A COMPARATIVE ANALYSIS OF THE AMERICAN AND CHINESE PHARMACEUTICAL INDUSTRIES

Undergraduate Honors Thesis

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A Comparative Analysis of the American Pharmaceuticals Industry and the Chinese Pharmaceuticals Industry

中美医药行业对比分析研究

Undergraduate Thesis

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Abstract

Following the growth of the Chinese pharmaceutical consumer market and innovative capability, comparisons between the American and the Chinese pharmaceutical industries have become commonplace due to two very divergent governmental, competitive, financial, and knowledge environments, as scholars and businesspeople alike attempt to predict shifts in power dynamics. Previous pharmaceutical industry research has focused on a single country, broad industry analysis (Ni, et al., 2017), or has conducted specific cross-border comparisons which fail to consider the respective macro-environments (Jiang & Luan, 2018; Zhao M. , 2021). This literary review examines four environments relevant to pharmaceutical innovation to achieve a broad and comparable understanding of the two industries, ultimately finding that the American industry is a well-established player focused on highly innovative activities, while the Chinese industry is a relative newcomer that is quickly developing innovative capabilities relevant to global competition dynamics.

随着中国医药消费者市场和创新能力的发展，中美医药行业之对比研究逐渐兴起，涉及政府、竞争、融资与知识环境等方面的差异，以往医药行业研究集中于一国分析 (Ni, et al., 2017) 或者范围较窄的跨国对比 (Jiang & Luan, 2018; Zhao M. , 2021)。本文考察与医药创新有关的四种环境，以达到对两国医药行业较为广泛且具有可比性的理解。最终发现美国医药行业较为成熟，专注于高度创新活动；而中国医药行业在初创阶段，正快速提高与全球竞争动态有关的创新能力。

Keywords: United States of America, People's Republic of China, Pharmaceuticals, Medicine, Regulation, Pricing, Patent Rights, Corruption, Strategy, Competitive Environment, Organization, M&A, R&D

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Introduction

The pharmaceutical industry plays a critical role in human health by discovering, developing, and producing drugs that are used to diagnose, treat, and prevent disease at the personal and public health level. Its importance to public health necessitates heavy government involvement in order to ensure drugs are produced ethically, with efficacy and are distributed in a manner that allows the greatest benefit to its citizens (meaning that intervention in the marketing, distribution, and sales of a drug should maximize the benefit delivered to the citizens). In addition to regulatory involvement, the industry faces significant internal obstacles to developing and successfully profiting from operations.

A key characteristic of the pharmaceutical industry is the extreme nature of initial costs for any given drug prior to market entry, often including years of research and development (R&D) expenses, followed by years of testing and clinical trials in adherence to local government laws. Once a drug is developed and approved, the actual cost of creating the drug is very low, making it difficult for companies to regain their years of R&D, testing, and overhead expenses.

Thus, market competition by industry competitors via. reverse engineering of the medicine or other means of imitation without themselves spending years of high cost on R&D expenses (i.e., generic drug firms) makes the drug innovator unable to sustainably compete and recoup enough return to invest in the next drug's development. This has led governments to maintain a heavy hand in the pharmaceutical industry to ensure that the drug innovator has an opportunity to profit through the use of patent exclusivity periods before generic drug firms begin competition through the use of patent exclusivity periods (a legal firm-centric monopoly based on a drug's intellectual property, usually for a set number of years).

The United States of America is often used as an industry standard for pharmaceuticals due to the highly developed nature of the industry and the highly internationalized state of participating firms, creating a phenomenon in which academic research into the industry may generally take the part for the whole, i.e., generalizing the U.S.' environment for the global environment. In fact, the United States' pharmaceutical industry is one of the most internationally active pharmaceutical industries – in part due to the relative lack of profit controlling regulation and extensive patent exclusivity period. The resulting environment encouraging pharmaceutical profitability and the knowledge-intensive focus of US industry has made the United States into the largest innovator of new drugs and new chemical elements – making it a driver of the industry.

When acknowledging the importance of the global pharmaceutical industry, particularly in regard to R&D ability and market competitiveness, one must also acknowledge macroeconomic and microeconomic trends at play, impacting the organization and power dynamics of the industry.

Though often used as a comparative foil to the United States, the People's Republic of China's developing pharmaceutical industry is infrequently wholistically compared to the U.S. With a growing role in the global pharmaceutical industry that is underrepresented in mainstream literature, it is shifting from a role of meeting the basic needs of the population to a high-end market segment (Hua, 2019). The PRC has undergone massive economic development in the

past 50 years to a magnitude and at a speed previously unseen in the world. Current projections estimate the China's consumer market will surpass the U.S.'s to become the largest consumer market in the world by 2030 (Buchholz, 2021). Various economic measurements indicate that the PRC economy is currently the second strongest economy, while some economic measures (such as GDP at PPP) indicate that the PRC has already surpassed the United States to become the most economically powerful economy (World Bank, 2020).

Yet despite this development and growth, the Chinese protective economic barriers highly restrict the ability of pharmaceutical corporations to operate. These restrictions are aimed at providing Chinese pharmaceutical firms an opportunity to develop and become more competitive. The situation may parallel similar protective barriers used in the online services industry, restricting foreign information technology and e-commerce via. the "Great Firewall" – which has resulted in the largest internet in the world with minimal presence by foreign firms such as Google or Meta (previously Facebook). For example, Alibaba is now the world's largest online and mobile commerce company.

In terms of the industry specific movement, international companies are attempting to migrate operations to China to access the large, aging population, access natural resources, and research traditional Chinese medicine (TCM), which, in a period of declining drug innovation, proves to be an asset in helping identify new chemical elements with medicinal properties (ex. development of Artemisinin for malaria treatment from TCM).

This paper attempts to review the available research on the development of the Chinese pharmaceutical industry in comparison with the U.S.' highly internationalized and dominant position in the industry. Existing research tends to focus on either the pharmaceutical industry in a specific country or focuses on specific attribute comparisons between the two countries. This literary review provides novel academic contribution by comparing significant environmental factors between two large and economically relevant countries at a macro-scale. Through this comparative analysis, greater understanding of the industry itself, industry movement, and the strengths and weaknesses of both parties are identified in hopes of creating a better understanding of this industry's role in the global marketplace. It should be noted that due to the wide breadth of this comparison and the sheer complexity of the pharmaceutical industry, the depth of the research has been limited.

In our examination of this highly complex industry, we refer to Ni et al.'s description of the pharmaceutical innovation system as consisting of four entity types, four environments, and four forms of innovation which ultimately result in drug innovation. We particularly focus on the regulatory environment and the market environment, and later briefly discuss the financial environment and the knowledge environment (referred to by Ni et al. as the technology transfer environment). We first discuss the U.S., as it is frequently used as a sort of 'model' for the industry. This section will provide the reader with a basic understanding of the industry, as well as its special characteristics. In the China section, we will attempt to refine this foundational understanding of industry to analyze a different regulatory and competitive landscape – observing how trends in the Chinese market are quickly driving it to a predominant and competitive position in the global industry.

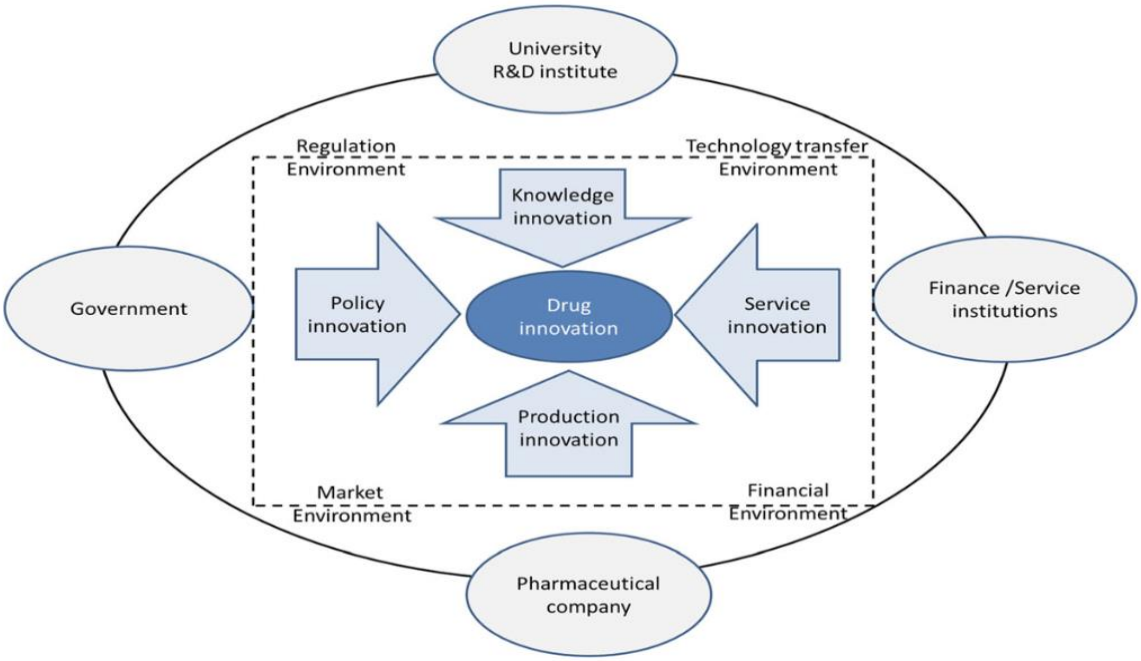


Figure 1 Pharmaceutical Innovation System, Ni et al.

The United States of America

Historical Background

Despite the U.S.' prominent role in modern pharmaceuticals, the pharmaceutical industry's infancy is not traced back to the United States. In the mid 19th century, the birth of the western pharmaceutical industry can generally be traced back to early innovators in the commercialization and distribution of drugs. One such innovator was Merck. Founded by Fredrich Jacob Merck in 1668, Merck began as a small apothecary. It wasn't until 1816 under the leadership of Emanuel Merck that the company isolated alkaloids and began manufacturing these alkaloids, plant extracts, and other chemicals in bulk – ultimately creating one of the first chemical pharmaceutical factories (Wang M.-L. , 2009).

Pfizer (1849), BMS (1858), Eli Lilly (1876) were some of the earliest American pharmaceutical companies and have since become some of the most famous. These ranks were later joined by such players as Johnson & Johnson and Bristol Myers Squibb.

For brevity, the main events in the development of the American pharmaceutical industry will be distilled to three main drugs that had significant or symbolic impact on the industry's development: insulin, penicillin, and cimetidine.

Fredrick Banting and Charles Best first presented their insulin derivatives to the American Physiological Society at Yale University – though receiving poor reception at first, their "thick brown muck" showed efficacy in the treatment of severe diabetes in dog-based animal experimentation, likewise proving successful in treating human diabetes in 1922 (Science History Institute, 2017). It was soon after this, Eli Lilly began their large-scale production of insulin in 1923, purifying the animal-based extract and distributing it (American Diabetes Association, 2019). By 1925 Eli Lilly had produced 217 million units of the "world's first life-saving drug" (Lilly, 2019).

