The sector has to deal with the strict adherence to clinical research protocols, protection of human rights and safety for participants in clinical trials, affordable pricing of biotech treatments for chronic illnesses, and, specifically, controversies around stem cell research involving embryos or cloning, which often involves sensitive religious matters (Silverman, 2004).

To sum up, the high degree of uncertainty and complexity associated with biopharmaceuticals is often an obstacle for companies to enter the market and invest in the newest discoveries of biotechnology and for the government to

prioritize the industry and mobilize budget. If such risks and uncertainties are left unaddressed, it may encourage financiers to invest their capital in other more promising areas that are less risky, and eventually negatively impact on the ecosystem of the biopharmaceutical industry where consistent innovation is a key to survive and grow (Deloitte, 2014). Therefore, it is important for a country to build a capacity to assess and reduce risks, manage complex operations, stakeholders and market dynamics, and be resilient to unintended consequences or unexpected events.

III. The Role of the Government and Research Institutes in the Development of the Biopharmaceutical Industry in Korea

While North America is currently dominating the global biotechnology market and predicted to continue capturing the biggest share of the overall industry, Asia Pacific is expected to witness the fastest growth and gradually gain substantial market share in the coming decade (Euromonitor, 2017; McKinsey, 2018). In particular, factors such as recent administrative and price reforms, evolving digital and advanced analytics in healthcare, and active partnerships with leading global biopharmaceutical companies, have enabled countries such as China, Japan and the Republic of Korea to survive and grow in an uncertain and complex biopharmaceutical market (McKinsey, 2018).

Among others, Korea has registered dynamic growth in the biopharmaceuticals in both quantitative and qualitative terms over a few decades. Once being heavily dependent on overseas humanitarian aid to combat parasitic diseases, Korea has seen the home growth of a number of globally competitive biopharmaceutical companies, and the industry is currently one of the fastest evolving and strategically important target (Wong et al., 2004; Konde, 2009).

On the back of the government's extensive regulatory and financial supports, the practical role of research institutes, robust R&D and a growing pool of highly-skilled human resource, have led bioventures and start-ups as well as large firms and chaebols to become competitive on the global arena, and the growth pace of its biopharmaceutical industry ranks among the top among emerging countries.

1. Entry into the Nascent Industry from a Virtually Non-existent Base in the 1970s and 1980s

Until the 1960s, foreign humanitarian aid was essential for the post-war recovery and economic reconstruction of Korea, and, in particular, it was the sole source of supply for pharmaceutical products. Foreign aid was still the main

channel for the public to get access to drugs for an extensive variety of parasitic diseases in the 1970s, even when the country experienced a spurt of rapid industrialization. However, while intestinal parasitic infections were prevalent and the importance of parasitology for national development was widely perceived, its attempts to build the local capacity to eradicate such disease, e.g., the establishment of the Korea Association of Parasite Eradication (KAPE) in 1964 with the goal to reach a zero rate of infection within 10 years, rarely brought out any tangible results (Harrison and Yim, 2017).

Only in the mid-1970s did the achievement start to become noticeable, with local Korean company Shin Poong Pharmaceutical Co. who successfully synthesized raw material for mebendazole in 1975. It was backed by the creation of the industry-academy-research consortium for the local production of Active Pharmaceutical Ingredient (API), with the participation of the Korea Institute of Science and Technology (KIST). To eradicate two important parasitic diseases-schistosomiasis and liver fluke - Shin Poong successfully developed an alternative synthetic process to produce praziquantel with the support of KIST and financial assistance from the government (Reich and Govindaraj, 1997; Alsaqabiand and Lotfy, 2014). It was different from the process Bayer used to monopolize praziquantel in the early 1980s. With significantly lowered production costs, Shin Poong seized opportunity to erode Bayer's monopoly and raise Shin Poong's share of the market in Korea from a negligible amount in the early 1980s to around 90% in the early 1990s (Reich and Govindaraj, 1997). The lower product price of praziquantel led to a major reduction in schistosomiasis infection from 41% in 1981 to 4% in 1993 (ibid.).

Shin Poong's success in developing a local capacity for fine chemical-based new drug production facilitated competitors' market entry and consequently put pressure on the Korean government to introduce chemical substances patent. The new patent system came into effect as the Korean National Assembly introduced a new Patent Act in 1987 for pharmaceutical and chemical products. The eestablishment of the Korea Drug Research Association (KDRA) in 1986 helped companies handle a new product patent system. Since its inception, KDRA was engaged in designing biotech-related policy and strategy and improving advanced R&D systems. It worked on business partnerships, technology transfer and licensing among the industry, academia and public research organizations, domestically and internationally[2].

Based on the government's robust financial and institutional support and strengthened R&D capacity, notable achievements were made by major pharmaceutical companies in the development of new drugs and global licensing during this period. Pharmicell, for example, developed the world first

[2] Read more on the Korea Drug Research Association (KDRA) at: www.kdra.or.kr/english/01web01.php

commercialized stem cell therapy product approved in 2011. Celltrion developed Remsima, the world first biosimilar monoclonal antibody, which was approved by the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) in 2013 and 2016, respectively. Hanmi, one of the three big pharmaceutical companies in Korea, on the other hand, generated technology licenses for more than $7 billion in 2015 with global pharmaceutical such as Janssen Pharmaceutical Company of Johnson & Johnson, while Genexine signed a licensing deal with China Biopharma in 2016 worth $548 million.

2. Building Biotechnology Industry Foundation

R&D investments expended hugely in Korea in the wake of a plan for the Highly Advanced National project (HAN), or so-called G7 project. To bring the country's capacity to the level of the world's top frontier countries, the Korean government funded R&D during the years between 1992 and 2001 targeted to strategic areas and specific product technologies such as new drugs and chemicals, Broadband Integrated Services Digital Network and high-definition television (Dedrick and Kraemer, 1998). The G7 project was one of a few R&D programs that was coordinated and jointly operated by different ministries who had conducted highly fragmented R&D support. While the project eventually fell short in many areas and could not achieve its ambitious goal to catch up G7 countries' national competitiveness, it contributed largely to fueling the growth of a pool of homegrown talents. The field of pharmaceuticals was also benefited to some extent, but the main target still was fine chemical-based drugs rather than biopharmaceuticals.