Fleming made his famous happenstance discovery of penicillin in 1928 in London, England after returning from a vacation in 1928. In the early 1940s, penicillin as a commercial product came to the United States. Due to cooperation between English scientists, the U.S. government and multiple drug companies, scaled penicillin production began in the USA with the U.S. government taking full control of production during wartime, ultimately developing techniques for large quantity production via. deep-tank fermentation which, by 1943, was able to satisfy the penicillin demand of the entire Allied Armed Forces (Gaynes, 2017). Those sharing in the following Nobel Price (Fleming, Florey, and Chain) had turned down the opportunity to patent the breakthrough drug's process due to ethical concerns; taking advantage of the opportunity, Andrew Jackson Moyer claimed the process patent of the method for production of penicillin in 1948 (US 2442141, US 2443989, US 2476107) (Moyer, Method for the Production of Penicillin, 1948; Moyer, Method for Production of Penicillin, 1949; Moyer, Method for Production of Penicillin, 1948). In response to the patent filing, Fleming reflected "I found penicillin and have given it free for the benefit of humanity. Why should it become a profit-making monopoly of manufacturers in another country?" (Allison, 1974). Despite misgivings

held by Fleming towards the American's patent filing, the U.S.-based penicillin patent was a boon to the U.S. pharmaceutical industry.

The 1940s are commonly recognized as the birth of the modern pharmaceutical industry, the start of the "Golden Age" of pharmaceuticals which helped open the door to the development and competition that was to come, with competition relying more and more on increasing R&D and marketing activity – in large part due to the U.S.' heavy patent protection (ex. the novel concept of patenting naturally occurring antibiotics in 1946, and the later tightening of the pharmaceutical patent regime (Malerba & Orsenigo, 2015). However, despite (or perhaps because of) this hugely impactful shift in the industry to R&D and marketing practices, we identify cimetidine as a defining moment in the pharmaceutical industry. In 1977 cimetidine, a drug developed by British Sir James Black to treat heartburn and peptic ulcers by binding to the then hypothetical H_2, was introduced to the American market. Developed under Smith, Kline & French (SKF) (originally based out of Philadelphia, USA and later acquired by Beecham Group and Glaxo Wellcome making it an English company) (Lohr, 1989), cimetidine became the first blockbuster drug under the trade name Tagamet, "blockbuster" meaning it broke $1,000,000,000 in annual sales, leading to skyrocketing competitions as companies race to identify and market the next blockbuster drug (PharmaPhorum, 2020; Li J. J., 2014).

From a historical perspective, the United States has had a significant presence and participation in the "birth" of the modern pharmaceutical industry and the following pivot to high-R&D, high-marketing model that dominates the industry today. One of the largest contributors to the birth and growth of this modern industry was the U.S.' unique willingness to patent drug manufacturing processes, synthetic drugs, and naturally occurring drugs and protect these patents in a way that was previously unheard of. Despite the controversy surrounding this generous patenting regime, there is no doubt that this was a significant driver of progress made during the Golden Age and continues to be motivation for the development of new, cutting-edge drugs.

Modern Background

The modern pharmaceutical industry is facing a period of change and fluctuation caused by both external and internal factors that have forced many pharmaceutical companies to alter their strategic position and their product pipeline to a more secure position. Global pharmaceuticals, and the U.S. as a major player therein, are facing significant changes such as the strengthening of IPR, increasing costs of R&D, an aging population, and the expiration of significant drug patents, referred to by some as the "patent cliff."

According to the 2020 Census conducted by the United States Census Bureau, the US population in 2020 was approximately 331,449,281 people (U.S. Census Bureau, 2021), making it the third most populous country in the world (behind India at 1,338,000,000 and China at 1,400,000,000) (World Bank, 2019). From this, there are two main factors that create an environment favorable to pharmaceutical companies. The first is the population age structure. The U.S. is one of many developed and emerging countries around the world undergoing rapid population aging trends. As people age, they create more demand for pharmaceutical products. More than 90% of seniors and 58% of adults in the U.S. rely on prescription medicine on a regular basis, with older individuals being more likely to contract illnesses (Kennedy, 2021). This expanding market segment grants a degree of stability and growth to American

pharmaceutical demand. In addition to the aging demographics, it is also notable that, despite only roughly 4.25% of the world population residing in the U.S., the U.S. population's health care demand is 17.4% of its GDP on healthcare – by far the highest rate in the world (distantly followed by France at 11.8%), with health spending predicted to reach 4,119,342,000,000 USD in 2021 (Fitch Solutions, 2020).

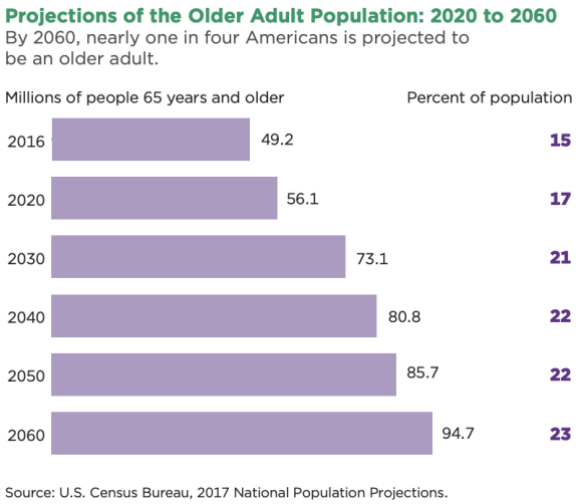


Figure 2 Projections of the Older Adult Population: 2020 to 2060, from US Census Bureau

Yet another boon for pharmaceuticals in the United States is the combination of strong IPR yielding a generous market exclusivity period, and the non-regulation of pharmaceutical prices – creating an ideal location for profitable market entrance. Intellectual Property Rights (IPR) are a vital aspect to how pharmaceutical firm's function. The pharmaceutical industry is characterized by extensive initial cost, especially when it comes to research and development cost and regulatory approval cost. With these massive pre-market costs, most countries issue some sort of IPR to ensure a period of market exclusivity in which the developer is the only firm that can sell the drug, in effect granting that company monopoly power. As the only developed nation without some sort of government regulation controlling pharmaceutical pricing – pharmaceutical firms price their medicines highly within the United States to cover losses of incurred from selling pharmaceuticals in other countries (Salter, 2015; Keyhani, Wang, Herbert, Carpenter, & Anderson, 2010), which has implications on the number and demographic of individuals attaining certain drugs. One beneficial effect of this is that most advanced and innovative drugs will arrive to the U.S. market before other markets, allowing American market access to the newest technology (Kang, et al., 2019).

This being said, the U.S. pharmaceutical industry's position is in flux: new markets are gaining power, drawing firms, the industry is restructuring in an effort to lower costs, heavy generic competitive pressure in the traditional drug market is driving a drug-pipeline shift towards biologic drugs (Kennedy, 2021). Increasing costs to U.S.-based pharmaceutical innovation provides a damper to the industry, though free 'monopoly pricing,' the largest purchasing market in the world, and long-standing industry infrastructure provide ample reason to take a deeper look into the state of affairs of the U.S. Pharmaceutical industry.

Policy and Regulatory Environment

How does the modern U.S. pharmaceutical industry interact with U.S. government regulation? What are the ways in which drug price and quality are determined? How does government IPR policy affect the motivation for innovation? How is quality ensured for the health of the end consumer? To what extent does corruption exist and how is it controlled? Does the government play a significant role in the long-term strategic movement of the industry's motivation and growth? We examine these questions below.

As the World Health Organization points out, "drugs are not ordinary consumers' products;" drugs are products that are heavily influenced by information imbalances – meaning that the consumer is not able to autonomously make decisions about drug use, as professionals function in a diagnostic and prescriptive capacity. Professionals (ex. physicians) are imperfect actors themselves and are subject to information asymmetry – they must rely on special training and information about particular products (Rägo & Santoso, 2008), and often use training provided by pharmaceutical firms to gain this knowledge (Schwartz & Woloshin, 2019). Therefore, to prevent the selection of ineffective, low quality, or even harmful medication, governments must ensure the use of fair and valid information in the market and must also ensure that all activities in the drug manufacturing itself are done in a safe and proper way, therefore, creating good quality, safe, and effective drugs for consumer use.

Distinct from this 'restrictive' role, regulation is also vital to ensure that a firm's return on investment can be made. Intellectual property rights must be established and enforced by governments. Once a patent expires and imitation products enter the market via. generic competition, 51% of the drug value is lost in the first year, with 77% of the initial drug value lost just 5 years after the loss of market exclusivity (IMS Institute for Healthcare Informatics, 2019). This means that to recover cost and profit from the development of the drug, pharmaceutical firms want the longest and soundest IPR possible, delaying imitative competition.

Though often viewed as negative, regulation serves an important and necessary purpose in the pharmaceutical industry. The highly impactful system of policy and regulations surrounding the industry goes far to create a complex and nuanced environment. In the following discussion, we attempt to focus on some central aspects of the policy and regulatory environment created by the government of the United States of America that are critical factors for the industry and/or important to the comparison between the American and Chinese industries: price control, patent rights, quality control, and corruption policy. We then briefly examine the centralized strategy set by the government to direct the industry's long-term development.

Price Control

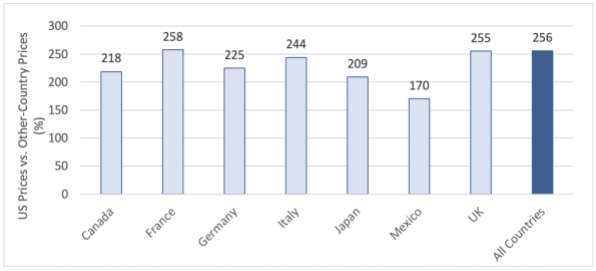
The pharmaceutical pricing system in the United States is unlike that of any other country – it is the only developed nation that does not use some sort of government regulation to control pharmaceutical and biologics pricing, with companies being able to freely set drug prices (Shaikh, Del Giudice, & Kourouklis, 2021; Salter, 2015). This means that for the average consumer, there is little to no government influence in pricing, relying wholly on market forces to find an equilibrium between demand and supply to yield a price suitable to the market. Because of this system, and extenuated by the market exclusivity of the patent-holding innovator, the U.S. bears a drug cost that is far greater than other countries. A 2019 study found

that 79 U.S. drugs were priced on average 220-310% greater than their Canadian, Japanese, and British counterparts (accounting for rebates), with price differentials ranging from 30% to 6,910% (Kang, et al., 2019). To further develop this, in an 8-year data analysis (including forecasts) Fitch Solutions found that health expenditure never fell below 17% of total GDP value, with forecasts predicting that expenditure will reach 19.11% in 2024 (Fitch Solutions, 2020). However, as Dabbous et al. points out, pharmaceutical expenditure is not analogous to health expenditure. In fact, they find that 11.9% of health expenditure is pharmaceutical expenditure, with the total value of the pharmaceutical expenditure reaching 2.04% of total GDP in 2016 (Figure 3) (Dabbous, et al., 2019). Through this distinction, we still observe that the U.S. expenditure is relatively high compared to the other countries observed (Figure 3), though to perhaps a more moderate extent. Regardless, it can be said that literature largely agrees that prescription and branded medicines are far more expensive in the U.S. than in other countries (Kang, et al., 2019) (Figure 4, Figure 5, Figure 6), with the exception of unbranded generic drugs (Figure 7) (Mulcahy, et al., 2021).

		Health Expenditure			Pharmaceuticals Expenditure			
Countries	GDP (million US Dollars)	Expenditure (US dollars/capita)	% of GDP	Expenditure Adjusted per GDP	% of Health Spending	Expenditure (US dollars/capita)	% of GDP	Expenditure Adjusted per GDP
Canada	1,625,361	4826	10.4%	.0029	17.8%	860	1.86%	.0005
France	2, 765, 185	4902	11.5%	.0017	13.9%	663	1.60%	.0002
Germany	4, 050,525	5728	11.3%	.0014	14.3%	777	1.59%	.0002
Japan	5,369, 479	4717	10.7%	.0008	19.7%	874	2.15%	.0002
Korea	1, 877, 123	2897	7.6%	.0015	22.5%	653	1.71%	.0003
USA	**18, 624, 475**	**10,209**	**17.1%**	**.0005**	**11.9%**	**1174**	**2.04%**	**.0001**
UK	2, 806, 915	4264	9.7%	.0015	11.4%	476	1.11%	.0002

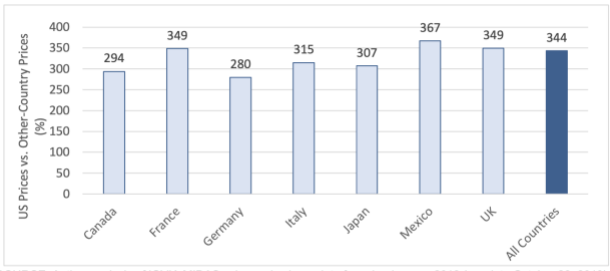
GDP = Gross Domestic Product, USA = USA of America, UK = UK.

Figure 3 International overview of health and pharmaceuticals expenditures, from Dabbous et al.



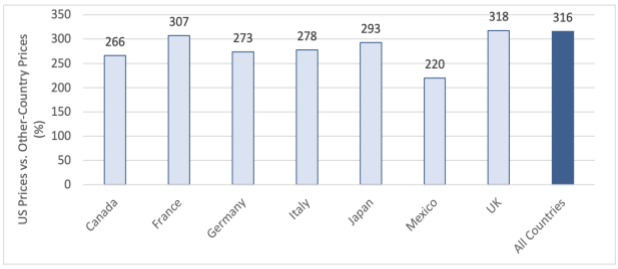
SOURCE: Author analysis of IQVIA MIDAS sales and volume data for calendar year 2018 (run date October 28, 2019).
NOTE: "All Countries" refers to all 32 OECD comparison countries combined. Other-country prices are set to 100. Only some presentations sold in each country contribute to bilateral comparisons.

Figure 4 U.S. Prescription Drug Prices as a Percentage of Prices in Selected Other Countries, All Drugs, 2018, from Mulcahy et al.



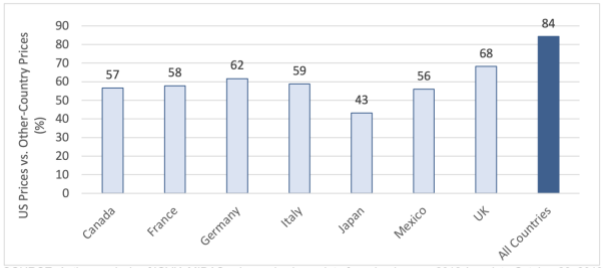
SOURCE: Author analysis of IQVIA MIDAS sales and volume data for calendar year 2018 (run date October 28, 2019).
NOTE: "All Countries" refers to all 32 OECD comparison countries combined. Other-country prices are set to 100. Only some presentations sold in each country contribute to bilateral comparisons.

Figure 5 U.S. Brand-Name Originator Drug Prices as a Percentage of Other-Country Prices, 2018, from Mulcahy et al.



SOURCE: Author analysis of IQVIA MIDAS sales and volume data for calendar year 2018 (run date October 28, 2019).
NOTE: "All countries" refers to all 32 OECD comparison countries combined. Other-country prices are set to 100. Only some presentations sold in each country contribute to bilateral comparisons.

Figure 6 U.S. Biologic Prices as a Percentage of Other-Country Prices, 2018, from Mulcahy et al.



SOURCE: Author analysis of IQVIA MIDAS sales and volume data for calendar year 2018 (run date October 28, 2019).
NOTE: Biologics are excluded. "All Countries" refers to all 32 OECD comparison countries combined. Other-country prices are set to 100. Only some presentations sold in each country contribute to bilateral comparisons.

Figure 7 U.S. Unbranded Generic Drug Prices as a Percentage of Other-Country Prices, 2018, from Mulcahy et al.

It is thus intuitive that U.S. political rhetoric is universally speaking to the expensive nature of drugs. The U.S. Former President Donald Trump (R) campaigned on promises to reduce drug prices (Dabbous, et al., 2019), Nancy Pelosi (D) is pushing the Elijah E. Cummings Lower Drug Costs Now Act of 2019 (H.R. 3) (Dusetzina & Oberlander, 2019), while sitting President Joe Biden (D) has likewise promoted action to lower the drug cost borne by the American consumer (Biden, 2020).

With data showing that prescription drug prices are, indeed, some of the most expensive in the world, and public and political attention on the issue of growing drug prices, one may ask why the U.S. has continued its longstanding precedent of unregulated drug prices. The main reason is because economists theorize that implementing price controls on the pharmaceutical industry's industrial products would put financial constraint on an industry that requires a massive volume of money and financial security to ensure expensive R&D and innovation processes can be maintained. Following price controls, certain economists theorize the ability of the U.S. market to continue to benefit from increasingly advanced, innovative, and necessary drugs would be reduced. Interestingly, because the trade-off between American-based pharmaceutical innovation and American drug prices is largely conducted on a theoretical basis, the literature contains some disagreement. We examine the two arguments below.

The classical theoretical support for the maintenance of the free-market, no-price control model of pharmaceutical drug pricing is often supported by the connection between R&D and profit – this is to say that as price regulation reduces drug prices, it has a direct effect on firm's willingness to create expenditure in general and on R&D in specific (Shaikh, Del Giudice, & Kourouklis, 2021). The relationship between the historical increase in drug prices since WWII has not been the result of existing technologies inflating in price but has resulted from the price for new technologies (Weisbrod, 1991). This led to two main principles (revealed in Scherer, 2001) – if internal funds are a cheaper source of R&D finance (as opposed to external debt or equity), then profits have a positive correlation on R&D spending through a cash-flow effect; likewise, when future profit expectations are dampened due to price regulation, a demand-pull investment in R&D may result (Abbott & Vernon, 2005) – though these effects are predicted to be more visible lags (Scherer, 2001). Due to these links between profitability and R&D price regulation will logically decrease in response to drug price decreases. In a Monte Carlo Simulation examining how drug price decreases impact R&D expenditure, Abbot and Vernon use a Net Present Value (NPV) framework that incorporates the uncertainty of R&D technical success, development costs, and future revenues. They find that reducing drug prices by 40-45% would significantly impact firm willingness to invest in R&D and may reduce the number of

compounds progressing from a laboratory setting to clinical trials by 50-60% (Abbott & Vernon, 2005) (Figure 8), meaning R&D would yield fewer new finished products. Abbot and Vernon additionally suggest that the spillover effects of R&D would result in a compounding long-term impact on future R&D investment (Abbott & Vernon, 2005). It should be clarified that this analysis focuses on NPV and does not include possible demand-side effects of price reductions. If demand were to increase as a result of a decrease in price, this may have moderating effects on the decrease of firm cash flow, as the finished drug production cost would be more affordable. By maintaining static demand through the analysis, it is possible Abbott and Vernon could under-represent the full impact of firm revenue created by the implementation of price controls. In following research, Vernon finds that regulating prices would lead to an R&D decline of 23.4-32.7%, a more moderate view of the negative implications of regulation (Vernon, 2005). Notably, this analysis was based on the implicit assumption that the U.S. would regulate prices to the level of markets outside of the U.S.

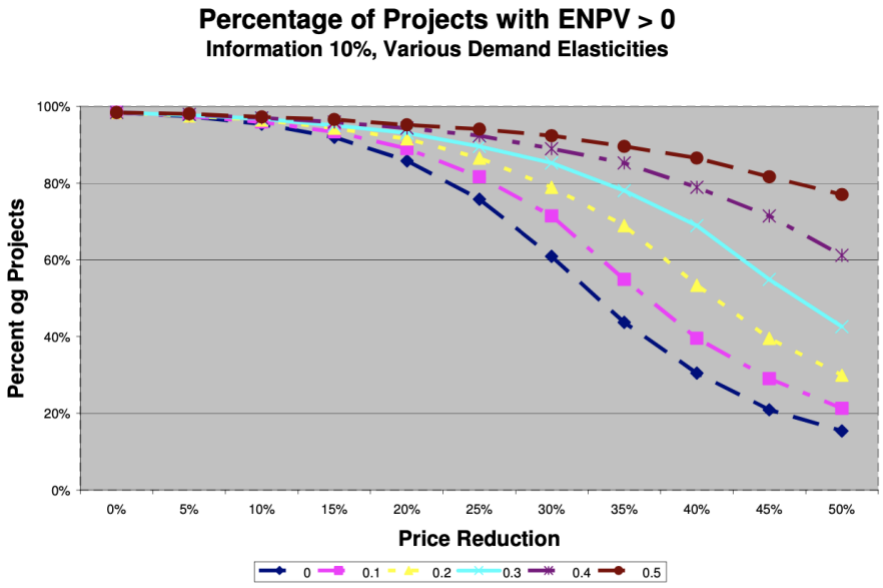


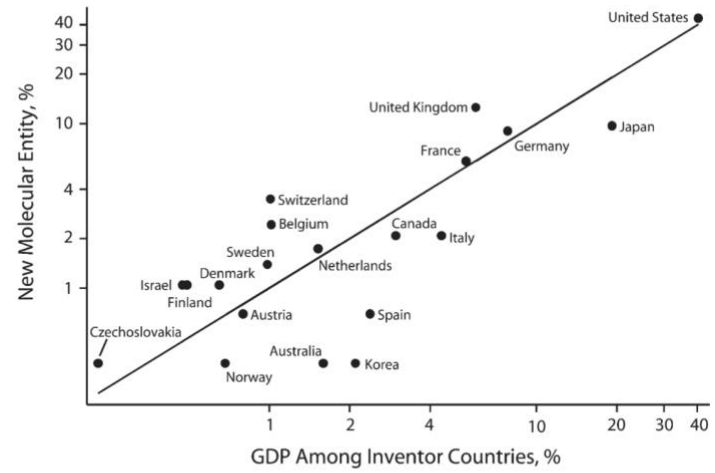
Figure 8 A Sensitivity Analysis on Price Elasticity, from Abbot and Vernon

An opposing view of the relationship between drug price regulation and R&D investment holds that regulation of drug price is recommendable. Research conducted by Shalkh, Del Gludice, and Kourouklis directly addresses Vernon's research by attempting to use the same logical framework. They use more recent data, spanning 2000-2017, to examine whether the quick-changing nature of the pharmaceutical environment would have any impact on Vernon's findings. They focused their two-way fixed effects model on the relationship between price regulation and R&D intensity by incorporating European markets as a comparison market, while most other literature examines the relationship between price regulation and profitability or that of profitability and R&D intensity. While Shalkh et al. maintain Vernon's conclusion that exposure to price regulation correlates negatively with cash flow and profitability, which therefore correlates negatively with R&D intensity, they do so by distinguishing these results from those that account for firm fixed effects. After incorporating fixed effects (as Cockburn and Henderson found R&D investment determinants may include *unobservable* and *difficult to measure factors* "such as scientific expertise collected in-house and tacit knowledge of products,

processes and markets that endow firms with competitive advantage"), a strategy for controlling omitted variable bias due to heterogeneity, price regulation was found to have no significant relationship with R&D intensity (though price regulation maintains its negative relationship with cash flow and profitability) (Shaikh, Del Giudice, & Kourouklis, 2021). These findings implicate that large firms do not use sales to fund the current and future drug pipeline, but rather to regain investment in existing products. Furthermore, these findings suggest that interference on such fixed effects may be relevant in price regulation/R&D intensity tradeoff analysis.