While the major reason for the success of mebendazole and praziquantel in Korea was doubtlessly attributable to Shin Poong's efforts in the development of innovative products and processes in the virtually non-existent industrial base, it was also due to supportive policies and programs of the Korean government and the timely establishment of leading institutes that created and fostered the nascent domestic industry. Recognizing the necessity of transitioning the country's industrial base from traditional manufacturing to a higher value-added knowledge-based industry, the Government set biotechnology as one of the key sectors of Korea's future development strategy. The Government promulgated the Genetic Engineering Promotion Law (also known as the Biotechnology Promotion Law) in 1983 in response to the emergence of genetic engineering and new biotechnology. Having almost non-existent industrial foundation to foster competitive biotechnology, R&D capability was designated as a prior target, and Korea Research Institute of Bioscience and Biotechnology (KRIBB) was established in 1985 as one of the spin-off institutes of KIST (Rhee, 2003).

KRIBB has played a pivotal role in biotechnology research in Korea, from basic research to applied studies in the fields of biomedical sciences, bioengineering, bio-infrastructure etc. KRIBB's achievements are well recorded, for example, in terms of publications in academic journals. Between 1991 and 2002, KRIBB and KIST accounted for nearly 15% of the total health biotechnology publications of the country in international peer-reviewed journals (Wong et al., 2004). The Korean government's prompt target-setting in response to the emergence of a new industry and the practical roles played by research institutes such as KIST, KRIBB and KDRA, helped prepare the ground of the rapid growth of biotechnology.

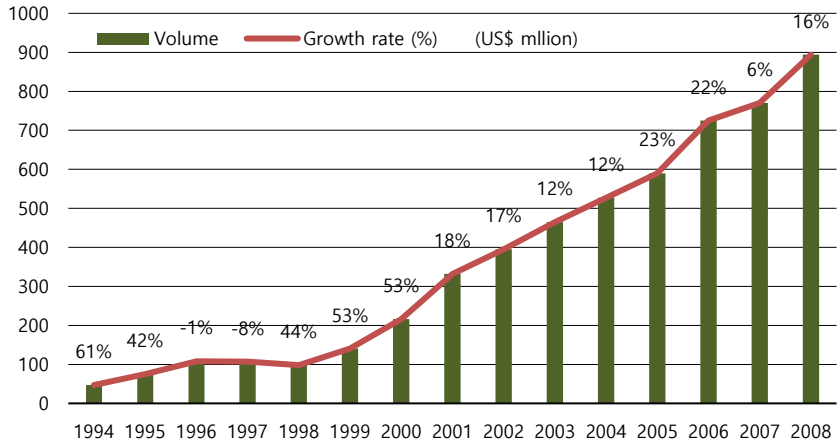
3. Integration of Biotechnology as One of the Highest National Priorities in the Early 1990s

The inception of the Human Genome Project in 1993[3] ushered in a period of multidimensional and scaled-up R&D in Korea. Rapidly increased investment in biotechnology R&D led biotechnology and bio-industry to become one of the highest national priorities .While Korea failed to participate in the Human Genome Project, the project motivated the Korean government and the private sector to invest more vigorously in biosciences and industrial development.

The cornerstone of the development of biotechnology, and consequently biopharmaceuticals, was the introduction of the First Basic Plan for the Promotion of Biotechnology (Biotech 2000) in 1994 as an offshoot of the G7 project. The Korean government declared that year "the Year of Biotechnology" to raise public awareness and industry's attention. The First Basic Plan was setup with the aim to place the level of Korea's biotechnological capabilities on a par with those of global leading countries by extensively increasing R&D and accelerating commercial applications of biotechnological research. The First Basic Plan geared the explosive growth of R&D of the sector by coordinating the fragmented policies of different ministries (including the Ministry of Education and HRD; Science and Technology; Commerce, Industry and Energy; Environment; Health and Welfare; Food, Agriculture and Forestry; and Marine Affairs and Fisheries) and other associated agencies and research institutes run by the government in a more elaborated manner (Ministry of Education, Science and Technology of Korea, 2009). With a total planned investment budget of $14.3 billion (of which public investment accounts for $5.5 billion and private investment $8.8 billion), R&D investment in biotechnology surged since the

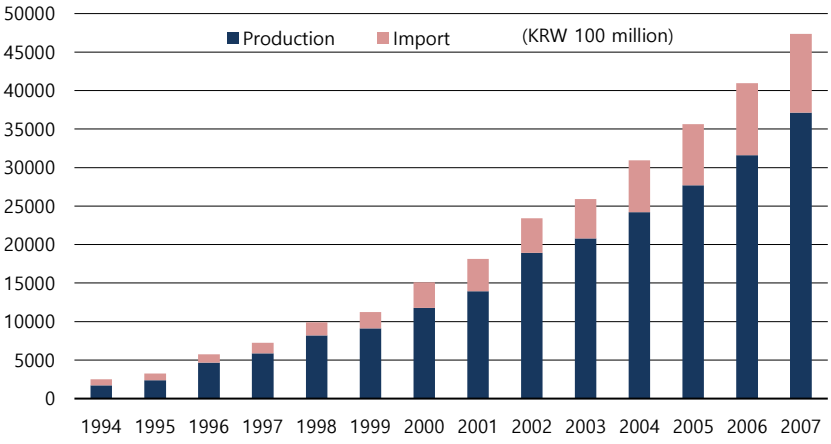
[3] The Human Genome Project initiated in 1990 was a vast international research collaboration to map the sequence of the entire human genome and identify the genes it contains. It was officially declared complete in 2003 with all of the goals of the project achieved.

inception of the First Basic Plan, at an annual average rate of 24% until 2008 (ibid.) (Figure 2).



Source: Authors' construction based on the Ministry of Education, Science and Technology of Korea (2009).

Figure 2 Government investment in biotechnology R&D since Biotech 2000



Source: Authors' construction based on the Ministry of Education, Science and Technology of Korea (2009) retrieved from the Ministry of Knowledge Economy (2008).