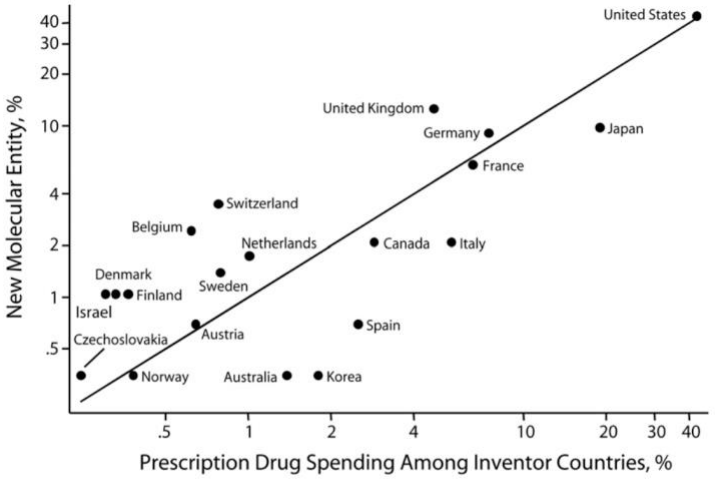
Some literature has additionally framed the question of the U.S.' price regulation according to a view of pharmaceuticals as a unique industry characterized by high information asymmetry at multiple levels (firm to physicians, physicians to end consumer, etc.), principal distinct agency, potential third-party payment, copayments, and surrogacy of the need for health (health being a direct need), suggesting that general equilibrium theory in traditional anti-price regulation research may have limitations when applied to pharmaceuticals. With these unique characteristics in mind, Sorato et al. suggest that "the healthcare market will not maximize the utility or welfare of the people if left to operate [under] the free market principle" (Sorato, Davari, Asl, Soleymani, & Kebriaeezadeh, 2020).

One argument, supported by Pharmaceutical Manufacturers Association of America (PhRMA), is that the U.S. is covering the majority of the global cost of NME development, while countries who implement pricing regulations are freeloading on U.S. innovation – the Trump Administration pushed for drug price increases in foreign nations to adjust this "freeloading" on U.S. innovation (Loiaconi, 2018). Keyhani et al. point out that from a purely theoretical standpoint, this view implies a country-specific source of innovation, despite the private and highly globalized nature of the industry. Further, they attempt to empirically verify whether freeloading is happening by identifying the percentage of yearly NME (an output-based measure of R&D involvement) by GDP (Figure 9). The results suggest that the U.S. is undoubtedly a major contributor to global prescriptive pharmaceutical innovation (excluding biotech innovation) with 36.4% of NME approvals assigned to inventors based in the US between 1992 and 2004, and 33.8% of NME patent assignees being in the U.S. (Figure 10). America also accounted for 42% of prescription drug spending and developed 43.7% of NMEs, but the economy size notably made up 40% of the GDP among NME innovator countries, indicating that the U.S.' contribution is proportional to GDP size, suggesting that "freeloading" is occurring only at the margins (3.7%). The U.K. (4.7%, 12.5%, and 5.9% for prescription drug spending, NME development, and GDP size, respectively) seems to have a larger proportional NME output as compared to spending and GDP, suggesting that the argument for the U.S. bearing an unfair or disproportional burden for drug innovation may be unfounded when examining size of output to input ratio – i.e. by paying higher prices for drugs, U.S. based pharmaceuticals are not disproportionally innovative (Keyhani, Wang, Herbert, Carpenter, & Anderson, 2010).



Note. GDP = gross domestic product; NME = new molecular entity. Axes are on a log scale. The United States almost falls on the 45 degree line where contribution to GDP and NME development is roughly proportional. Countries above the line develop a higher percentage of drugs compared with their percentage contribution to GDP. For example, the United States accounted for 40% of the GDP among NME innovator countries and was responsible for the development of 43.7% of the NMEs. The UK contributed proportionally more NMEs than its national income would indicate, and Australia and Japan proportionally less.

Figure 9 Pharmaceutical innovation (development of NMEs) as a function of gross domestic product (N=288): 2000, from Keyhani et al.



Note. NME = new molecular entity. Axes are on a log scale. Countries above the line develop a higher percentage of drugs compared with their percentage contribution to prescription drug spending.

Figure 10 Pharmaceutical innovation (development of NMEs) as a function of prescription drug spending (N=288): 2000, from Keyhani et al.

Supply-Side Pricing Policy. This form of policy deals with the ability of the drug or the pharmaceutical firm to access the market, the use of direct price controls, as well as the use of quality regulations. We first look at supply-side policy from the perspective of price regulation. The U.S. currently has extremely limited participation in supply-side pricing policy, with the vast majority of cases seeing no price control. However, Elijah E. Cummings Lower Drug Costs Now Act of 2019 (H.R. 3), a bill proposing the initiation of supply-based pricing regulation has passed the House of Representatives and sits in Congress. If passed, this bill would allow the Department of Health and Human Services (HHS) to negotiate prices for at least 25 drugs. Negotiations would focus on either 125 drugs accounting for the greatest national spending, or the 125 drugs accounting for the greatest Medicare spending. Under the proposed negotiation process, the drug price may not exceed 120% of the average price of Australia, Canada, France, Germany, Japan, and the U.K., or can be set at 85% of U.S. average manufacturer price. Under this six-point reference pricing system, negotiation nonparticipation on the part of the firm would

result in fees of 65% of the previous year's gross sales, with penalty growth of 10% in subsequent non-compliant years (United States 117th Congress, 2021).

The U.S. Government does participate in a few passive and nonbinding forms of price *influence* (distinct from regulation or policy), as pointed out by Santerre et al. in *The Impact of Indirect Government Controls on U.S. Drug Prices and R&D*, including such behavior as moral suasion, political threats, and crowding out (Santerre, Vernon, & Giaccotto, 2006). Santerre et al. argues that moral suasion is how governments persuade firms to moderate price increase via. moral appeal. In the 1990s, former President Clinton participated in this form of "government exhortation," or moral suasion, by pointing out high drug prices to the public which encouraged pharmaceutical firms to reduce prices to avoid adverse publicity. Political threat includes behavior in which the government acts as though it will implement more direct price controls in the near future unless firms take action to moderate prices increases (i.e., enduring defensive strategic behavior via. threatening rhetoric). Finally, and perhaps most significantly, crowding out allows the government to gain buyer power through expansion on Medicare and Medicaid plans ("crowding out" because increasing public insurance participants means decreasing private insurance participants); however, crowding out is still a passive price control strategy because it remains illegal for Medicare and Medicaid to negotiate prices. As these programs grow, the buying power of the U.S. Government likewise grows, meaning that moral suasion and political threat become more credible persuasion tools. Lowering the price of drugs offered within the Medicare and Medicaid programs would have an indirect impact on private insurance providers who would theoretically reduce price due to fewer high-risk plan-holders (elderly or sickly) holding private insurance policies (Santerre, Vernon, & Giaccotto, 2006).

Proxy-Demand Pricing Policy. Proxy-demand policies are policies that influence health care providers such as physicians and healthcare institutions, as these groups act as proxies for patients in making purchasing decisions.

Demand-Side Pricing Policy. Demand side policies are those that directly impact the patient demand. The U.S. Government has very limited exposure to demand-side pricing policy. Though some manufacturers may provide copay options to limit the out-of-pocket cost borne by the customer, these are not federally required.

Patent Rights

The United States did not always have a robust patent system. In fact, until 1891 the U.S. was a leader in IPR violations - it was fully legal for IPR of foreigners to be violated in the U.S., as domestic law only provided protection for U.S. citizens' IPR (Peng, Ahlstrom, Carraher, & Shi, 2017). This shift from a leading IPR violator to a leading champion of IPR fits with the theory arguing that countries have no interest in strong IPR until they become significant technology exporters (Qian, 2007). The current standard for IPR, based out of the World Trade Organization, is the Trade-Related Intellectual Property (TRIPs) agreement. TRIPs was championed by the United States and, further, championed by the pharmaceutical MNEs based out of the U.S. (Tyfield, 2008). Due to the pharmaceutical's evident stake in establishing and maintaining international IPR standards and because pharmaceuticals rely on patent protection and market exclusivity as a main avenue for funding (and thereby continued competition), it is critical to understand what the current IPR legal framework is like in the U.S., and how U.S. based policy has extended outward to influence global implementation and maintenance of IPR standards.

The current domestic process for obtaining IPR for a drug includes registering chemical compound innovations, a method of use for the product, a manufacturing process for the product, technology to administer the pharmaceutical product, etc. to the U.S. Patent and Trademark Office (PTO). If the innovator discovers an improvement to any of the above patentable technologies, that improvement is also subject to its own patent, thus resulting in the strategy of "evergreening" (alternatively known as life cycle management or patent layering) in which small improvements are continually made to the patented pharmaceutical to indefinitely extend exclusivity. Of the top 12 best selling drugs in the U.S., a drug has an average of 71 granted patents, with the world's top selling drug, AbbVie's Humira, having 132 granted patents of 247 patent applications (I-MAK, 2017). Under the PTO, the typical term for pharmaceutical patent life (without extensions or life cycle management strategies on behalf of the firm) is 20 years, though, through evergreening firms may gain significant opportunity to increase the patent lifespan. In many cases, FDA approval must then be achieved before market access is allowed including processes to ensure that the drug is safe and effective (i.e., regulatory approval) before the FDA may grant regulatory exclusivity. Regulatory exclusivity indicates that the FDA is limited in its ability to approve generic drugs or biosimilars that, in effect, help to establish and maintain the market exclusivity of drugs (Figure 11). These exclusivities come in the form of data exclusivity (nonaccess to the innovative drug's FDA data) and marketing exclusivity (FDA inability to approve other applications for the same drug and use). The exclusivity periods may last varying lengths of time depending on the size of the innovative contribution; for example, drugs containing NCEs are eligible for 5 years of data exclusivity while applications for "significant improvement" of existing chemical entities are eligible for 3-year data exclusivity. Under the Orphan Drug Act of 1983, a 7-year market exclusivity period is given to encourage the development of drugs to treat rare ailments. It is important to note that this stage in the market-entry process is distinct from the patenting process and establishes a second approval process helping to identify the *de facto* equilibrium between the contrasting natures of promoting both innovation and profit for the innovator and the public health and affordability of medicines. Market exclusivity stemming from regulatory exclusivities may be granted, which may vary in length from "as little as 6 months to as much as 12 years depending on the specific drug or biologic at issue," while patents allow the patent holder the exclusive rights to "make, use, sell, and import the invention for a term lasting approximately 20 years," though certain patent extensions that may be gained through firm participation in pay-for-delay innovator-generic settlements and evergreening (Hickey, Ward, & Shen, 2019). Like any IPR system, the goal is to find a balance between incentives for innovation and the costs levied on the public – in the case of pharmaceuticals, this means that balance should be created between the incentives for long-term growth of innovative medicines and the price the consumer must bear.

	Patents	Regulatory Exclusivities
Purpose	Provide incentives to encourage creation of new technologies	Balance pharmaceutical innovation and generic competition
Specific to Pharmaceuticals?	No; available to any "process, machine, manufacture, or composition of matter"	Yes
Relevant Agency	U.S. Patent & Trademark Office (PTO)	Food & Drug Administration (FDA)
Basic Requirements	Invention that is new, useful, nonobvious, and sufficiently disclosed in patent application	Successful completion of FDA regulatory process for a particular drug or biological product
Term	Generally 20 years from the date of the relevant patent application	Variable based on drug type and whether FDA approval has been previously obtained with respect to that product
Effect	Third parties cannot may, use, sell, or import the invention without the permission of the patentee	Third parties cannot seek, obtain, and/or use data for FDA approval with respect to particular product
Enforcement	By the patentee, usually in a judicial patent infringement lawsuit	By FDA

Source: CRS.

Figure 11 Summary Comparison of Patents Versus Regulatory Exclusivities, from the Congressional Research Service

One of the most significant developments in the realm of regulatory approval of generic drugs under the Food and Drug Administration Law is the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Act). This landmark act restructured the way generic drug companies could enter the market and compete with innovator firms by allowing potential generic competition to complete an "Abbreviated New Drug Application" (ANDA), which enables the use of the FDA's prior approval of an active ingredient to be used as evidence of safety and efficacy which thereby reduces the high cost of running independent and extensive data collection (clinical trials) for the FDA (Olson & Wendling, 2018; Hickey, Ward, & Shen, 2019). Furthermore, Hatch-Waxman allows generic pharmaceutical firms to begin the development of generic medicine while the innovator is still on-patent exhortation (a practice previously not allowed, which in effect further extended the exclusivity period of originators), which is paired with 180 day period to exclusively market the generic drug (Food and Drug Administration, 2022). This Act has increased the willingness and ability of generics to compete with the innovating firm by inserting exceptions to patent and regulatory exclusivities to create a more malleable IPR system for generics, ultimately reducing the time and expense necessary to get the generic drug on the market.

Much controversy still surrounds the current patent-based barriers to competition both in politics and literature. As we have discussed, the very nature of a patent system as it applies to pharmaceuticals indicates that, in the absence of price regulation, one firm will have significant control over the price of and access to drugs – a tradeoff for heavy resource and time investment into high-risk R&D activity. When applied to pharmaceuticals, this indicates that some of the individuals who need access to the drug may not have access, damaging the overall health of a population. The question posed by many in the political and research field stands as "What degree of IPR protection, the control over price it creates, and the potential future pharmaceutical innovation it stimulates reaches an acceptable equilibrium with the public's morbidity and mortality resulting from limiting the access to drugs?" – a question with a largely philosophical basis. Even within this framing, actors have yet to reach a definitive consensus as to what degree

IPR and price influences future R&D intensity (Qian, 2007; Abbott & Vernon, 2005; Shaikh, Del Giudice, & Kourouklis, 2021).

Quality Control

Quality of commercial goods holds a particular importance in the pharmaceutical and pharmaceutical manufacturing industries due to the large impact drugs have on the health and wellness, and the potential manifestation of adverse effects in the public. Common manufacturing quality issues causing drug shortages (emerging pre- or post-market launch) include endotoxins, bacterial or fungal contamination; particles of glass, metal, fibers, or foreign matter; precipitate formation due to unanticipated chemical reaction or the container/stopper; impurities; or drug degradation (Dill & Ahn, 2014).

Ball et al. identifies three distinct characteristics of the pharmaceutical market that provide opportunity for quality issues: quality opaqueness, buyer-user separation, and product competition regulation (Ball, Shah, & Wowak, 2018). They discuss that product quality is far more difficult to observe and measure than in more common consumer-oriented goods and service industries. When facing a typical consumer goods industry such as the textile industry, consumers are able to identify lapses in quality through stained, ripped, or otherwise damaged or faulty product quality. This stands in stark contrast to the pharmaceutical industry due to high physical homogeneity. Buyers of pharmaceuticals "consider any generic product as perfect substitutes," and simply "[do] not sufficiently recognize or reward quality," and are therefore unresponsive to lapses or shortcomings in quality (Woodcock & Wosinska, 2013). Buyer-user separation is also a significant promoter of quality deficiencies. The pharmaceutical supply chain is significantly complex, with drugs having to pass from the drug manufacturers, wholesalers, pharmacies, and finally the consumers (in a simplified supply chain design). As the number of intermediaries increases (i.e., the supply chain complexity increases) product quality accountability to the manufacturing firm may be reduced or inhibited, allowing the realization of quality reduction (Ball, Shah, & Wowak, 2018). Ball et al. finally proposes that product competition regulation provides opportunity for quality issues to arise. They argue that significant competitive pressure is applied by generic producers, especially when genetic competition is federally mandated. Ball et al. points to a Wall Street Journal article: "U.S. generic-drug prices are falling at the fastest rate in years, eating into the profits of pharmaceutical wholesalers and manufacturers alike … the trend has been good for the employers and government programs that ultimately pay for drugs … but it is taking a hard toll on wholesalers and generic-drug makers" (Walker, 2017). By exclusively focusing on increasing price-based competition in the generic manufacturing subsector in order to decrease the cost borne by government and private consumers, regulation may be causing generic manufacturers, already a low margin area, to compromise process integrity, leading to greater quality issues. FDA Center for Drug Evaluation-backed literature points out that there is indeed discussion on regulatory effects in increasing price-based competition among generic producers, particularly pointing out the Medicare Modernization Act of 2005 (MMA). The MMA is believed by some to have adversely impacted generic sterile injectable drug profit margins by reducing Medicare's price-paid and thus creating pressure for the generic manufacturers - though some literature proposes this was a nonspecific trend rather than a reaction specific to MMA (Woodcock & Wosinska, 2013; Jacobson, Alpert, & Duarte, 2012).

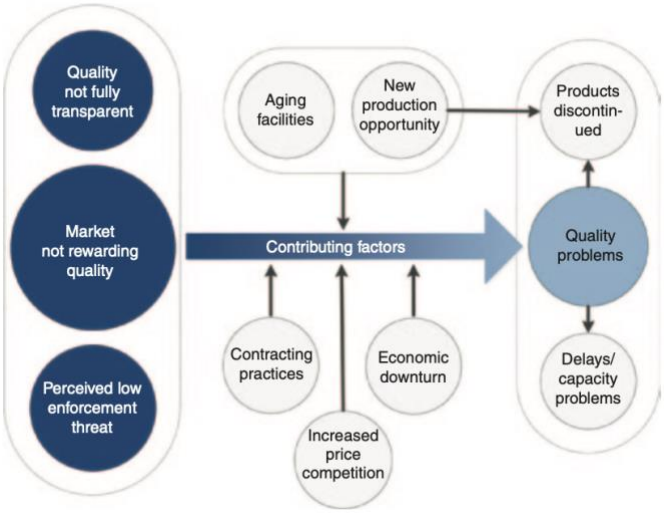


Figure 12 Economic drivers of manufacturing quality problems, from Woodcock and Wosinska

The FDA, the U.S. regulator for drugs, enforces multiple control systems for companies who wish to market and sell drugs in the United States of America in order to ensure the health and safety of the consumer. In order to strengthen pharmaceutical quality in an environment of growing globalism and thereby greater quality surveillance difficulty, the FDA founded the Office of Pharmaceutical Quality (OPQ) in 2015 – this office was founded to "ensure a uniform drug quality program across all sites of manufacture, whether domestic or foreign, and across all human drug product areas – new drugs and biologics, generics, and biosimilars—and also over-the-counter drugs and compounded drug products" (Food and Drug Administration, 2022). This office is also internally oriented, and focuses on improving quality surveillance and control in both domestic and foreign firms who will sell drugs in the U.S.

The main tool used by OPQ to ensure standard quality of drug manufacturers is the Current Good Manufacturing Practices (cGMP) guidelines. cGMP is a system that "assures proper design, monitoring, and control of manufacturing processes and facilities," by setting a minimum level of quality required for a product to be marketed within the U.S. (Center for Drug Evaluation and Research, Office of Pharmaceutical Quality, 2019). Though this is an international standard for drug quality, it is not without criticism. Some academics believe that cGMP is structured as a measure of *how* work is done, rather than *what* work is done (Ball, Shah, & Wowak, 2018). For example, under cGMP, suppliers must be regularly audited, but which suppliers conduct the audit is at the manufacturers discretion; employee training is required, but what training is used is at the manufacturers discretion – displaying a variability in the potential implementations of cGMP that can be seen in China as well (招伟汉, 2015). Figure 13 displays the cGMP ratings (out of 10) based on region, application type, and manufacturing sector. Notably the worst performing sites are those in the "No Application" application class, a classification which includes Over-the-Counter (OTC) Monograph (OTC drugs [safe and effective for the general public without seeking treatment from a health professional] that does not need FDA pre-approval for marketing), unapproved drugs, and homeopathic drug products (a form of alternative medicine). Its 6.7/10 cGMP score was the lowest sector score (note: "No App" is composed of the manufacturing sectors "homeopathic" and "Sterile-No App") (Center

for Drug Evaluation and Research, Office of Pharmaceutical Quality, 2019). Though it constitutes 1.4% of applications, immunological agent products accounted for 17% of product quality defects in 2018, (Figure 14 and Figure 15) (Food and Drug Administration, 2022) (Center for Drug Evaluation and Research, Office of Pharmaceutical Quality, 2018), with this trend dampening slightly in 2019. The majority of these immunological product defect volume is attributed to combination immunological products (referring to the drug prepackaged in a prefilled syringe or other administration device) that experienced device issues (Center for Drug Evaluation and Research, Office of Pharmaceutical Quality, 2019).