Figure 3 Growth of the size of biotechnology market in Korea since Biotech 2000

Various ambitious national R&D programs that solidly anchored the country's vision to nurture biotechnology capacity supplemented the First Basic Plan. The

21st Century Frontier Research Program launched in 1999 funded 23 projects over a 10-year period in the specific target growth areas, e.g. neuroscience, stem cell research and new drug development. The Program involved diverse institutions ranging from KRIBB, Korea Biotechnology Research Association, and Korea Bioventure Association to private companies and universities, including Seoul National University. The Government's strategic biotechnology promotion plans and programs fueled the rapid expansion of the size of the domestic biotechnology market. Between 1994 and 2007, the total value of the biotechnology market of Korea increased nearly 20-fold with an average annual growth rate of 30.5% (Figure 3).

4. The Asian Financial Crisis and the Growth of Bioventure Firms in the Late 1990s and 2000s

Such growing interest and investment by local companies backed by policies and financial support from the government have widened the pool of highly educated human resource produced from research institutes as well as universities. However, being severely hit by the Asian financial crisis in early July1997, many businesses collapsed, and large biotech companies were no exception. A number of leading chaebols - a group of large, often family-run, conglomerates - either went bankrupt or had to obtain bank protection; they implemented a full-scale financial and non-financial reform which resulted in massive layoffs.

However, this sudden turmoil exacerbated by the tumbling chaebols triggered the Government to restructure the country into a knowledge-based sustainable economy through the development of new technologies and systemic fostering of venture firms. The "Special Law to Promote Venture Capital Companies" passed on July 30, 1997, enabled venture firms to be given more flexible and extensive direct and indirect subsidies, and benefitted from the relaxation of regulations. The Government also lifted the restrictions on foreign investment in Korean venture capital, increased tax benefits and launched venture capital funds in 1998 (Kenney et al., 2004). A series of measures taken during this period suggests that this enabling environment for the birth and growth of venture firms was credited to the strong initiative of the central government for the system institutionalization, which is one of a very few cases found in other countries. Also, KRIBB notably contributed to the foundation of the bioventure ecosystem. Since its critical role in the establishment of Bioneer Corp., the first bioventure, in 1992, KRIBB, together with LG, has spin-offed nearly one-third of bioventure firms in Korea.

Motivated by the fully supportive policies of the Government, many high-tech ventures sprouted up and fueled Korea's rapid recovery from a devastated

economy. Along with the explosive venture boom in the information and communication technology (ICT) sector, the country also witnessed the first bioventure boom in 2000. It attracted many graduates and experts in the field of biotechnology who could once hardly find relevant jobs in Korea and migrated to the United States.

With the exponential growth of bioventures, the Korean government selected Novel Biomedicine and Organs as one of the next-generation engines for industrial growth in 2004. In 2006, the Second Framework Plan for the Promotion of Biotechnology (also known as Bio-Vision 2016), a pan-governmental biotechnology promotion plan, was published with specific focus on visualizing industrial achievement. The specific goals to be achieved by 2016 include: a) raising the national rankings in both the number of published peer-reviewed science technology papers and the number of technology patents to raise Korea to 7th position - in 2006, the country was 12th and 15th, respectively; b) doubling the R&D workforce by fostering postgraduate degree recipients in the biotechnology-related field from 9,500 to 17,300 by 2016; and c) increasing the industrial market value by more than 20-fold, from KRW2.7 trillion (approximately US$2.4 billion) to KRW60 trillion (approximately $53 billion) (Brendan et al., 2014).

Since 2004, in particular, there was massive investment in stem cell research from both the government and the private sector. It was fueled by Hwang Woo-Suk, highly regarded Korean geneticist, who claimed in two articles published in Science magazine in 2004 and 2005 that he had derived eleven stem cell lines from cloned human embryos, for the first time. Before this supposedly groundbreaking research was revealed to be a fraud and riddled with ethical lapses, stem cell research had been given phenomenal public attention with the hope to solve incurable diseases. While this stem cell fever was severely hit by the scandal, it facilitated the nationwide expansion of biotech development, and later motivated scientific research integrity.

5. Ever-growing Government Support and Expansion of the Global Bio Market in the 2010s

Backed by multidimensional policy and financial support from the government and a mutually-reinforcing network of industry-academy-research institutes, the biotechnology and associated industries achieved both quantitative and qualitative growth over a decade. The share of government R&D in biotechnology rose from 15.7% in 2007 to 17.5% in 2016. The total number of graduates (i.e. holders of master's and doctoral degrees) in the biotechnology fields produced between 2007 and 2016 was around 11,000, and the number of researchers working in biotech companies numbered 304,808

(69.7%), followed by 99,137 at universities (22.7%) and 33,322 at public institutions (7.6%). In terms of biotechnology level comparison, Korea is estimated to have reached nearly 78% of the efforts to be the No.1 country. Of note, Korea is currently the world's first in stem cell treatment and second in stem cell clinical research. Korea has shown rapid growth in the number of journal papers targeted in Bio-Vision 2016. Some 54,831 SCI papers were published in 2014, which accounted for 3.75% of the world total. A total of 39,270 SCI papers were published in six biotechnology fields between 2010 and 2014, and the country ranked 8th in the world for paper published in microbiology and pharmacology, which was higher than the average share of the six fields. The average number of citation of Korean SCI papers in the 5-year period was 5.94 times, i.e. 75% of the world average (8.04). The number of SCI papers in molecular biology and genetics had a compound annual growth rate (CAGR) of 19.8% over the past decade, followed by immunology (18.2%), neuroscience and behavioral science (11.7%), biology and biochemistry (9.4%), pharmacology (6.9%), and microbiology (5.8%).

The accumulated number of patents in Korea's biotechnology field reached a combined total of 30,392 over the 13 years since 2001, showing a consistent CAGR of 5.56%. Among the top 15 countries with patents registered in the United States, the number of registered patents in Korea's biotechnology fields has increased consistently. The cumulative total from 2002 to 2014 stood at 1,683, which translates in a CAGR of 3.35%, which helped the country join the ranks of the top 10 countries for the first time.

6. Promulgation of the "Bio-Economy Initiative 2025" in 2017

The first biotechnology promotion plan in 1994 aimed to expand R&D bases, prepare research facilities, promote basic science and foster researchers. The second plan in 2006 focused on visualizing industrial achievements by expanding infrastructure, promoting bioventure companies and bio cluster. The Ministry of Science and ICT promulgated the Third Biotechnology Fostering Basic Plan (so-called Bio-Economy Initiative 2025) in 2017 to accelerate the expansion of Korea's global bioengineering market share. What is noticeable about the new plan is that the role of the government changed from 'player' to 'mediator' and 'supporter' that provide extensive assistance to the firms to discover market where their R&D achievements can be maximized.

Having three major strategies - bio R&D innovation, bio-economy creation, and establishment of the national ecosystem base - the government initiative aims at increasing Korea's share in the global bioengineering market from the current 1.7% to 5% (Ministry of Science and ICT of Korea, 2017). To achieve this goal, it also set an ambitious objective to record an output increase from

KRW27 trillion (approximately $24 billion) to KRW152 trillion (approximately $135billion) and global technology exports from the current $522 million to $2.73 billion by 2025. The initiative includes a plan to invest KRW500 billion (approximately $440 million) into R&D for 100 new drug discovery by 2026, which strongly calls for the leadership of companies, hospitals, universities and research institutes through their symbiotic network. In particular, the initiative is expected to encourage an active role for hospitals to become bases for bio-health industry innovation, by allowing them to conduct independent bio-health R&D.

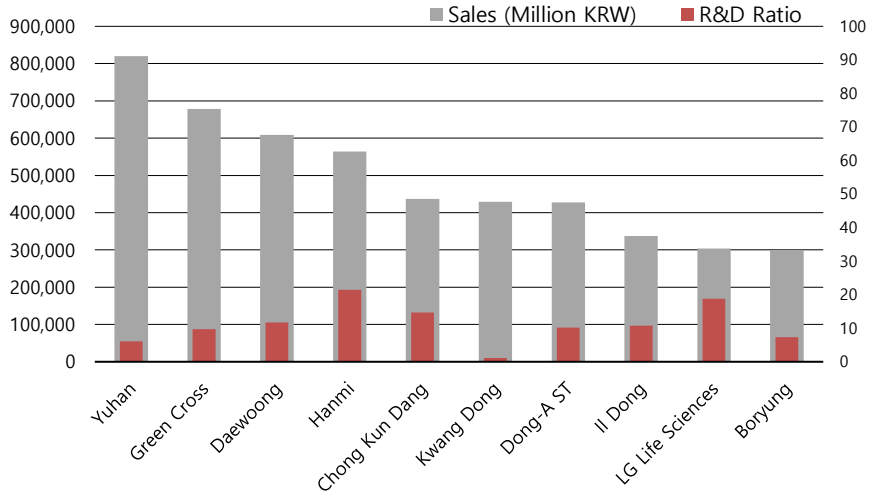
Under the initiative, the Korean government also aims to create 120,000 new biotechnology-based jobs to reach 145,000 by 2025, from 26,000 in 2015. For this, it also plans to support the creation of 1,250 new bioventure companies and 30 technology-specialized listed companies, four global companies and the construction of two global clusters with over 30,000 employees. The Government also plans to utilize sophisticated ICT such as bio Big Data, AI and robots to accelerate bioresearch. It is expected to center on, for example, the creation of the Korean Precision Medicine Initiative, Korea Brain Initiative, and development of next-generation medical equipment through the healthcare paradigm shift from cure to care bringing together biotechnology and ICT.

IV. The Role of Fine Chemical Pharmaceuticals, Chaebols and Venture Firms in the Creation of System Dynamics

1. Transformation of Finechemical Pharmaceuticals

Korean pharmaceutical companies have begun to sprout up and engaged in the new fine chemical-based drug development since the mid-1980s, and they are now one of the key stakeholders in biopharmaceuticals in Korea. Most of them have pursued differentiation strategies since the generic sales business is not sustainable in Korea, and more than half of the major Korea listed pharmaceuticals increased R&D investment to more than 10% of their sales (Figure 4). Especially Hanmi, whose share of R&D investment to sales in 2015 accounted for more than 21%, has allocated around 10-20% of sales into R&D since 2007 with accumulated investments of more than US$700million.

According to KDRA, 26 companies signed technology licensing transfer contracts in 2015, with contracts amounting to KRW 9.288 trillion (more than KRW10 trillion if various undisclosed items are included) for the 20 deals announced. Korean pharmaceutical companies are also actively collaborating with domestic and foreign stakeholders to develop new technologies and products.



Source: Biotech Policy Research Center mimeo

Figure 4 Sales and R&D ratio of Korean listed pharmaceuticals (3rd quarter of 2015)

Their partners are diverse ranging from domestic and international bio-ventures to research institutes and universities.

- **Hanmi:** collaboration with domestic and international bioventures
- **Yuhan:** candidate substance and generic technology in partnership with domestic and international bioventures
- **Handok:** strategically targeting "a few good projects" with sizable market and tangible chances of success with focus on new bio drugs for rare disease
- **Boryung:** joint research with the National Cancer Center and Korea Research Institute of Chemical Technology
- **CJ HealthCare:** new articular rheumatism drug development with Seoul National University and Virginia Tech

Korean pharmaceuticals such as Dong-A, Green Cross, and Daewoong have established their own venture capital to invest in bioventures and continued to expand their international alliances. In the years of 2001-2005, they struck 19 alliances, while the number of alliances increased to 79 in the years 2011-2015. A few bioventures have also acquired pharmaceutical companies (Table 1).