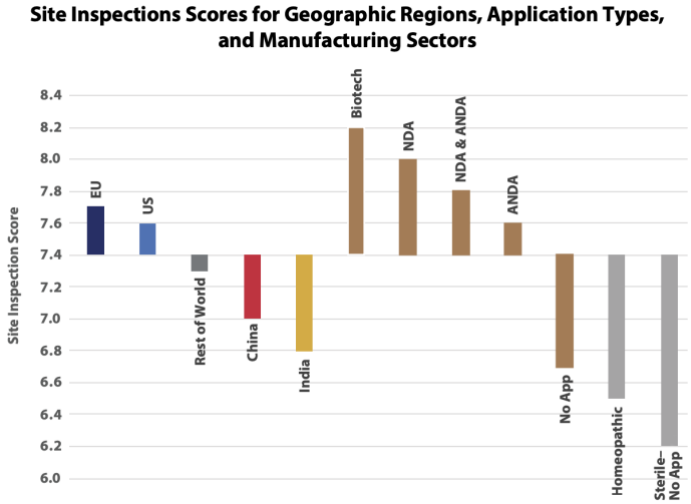


Figure 13 Site Inspections Scores for Geographic Regions, Application Types, and Manufacturing Secotrs, from FDA's OPQ

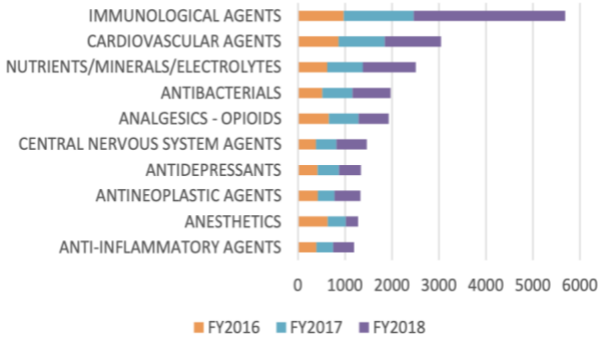


Figure 14 Product Quality Defect counts by USPTC, 2016-2018, from FDA

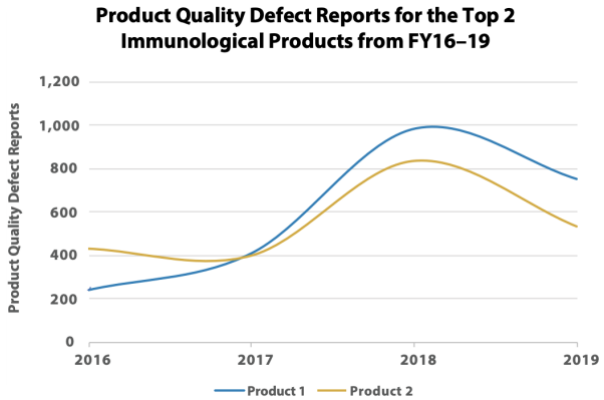


Figure 15 Product Quality Defect Reports for the Top 2 Immunological Products from FY16-19, from FDA

The Office of Pharmaceutical Quality's 2020 report discloses statistics relating to non-compliant test results grouped by drug classification (Figure 16). Non-compliant testing results indicate that test results for at least one critical quality attribute were violated or failing. The most notable change in 2020 was antibacterials due to the grassroot mobilization of hand-sanitizer production efforts that developed in response to COVID-19, ultimately leading to 6,743 new facility registrations, compared to the typical 740 new facilities seen in 2019 (Center for Drug Evaluation and Research, Office of Pharmaceutical Quality, 2019).

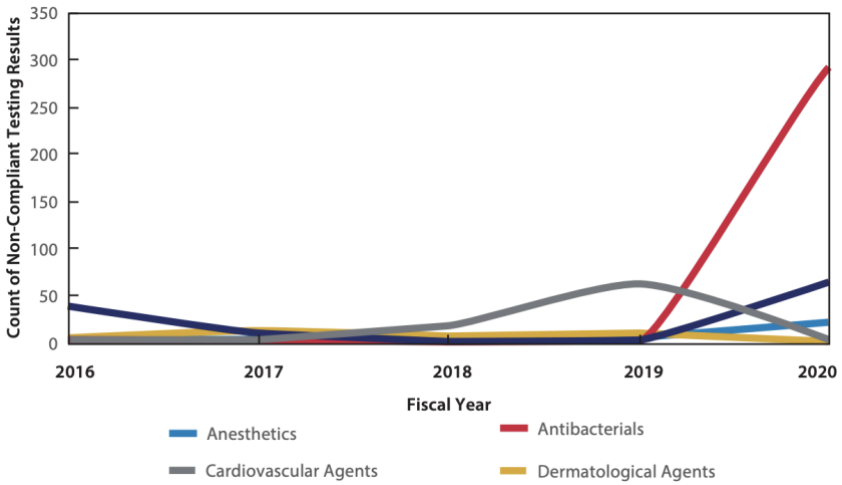


Figure 16 Non-Compliant Testing Results for Sampled Products, FY2016-2020, from FDA OPQ

Outside of cGMP and inspections, the FDA began the New Inspection Protocol Project (NIPP) oriented at sterile drug manufacturing facilities in 2018 after beginning the pilot program in 2015 (Center for Drug Evaluation and Research, Office of Pharmaceutical Quality, 2018). NIPP is aimed at semi-quantitative inspection reports, which are planned to improve the quality of inspections conducted by using more standardized electronic inspection protocols (Center for Drug Evaluation and Research, Office of Pharmaceutical Quality, 2018; Woodcock & Yu, 2015). The increased quantitative focus of NIPP parallels ongoing efforts by the FDA to "modernize the regulation of pharmaceutical manufacturing," a modernization that is being emphasized by the former long-time Director of the FDA CDER, Dr. Woodcock (Woodcock & Yu, 2015).

Corruption Policy

Corruption is often used by the public as a 'buzzword,' with the assumption that everyone understands exactly what it is, but for the purposes of research and academic discussion, this "common understanding" must be set as a reference point for discussion: corruption is a broad range of behaviors that range from intentional "personal aggrandizement," to "willful ignorance" of a coworker's corruption (Montgomery, 2021). As defined by Little et al., corruption is "distinguished by the public perception of the intentional hijacking of a benign or benevolent social entity" (a system, organization, or institution) for the benefit of a select group who pose as fair traders on behalf of the entity. It is the intentional leverage of trust or assumption of beneficence (Little, Lipworth, & Kerridge, 2018). Corruption comes in the form of individual or institutional corruption, in which individual corruption is with the intention of personal gain for individuals in an institution. Institutional corruption represents a situation in which an institution fails to orientate individual behavior to the organization's primary shared goal, potentially stemming from a superordinate system ("healthcare system"), subsystems ("pharmaceuticals"), or individual organizations ("Firm A") (Sommersgutter-Reichmann, Wild, Stepan, Reichmann, & Fried, 2018). This distinction between individual and institutional corruption is a necessary step in describing and analyzing corruption by allowing the

identification of two separate means of corruption growth and remains relevant when discussing the subsector of pharmaceuticals. However, despite these broad definitions defining and classifying corruption it remains difficult to distinguish corruption because "the point at which accountability to constituents turns into corruption is not easy to discern either in theory of practice" (Thompson, 1995), making it difficult for outside observers to identify corruption.

Corruption is present in all industries and most organizations due to how "corruptogenic" organizations are, manifested in the fact that they contain and grow latent opportunities that are easily accessible for individuals to use to one's own advantage via. the manipulation of relationships (Montgomery, 2021). The degree to which the pharmaceutical industry is characterized by corruption should be analyzed. Rawlinson notes that recent scandals have involved GlaxoSmithKline, Pfizer, and Merck and have resulted in fines for "serious lawbreaking," helping to brand the industry as "recalcitrant" in the eyes of the public (Rawlinson, 2017). One only needs to examine the massive and unparalleled corporate lobbying efforts of the pharmaceutical industry to examine scope: data from January 1, 2021 to September 30, 2021 indicates $266,845,347 spent in a 9 month period, *twice* the amount of the second largest lobbying industry (Electronics Manufacturing and Equipment $134,894,440), with 1998-2021 totals reaching $4,990,257,367, leading the second largest industry for the time period (insurance $3,210,878,114) by over $1,500,000,000 (OpenSecrets, 2021). On the background of a massive, highly influential industry, it is understandable that public trust in medical professionals has, and continues to decline (Montgomery, 2021).

We discuss three facets of corruption: information asymmetry, bribery, and lobbying. We do not discuss fraud, embezzlement or other more widespread schemes.

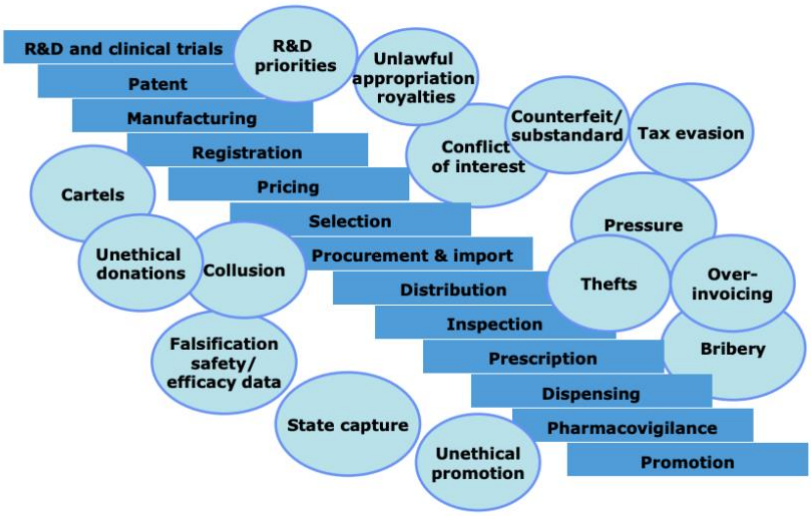


Figure 17 Unethical practices can happen throughout the medicine chain, from WHO 2010

Information Asymmetry. Information asymmetry is manifested when patients do not know what they need, allowing professionals the flexibility to self-deal and create opportunity for personal- or localized-profit (Rose-Ackerman & Tan, 2014) because end-consumers are subjected to a vulnerable or trust-based situation when receiving treatment due to their limited knowledge of the service they are being provided. The physician is expected to act on the patient's well-being while financial incentives may promote contrasting behavior, resulting in a

conflict of interest (Rodwin, 2012). However, this information is not confined to the patient-physician relationship level – in fact, here we analyze how relationship dynamics are impacted by information asymmetry at two levels: pharmaceuticals to doctors and pharmaceuticals to patients.

In recent years, greater scrutiny has been given to the relationships between physicians and the pharmaceutical industry – from pharmaceutical's marketing efforts to the funding of academic research and peer-reviewed academic journals, marketing via. education is a growing means of influencing the popularity of a product. In fact, in a study by Schwartz and Woloshin on facets of pharmaceutical marketing, marketing to medical professionals saw the greatest increase from 1997 to 2016, increasing by almost $5,000,000,000 to $20,300,000,000 (Schwartz & Woloshin, 2019). The prescription medication marketing to professionals has been largely recognized to exist in continuing medical education, which may serve to slant the information provided to medical students about the safety and effectiveness of drugs which may create a bias in education (Yager & Feinstein, 2010). Pharmaceutical firms may form relationships with physicians by the strategic use of "seeding trials[1]" to introduce a product to physicians and form a financial participatory relationship that implicitly promotes drug-specific prescription (Sommersgutter-Reichmann, Wild, Stepan, Reichmann, & Fried, 2018).