Table 1 Acquisition of pharmaceuticals by bio ventures

	Bio venture	Pharmaceuticals
May 2009	Celltrion	Hanseo Pharm
Aug 2011	HS Biopharm	Kyungnam Pharm
Dec 2015	CrystalGenomics	BTO Pharm
May 2016	LegoChemBio	Hanbul Pharm
July 2016	Protox	Medica Korea

Source: Biotech Policy Research Center mimeo

2. Chaebols' Aggressive Investment and Increasingly Intense Competition in the Biosimilar Market

Robust government investment enticed not only fine chemical-based local pharmaceutical companies to reinforce R&D activities for the development of new bio drugs with in-house technology, but also chaebols[4] to vigorously explore the market. Especially in the pharmaceutical industry, chaebols are those who could afford tremendous amounts of investment in facilities, technologies and high quality human resource, which require a long R&D process that often leads to failure. For example, after nine years of R&D, SK Chemicals, a member of the SK Group, developed a new anti-cancer agent "Sunpla" and obtained final permission from Korea Food & Drug Administration (KFDA) as the first domestically-developed new drug in 1999. The company also developed Joins, Korea's first officially recognized natural drug made with herbal substances for arthritis. SK affiliates SK Biopharmaceuticals, a major business developing synthetic biomedicine, and SK Biotech, who specializes in custom chemical development, advanced intermediates and API manufacturing. SK Biotech is expected to expand its global presence with its four production facilities approved by the US FDA, European Medicines Agency (EMEA) and the Ministry of Health, Labour and Welfare of Japan.

LG Life Sciences, which was setup in the early 1980s as a genetic engineering unit within LG Chemicals, has focused its business on the development of

[4] Chaebols - a distinct form of a group of large, mostly family-run, business conglomerates - have exerted a firm grip in Korean economy with their central role in achieving country's rapid export oriented growth since the end of the Korean War. They spearheaded the reconstruction of the ravaged economy in the War's aftermath and hyper-growth of strategic sectors such as chemicals, automobile and consumer electronics between 1960s and 1980s and high-tech industries such as semiconductors later on. Many chaebols now often control a number of diversified affiliates that extend across many industries.

medicines for, for example, chronic disease, obesity and growth hormone deficiency. It successfully developed in 2003, Active, the next-generation quinolone antibiotic for treating pneumonia and chronic bronchitis, which became the first domestically-developed novel chemical drug approved by the US FDA. Having such notable accomplishment driven by competitive R&D capabilities, LG Life Sciences has swiftly moved to drive up its presence in biosimilar. After its merger with LG Chem in 2016, there has been a boost in R&D for developing biosimilar version of, for example, rituximab, infliximab and Etanercept. In particular, Etanercept BS, developed by LG, is the first biosimilar to Etanercept, or Amgen Inc.'s Enbrel, introduced to Japan. The presence of biosimilar and innovative drugs developed by LG continues to grow with expected sales of $5 billion by 2025.

To further its in-house R&D expertise and global networks, LG has pursued an open innovation strategy and it collaborated with international pharmaceutical and associated companies with innovative platform technologies. LG Chem entered into collaboration with HitGen Ltd, a Chinese DNA screening company, by conducting a major multi-year drug discovery research in 2018. This collaboration is expected to enable LG Chem to get access to HitGen's advanced technology platform including DNA-Encoded Library, while HitGen receives technology access as well as research support payments. Several months later, LG Chem also signed a collaboration agreement with Cue Biopharma, an immunotherapy company in the United States, to jointly develop cancer immunotherapy drugs. It will pay up to $400 million in research and development, equity investment, and sales milestone payments, as well as tiered royalties on future sales.

Samsung, on the other hand, has two affiliates in biotechnology - Samsung Biologics and Samsung Bioepis. Leveraging its semiconductor process technology, Samsung Biologics is growing into one of the leading contract manufacturing organization (CMO), and recently constructed its third plant with an annual production capacity of 180,000 liters, which is the world's largest biopharmaceutical manufacturing facility. Together with its first plant (30,000 liters) and second plan (152,000 liters), the firm acquired a combined annual production capacity of 362,000 liters, which exceeds other top contract manufacturers Lonza, Switzerland, (240,000-290,000 liters), and Boehringer Ingelheim, Germany (240,000 liters).

Another arm of Samsung's biopharmaceuticals is Samsung Bioepis, a joint venture between Samsung and US biotechnology company Biogen Idec, which focuses on developing various biosimilar products. Despite its short lifespan since the establishment in 2012, the firm has already gained European Commission (EC) approval for Benepali, Flixab, Imrald and Ontruzant, biosimilarstoEnbrel® (etanercept), Remicade® (infliximab), Humira® (adalimumab), and Herceptin® (trastuzumab), respectively. In particular,

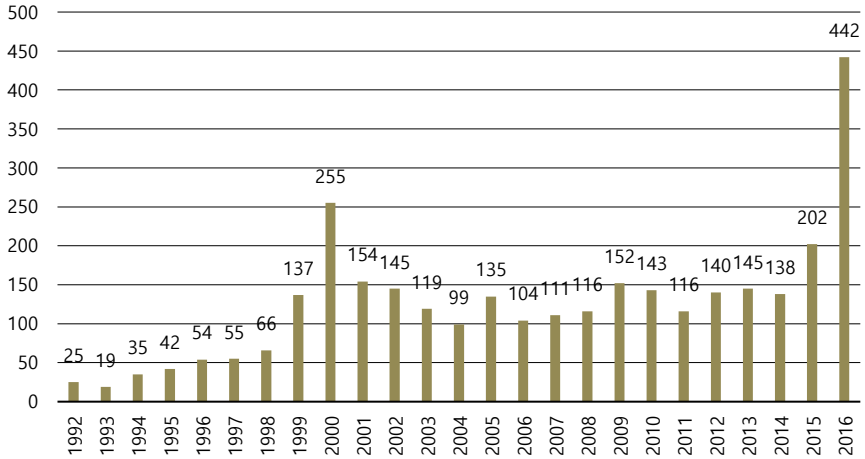
Benepali, its first biosimilar of Enbrel, recorded almost three-fold increase in European sales between 2016 and 2017, from $100.6 million to $370.8 million. The Samsung group recently identified four specific areas - AI, 5G telecommunications, automotive electronics components, and biopharmaceuticals - as new growth engines, where it plans to pour a total of KRW25 trillion (approximately $22 billion) investment by 2021.

Owing to many chaebols' aggressive investment and progress in developing new products by pharmaceutical companies, Korea is now one of the outstanding countries in terms of growth of biosimilar in the region (Annunziata, 2016). Motivated by their achievements, the Korean government has set the ambitious target of capturing 22% of global biosimilar drug sales by 2020. As a large number of capable competitors are expected to enter the market with patents for more than 20 biologic products that will expire by 2022, competition among chaebols will also become more aggressive.

3. Bioventure Booms and their Role on Heightening Competitiveness of Biotech Ecosystem of Korea

One of the key contributors to the creation of the biotech ecosystem in Korea that can sustain complexity and uncertainty is bioventures. Korea's bioventure history is as short as the history of Korean venture companies in general. The first bioventure, Bioneer Corp., was founded in 1992, spun out of Korea Advanced Institute of Science & Technology (KAIST) and incubated at the Bioventure Center in the KRIBB. Successfully achieving the local production of molecular biology products and technologies and providing local researchers with high-tech research infrastructure, it was ranked the second fastest growing biotech firm in the Asia Pacific region by 2003 (Wong, 2011). Bioneer was listed on the local tech-heavy KOSDAQ market in 2005, and applied and registered approximately 440 patents as of 2016.

The Korean government's promotion policies and active involvement of KRIBB and large firms such as LG to create spin-offs as well as Bioneer's success motivated the emergence of a number of bio-venture firms. In particular, due to the collapse of many chaebols during the financial crisis between 1997 and 1998 and the aggressive government campaign to restructure the country into a knowledge-based economy through the development of new technologies, many high-tech ventures emerged. Along with the explosive venture boom in the ICT sector geared by the worldwide dot-com bubble between 1997 and 2000, the first bioventure boom of 2000 was ignited. With the first venture boom, the number of biotechnology companies almost doubled, from 137 to 255 between 1999 and 2000 (Figure 5).



Source: Authors' construction based on Biotech Policy Research Center (2017).

Figure 5 Number of biotechnology companies in Korea

The top talents who used to work in the chaebols and pharmaceutical companies, research institutes and universities, as well as those who once moved to the United States due to the small domestic market size in the early 1990s, came back to Korea after the financial crisis. Those so-called first-generation venture entrepreneurs who saw business opportunities in the bio-industry in Korea started firms, and venture capital available in biotechnology increased significantly. The role of KRIBB and LG are to be noted as almost one-third of Korean bioventures are spin-offs from these two organizations. For example, with a number of important bioventure spin-offs from LG since it closed the new drug division in the early 2000s, LG was broadly known to be the "Bio Venture Military Academy."

The expertise nurtured in the US firms and research institutes in San Francisco and the University of California, New York, Boston, San Diego, NIH and North Carolina Research Triangle Park became without doubt a firm foundation for the significant growth of the biopharma business of venture companies in Korea during the first venture boom. A broadened pool of capital and highly educated human resource further geared the advancement of domestic biotechnology even with the unprecedented venture boom ending soon. As the number of venture firms, which once soared, suddenly plunged in the aftermath of the dot-com bubble burst, the number of biotech companies also decreased to the same level as it was before the boom. However, those who survived went on to grow as major biotech companies, and the number of special technology-listed biotech companies increased from 2 to 24 in a decade, from 2005 to 2015.

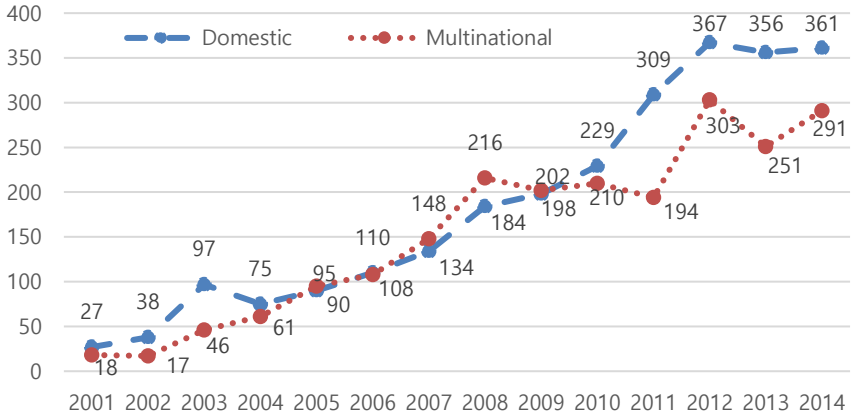
Along with the recent worldwide venture boom that funneled one of the largest investment into life sciences and biotech companies, Korea has again witnessed the second biotech venture boom, which brought about a surge in the number of biotechnology companies from 202 in 2015 to 442 in 2016 (Figure 5). The second boom was fueled by many start-ups created by former researchers of multinational pharmaceutical companies and large domestic biotech firms, and backed by favorable government promotion policies. According to Korea Biotechnology Industry Organization (Korea BIO), biotechnology and medicine was the third preferred sector to invest capital after ICT services and distribution/ services, with 25% of gross venture capital investment to the sector in 2017. The value of venture capital investment to the bio-medical sector to develop the pipelines is the highest ever as well. In the first half of 2018, venture capital's fresh investment in the sector ($344 million) was 2.7 times the amount in the same period in 2017 ($128 million), and it even surpassed the total investment of the previous year to $315 million (Business Korea, 2018).

V. System Dynamics, Policy Interventions and Beyond

1. Creation of System Dynamics and Policy Interventions

The Korean biopharmaceutical system is currently leading the development of biosimilar products, while next-generation antibody drug products, including gene and cell therapy and anti-cancer precision diagnostic treatment, are under development. In terms of cell therapy, Korea’s commercial clinical trials of biomedicine are the second largest in the world while a few globally competitive candidate substances are developed for the gene therapy. Figure 6 demonstrates the performance with regard to biomedicine clinical trial approval of the domestic and multinational businesses within the Korean system.

The system dynamics of innovative drug development and global market deployment has been fueled by the process technology, biopharma research capacity backed by human resource and infrastructure, and marketing and regulation strategy (Figure 7). Firstly, fine chemical-based pharmaceutical companies started with API synthesis to address endemic disease of parasite and later the new substance patent, which was enforced by advanced countries, has triggered them to explore new drug development with the support of various government programs. The specific process technology and drug development capacity were the foundation to move from fine chemical to biopharmaceutical businesses.