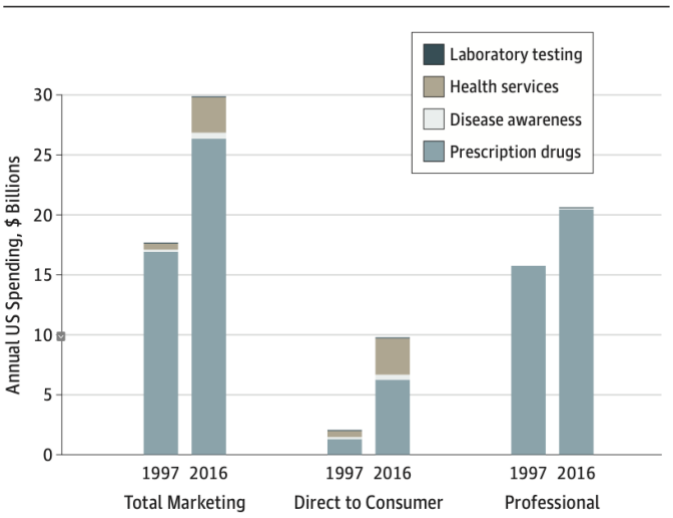
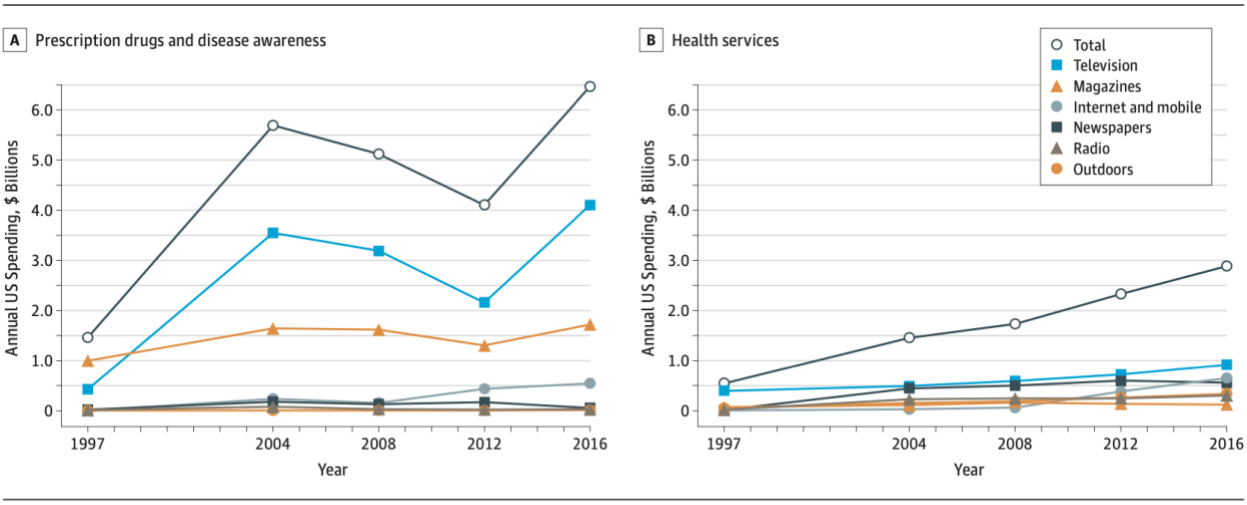


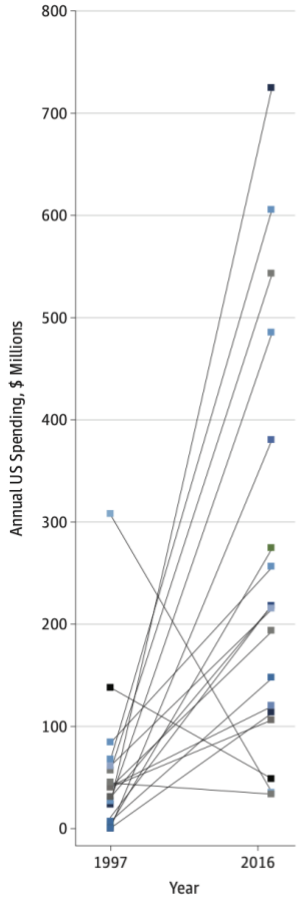
Figure 18 Medical Marketing 1997 vs 2016, from Schwartz and Woloshin

[1] "Seeding trials" refers to clinical studies or research activity that are deceptively framed as patient studies, that are actually meant to promote under-review or approved drugs (Krumholz, Egilman, & Ross, 2011).



The outdoor category includes billboards and mass transit posters and banners.

Figure 19 Direct-to-Consumer Advertising for Drugs and Health Services, from Swartz and Woloshin



Therapeutic Category	US Spending, $ Millions 1997	2016	Top Advertised Drugs 1997	2016
Diabetes/endocrine	23	725	Glucophage, Humalog, Glucotrol XL	Trulicity, Farxiga, Victoza
Dermatology	67	605	Sporanox, Lamisil, Differen	Cosentyx, Humira, Otezla
Pain/central nervous system	56	542	Imitrex	Lyrica, Tecfidera, Botox
Cardiac	0	379	Not applicable	Eliquis, Entresto, Xarelto
Arthritis	27	484	Naprelan, Lodine XL, Relafen	Xeljanz, Humir, Orencia
Cancer	3	274	Novladex, Zofran, Taxol	Opdivo, Keytruda, Ibrance
Respiratory	84	255	Accolate, Serevent, Flovent	Breo, Symbicort, Anoro, Ellipta
Immunology	11	218	Crixivan, Combivir, Norvir	Prevnar, Gardasil, Trumenba
Infection	30	217	Zithromax, Havrix, Denavir	Harvoni, Tamiflu, Neulasta
Gastrointestinal	61	215	Prilosec, Propulsid, Helidac	Humira, Xifaxan, Viberzi
Depression	40	193	Prozac, Serzone, Paxil	Pristiq, Rexulti, Trintellix
Impotence	7	147	Erecaid, Caverject	Viagra, Cialis, Erecaid
Contraception	41	119	Ortho Tri-Cyclen, Depo-Provera, Norplant	Nexplanon, Skyla, Paragard
Ophthalmology	0	113	Not applicable	Restasis, Xiidra, Ciprodex
Menopause	40	106	Prempro, Premarin, Climara	Premarin, Estring, Osphena
Cholesterol	138	48	Pravachol, Zocor	Praluent, Crestor, Repatha
Allergy	307	35	Allegra, Claritin, Zyrtec	EpiPen, Pazeo, Dymista
Osteoporosis	44	33	Fosamax, Miacalcin	Prolia, Forteo, Synvisc

Box colors vary for differentiation purposes only, to assist with viewing.

Figure 20 Direct-to-Consumer Drug Advertising by Therapeutic Category, from Schwartz and Woloshin

Additionally, the relationship between pharmaceuticals and patients has characteristics unique to both the pharmaceutical industry and to the United States. The U.S. is one of only two countries (the other being New Zealand) that permit Direct-to-Consumer marketing of drugs and other health products (Shmerling, 2019) - a practice that aims to directly market to the end consumer in order to positively influence the sales of drugs (which has faced criticism but persists due to corporate First Amendment rights arguments). This includes TV commercials, magazine ads, internet ads, newspaper ads, and other forms of advertising (Figure 19 and Figure 20). Though receiving some federal-level regulation to limits this, it is listed under corruption because it is an intentional use of information asymmetry that typically shares low quality information using testimonials to qualify information rather than quantify it, resulting in higher patient expenditure and high quantity of requests for brand-specific medication (Schwartz & Woloshin, 2019).

Bribery. Bribery, frequently manifested in pharmaceuticals as informal payments and kickback payments (defined by 42 U.S.C.§1320a-7b(b) as the knowing and willing payment of remuneration to induce or reward patient referrals or the generation of business), is defined as a financial or other advantage that is offered, given, solicited, or accepted in exchange for privileges or treatments. This is highly likely on an individual scale, but possible on an institutional scale (Sommersgutter-Reichmann, Wild, Stepan, Reichmann, & Fried, 2018). Drug procurement is identified by Sommersguter-Reichmann et al. as being an area of particular trouble, in which bribes and kickbacks are used to convince public officials to award contracts or act with favoritism towards the firm – found to be a significant causative factor for global inequalities in access to pharmaceuticals (Sommersgutter-Reichmann, Wild, Stepan, Reichmann, & Fried, 2018; Fidler & Msisha, 2008). The Centers for Disease Control and Prevention (CDC) was revealed to have accepted regular Congress-approved donations that lead to recommending tests and drugs while still overseeing controversial studies of the tests and drugs (Rawlinson, 2017). However, bribery and other forms of corruption are, of course, not simply limited to those activities which are illegal. With this mindset, Skyler posits that the role of Pharmacy Benefit Managers (PBMs), a middleman in the pharmaceutical supply chain wholly unique to the U.S., is a corrupt practice because PBMs "add no value to the product" while greatly profiting by "forcing manufacturers to pay [PBMs] rebates for formulary access and position." His argument holds that if this rebate system occurred outside of the U.S. border, it would violate the Foreign Corrupt Practices Act's restrictions on bribery and kickbacks (Skyler, 2020).

Lobbying. A complex topic in American politics, lobbying must be examined with a nuanced view and an understanding of how it is used for the betterment of Americans while simultaneously understanding how these powerful lobbies may abuse power and the trust placed in them. Transparency International defines lobbying as "any activity carried out to influence a government or institution's policies and decisions in favor of a specific outcome…these acts can become distortive if disproportionate levels of influence exist," a definition which aptly describes the nuance between beneficial and harmful lobbying as being beneficial when transparent and done with integrity, but causing problems to arise when "non-transparent and unregulated" (Transparency International, 2022). This leads to the diminishment of negative effects of drugs, reduced emphasis on patient safety, and the approval of drugs with little clinical benefit (Sommersgutter-Reichmann, Wild, Stepan, Reichmann, & Fried, 2018). Lobbying data from January 1, 2021 to September 30, 2021 indicates $266,845,347 spent in 9 months - *twice* the amount of the second largest lobbying industry (Electronics Manufacturing and Equipment at $134,894,440), with 1998-2021 totals reaching $4,990,257,367, leading the second largest

industry for the time period (Insurance at $3,210,878,114) by over $1,500,000,000 (OpenSecrets, 2021). The largest contributor was Pharmaceutical Research and Manufacturers of America (PhRMA), a pharmaceutical trade group lobby which spent $422,300,000 from 1999 to 2018 (Figure 21 and Figure 22) (note Figure 22 is exclusively for campaign expenditure).