Source: Biotech Policy Research Center mimeo

Figure 6 Continuous growth of biomedicine clinical trial approval

Secondly, biopharma research capacity backed by human resource and infrastructure has been another important arm of the biopharma system dynamics creation in Korea. Various national research initiatives influenced by the global human genome project have prepared stepping-stones for the biopharma industry, especially bioventures in Korea with qualified human resource and infrastructure such as KRIBB. In terms of human resource development, Korea has prioritized investment in the education of bio scientists and engineers as it did for the six strategic heavy and chemical industries in 1970s - steel & iron, machinery, shipbuilding, automotive, petro-chemical, electronics & electrical. While there was a time gap to establish the biopharma job market in Korea and it resulted in most of these sectors moving out of the country, especially to the US, they later became the fundamental source of the new industry development in Korea.

Thirdly, global marketing and regulation strategy nurtured through earlier experiences of existing industries have played a crucial role for the creation of the system dynamics. Chaebols have explored international markets and dealt with strong regulations including those in the US market. These experiences have been embedded in the human resource and could facilitate various pharmaceutical and bioventures' technology licensing businesses with global business stakeholders as well as market access of Celltrion and Samsung Biologics into the EU and US biopharmaceutical market.

The historical evolutionary process of the Korean biopharmaceutical industry has shown that diverse government interventions have transformed the former from merely a drug manufacturing pharmaceutical industry with imported API to one exploring new (biopharmaceutical) drug development, creating bio-venture companies and ecosystem, and encouraging chaebols to enter into the

biopharmaceutical markets. The collective and dynamic system was created through, firstly, diverse drug development consortia in the industry, universities and research institutes; secondly, bioventure spin-offs from chaebols, pharmaceutical companies, research institutes and universities; and thirdly, returning bio scientists and engineers, facilitating biopharmaceutical industry development in Korea.

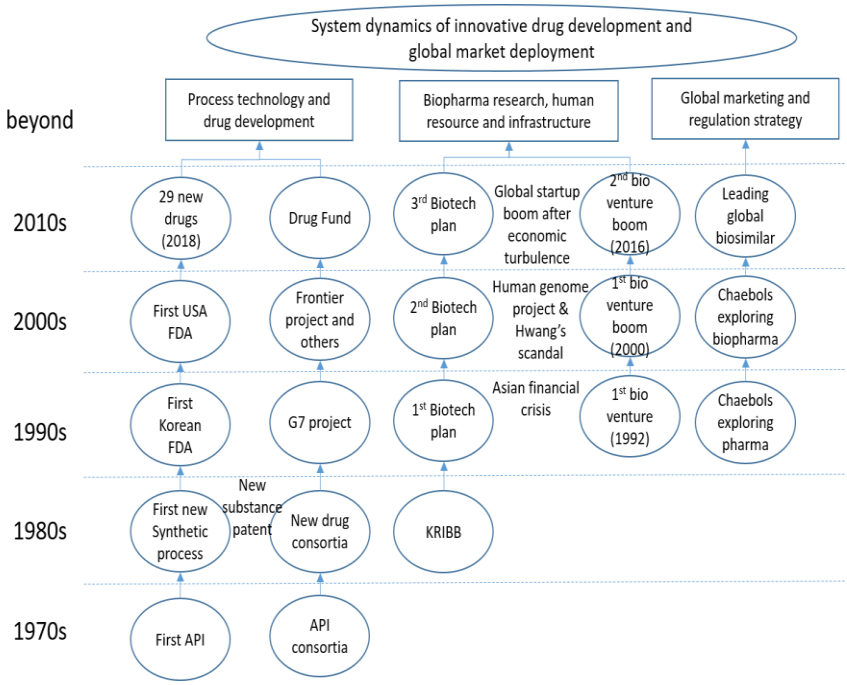
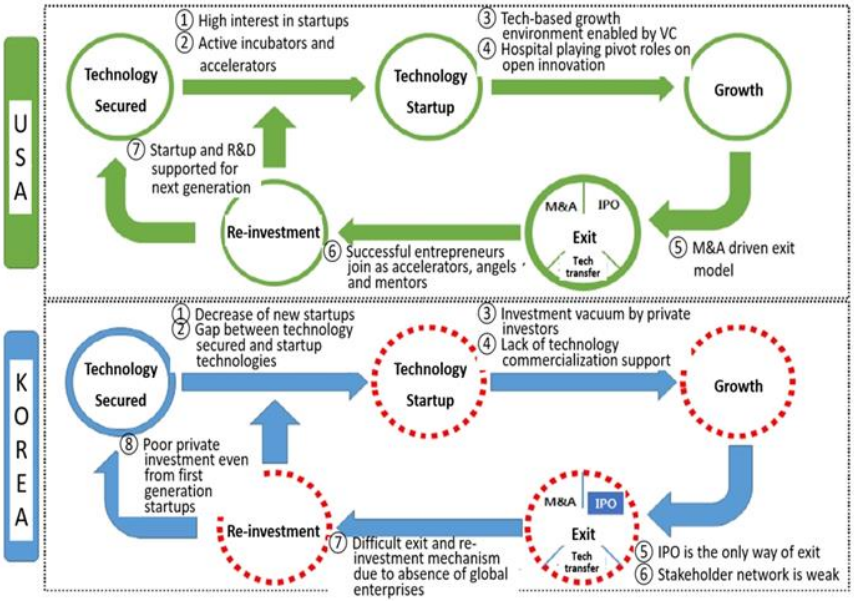


Figure 7 Creation of system dynamics

As the third biotechnology promotion plan is announced, Korea is now accelerating the expansion of its global market share, following the development of R&D bases through the first plan and a few visible demonstrations of industrial achievements through the second plan. It is also noteworthy to acknowledge the role of the Biotech Policy Research Center in the KRIBB, which was led by Prof. Hyeon Byung-Hwan. The Center has drafted three biotech plans, 30 laws and 50 promotion plans, and designed various supporting schemes for local bio startups to use KRIBB facilities. Lastly, it also facilitated inter-ministerial coordination through fora, roundtables and symposia, and periodicals, white papers, policy portals with the support of government programs. With such achievements, the Center could help anchor the biopharmaceutical industry within the Korean system.



Source: Biotech Policy Research Center mimeo

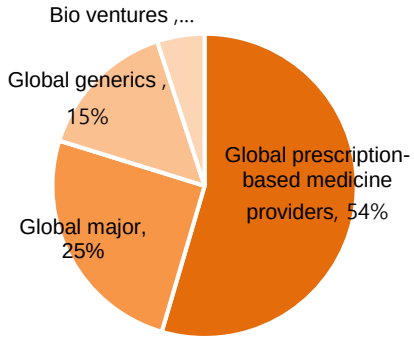
Figure 8 Vicious circle of Korean biopharmaceutical system

2. Limitations of the Current System

In 2016 the Biotech Policy Research Center reported to the Presidential Advisory Council of Science and Technology that a certain vicious cycle had hampered the consolidation of the Korean biopharmaceutical system (Figure 8). The initial public offering (IPO) is the only active exit model in the Korean system unlike the US where M&A is a driving exit model beside technology transfer and IPO. The IPO-focused exit model has limited exits and reinvestment, hence fewer technology and startups are developed, and poor private investment is induced in Korea.

As discussed in the previous chapter, a few pharmaceutical companies have acquired bioventures or invested in them while the leading bioventures have also acquired pharmaceutical companies to strengthen production capacity. Recently, the leading pharmaceutical companies and bioventures are continuously developing global technology license businesses. While these M&A in domestic market as well as technology licensing with global partners are an emerging trend in the Korean biopharmaceutical system, the M&A market needs to be further encouraged since the majority of Korean biopharma companies (54%) prefer to be global prescription-based medicine providers, while the second

preferred business type is global major (25%) followed by global generics (15%) and bioventures (5%) (Figure 9).

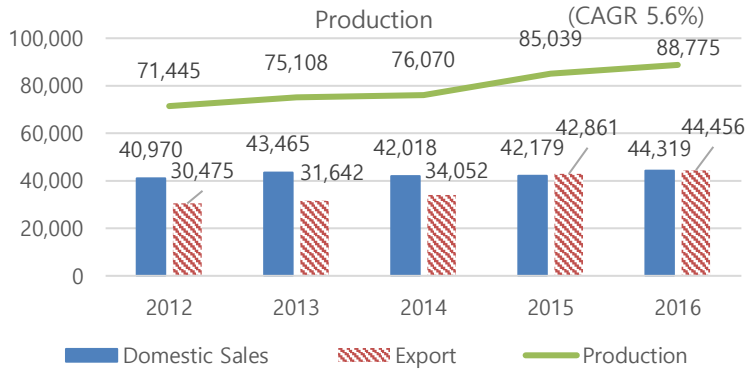


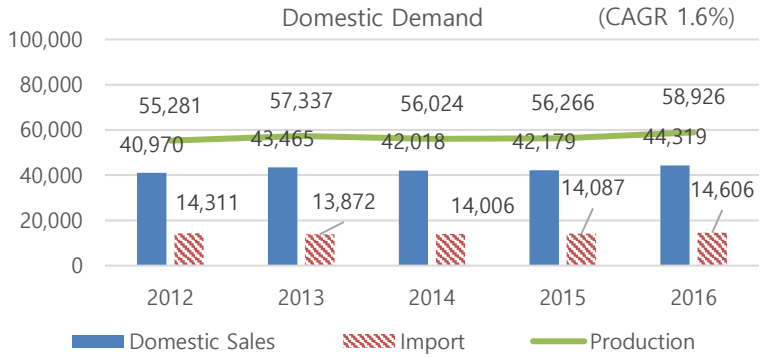
Source: Biotech Policy Research Center mimeo

Figure 9 Business model preferred by Korean biopharmaceutical companies

3. Active Global Partnership as an Alternative Solution

The lack of M&A and technology transfer is structurally related to the limited size of Korea's biopharmaceutical market, which also negatively affects the size of private investment and new technology or product development capacity. While biopharmaceutical product production continues to increase, it mainly targets the export market (Figure 10). Domestic demand, on the other hand, has reached saturation in Korea. As the domestic market is not sufficient for sustainable business and global competition, firms such as Samsung Biologics continue to invest in new production lines and actively engage in the global market, and it points to the importance of the Korean biopharmaceutical companies addressing the export market.





Source: Biotech Policy Research Center mimeo

Figure 10 Trend of supply and demand of Korean biopharmaceutical industry (unit: 100 million Won)

At the same time, technology and product development also require domestic and international partnerships. Considering the uncertainty and complexity of the biopharmaceutical technology and product development, the increase in partnership is inevitable. However, domestic partnership is currently dominant among the Korean biopharmaceutical companies while international partnership accounts for less than 10% of the total partnership cooperation (Figure 11). This may be increased to effectively address the current challenges.

Classification	Cooperative Relationships In Total	Domestic					Overseas				
		Total	Joint Invest -ment	Joint R&D	Technical Tie-up	Technical Manpower Exchange	Total	Joint Invest -ment	Joint R&D	Technical Tie-up	Technical Manpower Exchange
Total of 2015	1,119	1,003	30	798	112	63	116	9	58	41	8
Total of 2016	1,157	1,050	38	822	116	74	107	9	50	40	8
Basic Research Stage	339	324	22	237	30	35	15	2	9	3	1
Experiment Stage	389	365	9	300	35	21	24	3	14	6	1
Prototype Stage	197	156	2	129	19	6	41	1	15	23	2
Product Development Stage	153	141	4	109	18	10	12	1	6	4	1
Commercializ-ation Stage	79	64	1	47	14	2	15	2	6	4	3

Source: Biotech Policy Research Center mimeo

Figure 11 Domestic and overseas cooperation stage (unit: cases)

Korea has grown its unique bio and biopharmaceutical industrial system. The IPO exit model, however, has limited its sustainable growth. A few leading pharmaceutical companies and bioventures are overcoming the limitation with

the technology licensing global partnership. A few strategic partnerships, including those with the ASEAN market, may help Korean bio and biopharmaceutical industry to overcome the limited market size and hence investment capacity, while foreign partner systems can build specific engineering capacity.

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