Rank	Organization[b]	Expenditures, $ in millions
Lobbying spenders		
1	Pharmaceutical Research and Manufacturers of America	422.3
2	Pfizer	219.2
3	Amgen	192.7
4	Eli Lilly and Company	166.2
5	Biotechnology Innovation Organization (BIO)[c]	153.4
6	Merck	143.0
7	Roche Holdings[c]	135.9
8	Novartis	130.2
9	Johnson & Johnson	129.9
10	Sanofi[c]	116.7
11	Bayer	111.0
12	GlaxoSmithKline	110.8
13	Bristol-Myers Squibb	101.6
14	Abbott Laboratories	96.6
15	Advanced Medical Technology Association	79.4
16	Seniors Coalition	65.3
17	Medtronic	63.8
18	Baxter International	58.4
19	AstraZeneca	54.6
20	Teva Pharmaceutical Industries	53.3
Total		2604.3
Campaign contributors[d]		
1	Pfizer	23.2
2	Amgen	14.7
3	Eli Lilly and Company	13.3
4	GlaxoSmithKline	12.6
5	SlimFast Foods	11.3
6	Johnson & Johnson	11.2
7	D.E. Shaw Research	11.0
8	Merck	10.6
9	Abbott Laboratories	10.0
10	Bristol-Myers Squibb	7.7
11	Exoxemis	6.9
12	McKesson	6.8
13	Ischemix	5.7
14	Pharmaceutical Research and Manufacturers of America	5.6
15	AstraZeneca	5.4
16	Pharmaceutical Product Development	5.2
17	Schering-Plough	5.1
18	AmerisourceBergen	4.9
19	Sanofi[c]	4.3
20	Novartis	4.0
Total		179.5

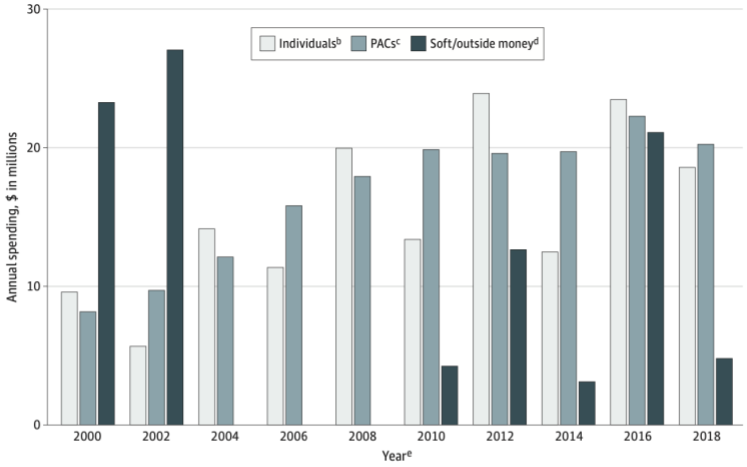
[a] Data from the Center for Responsive Politics.[23] Amounts were inflation adjusted to 2018 dollars using the US Consumer Price Index.

[b] Expenditures by subsidiary organizations were attributed to the parent organizations. Amounts included contributions from organizations' political action committees and from individuals. Companies that merged or were acquired were treated as separate entities prior to the transaction.

[c] BIO changed its name from Biotechnology Industry Organization to Biotechnology Innovation Organization in 2016; the figure for BIO included expenditures under both names. The figure for Roche Holdings included expenditures by Roche Group. Sanofi changed its name from Sanofi-Aventis to Sanofi in 2011; the figures for Sanofi included expenditures under both names.

[d] Amounts included contributions to candidates, party committees, and outside spending groups. These figures included contributions from organizations' political action committees and from individual members, employees, or owners of companies or organizations in an industry or from their immediate family members.

Figure 21 Top 20 Lobbying Spenders and Campaign Contributors in the Pharmaceutical and Health Product Industry at the Federal Level, 1999-2018(a), from Wouters



PAC indicates political action committee.

[a] Data from the Center for Responsive Politics.[23] Amounts were inflation adjusted to 2018 dollars using the US Consumer Price Index.

[b] Contributions from individual members, employees, or owners of companies or organizations in an industry or from their immediate family members; there are limits on individual contributions to candidates and national party committees during elections.

[c] PACs pool campaign contributions from members of corporations, labor unions, and ideological groups and disburse the funds to political candidates and national party committees; there are limits on PAC contributions to candidates and national party committees during elections.

[d] Soft money contributions (banned as of November 6, 2002) and donations to outside spending groups and Levin funds. Outside spending groups, which include so-called super PACs, operate independently of and not in coordination with candidates' committees; spending by outside groups is largely unregulated and unlimited.

[e] Each year corresponds to a 2-year election cycle; eg, 2000 refers to January 1, 1999, through December 31, 2000. Presidential elections occurred in 2000, 2004, 2008, 2012, and 2016.

Figure 22 Campaign Contributions by the Pharmaceutical and Health Product Industry to Federal Elections by Source, 1999-2018(a), from by Wouters

Despite the challenges posed by forms of corruption, the U.S. government has taken steps to reduce or eliminate certain opportunities for corruption to grow. One significant resolution is the Anti-Kickback Statute and Stark Law, which are aimed at reducing individual corruption in the larger health sector. The Stark Law penalizes the referral of patients for specific health services when paying fees to Medicare or Medicaid if the physician or a family member has a financial relationship with the specific health service provider (Sommersgutter-Reichmann, Wild, Stepan, Reichmann, & Fried, 2018). The Anti-Kickback Statute (42 U.S.C.§1320a-7b(b)) prohibits the payment of renumeration to induce/reward patient referrals involving items or services that are paid by Federal healthcare programs (Medicare or Medicaid) (U.S. Department of Health and Human Services, 2022). These two laws aim to reduce the potential for corruption in the pharmaceutical/physician relationship. The FDA's Division of Drug Marketing, Advertising, and Communications (DDCMAC) overseas direct-to-consumer pharmaceutical advertising and prescription drug labeling to ensures that ads are not false or misleading, present a balance between the benefits and risk, include relevant facts and a brief summary enumerating potential risks, though the FDA loosened this requirement in 1983, 1999 and 2004 which allowed the use of a "simplified brief summary" (presentation of major risks) of negative effects rather than the longer "brief summary" (Ventola, 2011).

By nature of pharmaceutical firms being for-profit corporations in a competitive environment, it is expected that all available resources will be mobilized to gain profit and capture market space. Though firms should not be absolved of blame for corrupt practices and failure to adhere to both voluntary and self-imposed ethical guidelines during the pursuit of profit (David-Barrett, Yakis-Douglas, Moss-Cowan, & Nguyen, 2017), "wagging fingers at companies," as Vogel emphasizes, "for taking the fullest advantage of flawed regulation and lax

enforcement is missing the point…it's up to governments to make sure crime doesn't pay" (Vogel, 2017). Government policy plays a vital role in the pharmaceutical industry, and thus has the ability to better control corrupt practices either directly through regulation or through the influence the government holds in its role as a buyer (Rodwin, 2012). Governmental strategies for pharmaceutical corruption mitigation must be the practice of realigning competitive and institutional motivators to ensure fair industry competition and continually protect the health and the autonomy of the final consumer.

Strategic Approach

When it comes to government strategic policy impacting the pharmaceutical industry, the government of the United States of America is in a policy flux between traditional policy style that has been implemented since the 1980s, and a new era of policy that has potential to alter the way government is willing to interact with industry. U.S.-based policy seems to have been implemented with a directed approach (when it comes to strategically guiding pharmaceuticals) in the later part of the 20th century, seen through the passage of law such as the Orphan Drug Act of 1983 which aimed to increase the R&D attention of pharmaceutical firms on rare illnesses (under 200,000 Americans) by offering tax credit for 50% of development costs, greater market exclusivity, and fast tracked approval; and the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Act) which significantly strengthened the generics drug manufacturing (among other policy that are oriented towards safety regulation and bureaucratic structuring; Nutrition Labeling and Education Act, Safe Medical Devices Act, FDA Modernization Act, etc.). The 21st Century Cures Act both increased interoperability of health information while, notably, reducing red tape for biomedical research by eliminating the Paperwork Reduction Act and removing restrictions on scientific meetings. Only very recently has the U.S. implemented a more hands on approach to strategic industrial policy, largely in reaction to perceived instability in global supply chains – yielding policies like Executive Order 14017 and the Build Back Better World (B3W) foreign policy. We discuss three notable policies below:

Healthy People 2030. The **"**Healthy People" policy series was started in 1979 with *Healthy People: The Surgeon General's Report on Health Promotion and Disease Prevention*, which emphasized the use of preventative strategies to improve the health of the American people (McGinnis, 2021). This original policy addressed laws and regulation pertaining to wearing seatbelts and other automotive safety laws, labeling food with consumer information, etc. (Teitelbaum, et al., 2021). In the four decades since, Healthy People 2000, Healthy People 2010, Healthy People 2020, and Healthy People 2030 have all advanced preventative public health measures. The most recent iteration, Healthy People 2030 contains 355 10-year objectives with law/policy objectives addressing environmental health, oral health, and tobacco use, and nonlaw/policy objectives addressing 39 other subject areas (U.S. Department of Health and Human Services, 2022). As Teitelbaum et al. points out, legal means will be taken to maintain vaccination rates, and increase the number of citizens able to access medical care (Teitelbaum, et al., 2021). The preventative nature of Healthy People may have mixed impact on the pharmaceutical industry – preventative public health action has the potential to reduce the number of Americans needing reactionary drug-based medical treatments, thereby negatively

impacting the industry in the medium- and long-term; however, the policy also aims to simultaneously create greater access to health treatment which would have a net benefit to the industry. Though the impact to the pharmaceutical industry may be mixed, Healthy People will continue to have an impact.

Building Resilient Supply Chains, Revitalizing American Manufacturing, and Fostering Broad-Based Growth, E.O. 14017. Though not law nor regulation, Executive Order (E.O.) 14017 has significant impact to the global and domestic pharmaceutical industry by signaling governmental concerns over the extent of foreign outsourcing of pharmaceutical activities and the effect this may have on domestic availability of critical medicines if a crisis event were to occur. Pharmaceuticals and APIs is one of four areas for which E.O. 14017 calls for a "whole-of-government approach to assessing vulnerabilities in, and strengthening the resilience of, critical supply chains" (United States White House, 2021). Recommendations for action promoted by the E.O. include (but are not limited to): increasing domestic production by mobilizing existing financial infrastructure, increasing R&D capacity by expediting regulatory testing/review, expanding production on-demand technologies, improve domestic quality transparency via. a new rating system to encourage private sector investment in quality, developing a greater information collection system to better understand the drug supply chain, and improve government stockpiling of API and critical drugs (United States White House, 2021). Though the regulatory impact of this E.O. is limited, it signals a broader shift in government attention. In response to E.O. 14017, the seemingly bipartisan *Building Resilient Supply Chains Act* (H.R. 5495) has entered the House of Representatives, which highlights "biotechnology, medical technology, genomics, and synthetic biology" as a key focus (117th Congress, 2021). Granted the ability to become law, this Act will put weight behind the recommendations of E.O. 14017 and will have a significant impact on the U.S. pharmaceutical industry.

Build Back Better World Initiative. The Build Back Better World (B3W) initiative was launched at the 2021 G7 Summit (consisting of Canada, France, Germany, Italy, Japan, the United Kingdom, and the United States) as a response to China's massive infrastructure policy, the Belt and Road Initiative. The Middle East Institute argues that it is "not necessarily aimed at countering China's Belt and Road Initiative" (Chaziza, 2021), though the current government's rhetoric seems to suggest U.S.-China competition is in fact a significant factor (Biden to a Joint Session of Congress, April 28, 2021: "We're in competition with China and other countries to win the twenty-first century" (United States, Office of the Press Secretary, 2021)). The B3W aims to mobilize democracies to "provide support to developing countries' infrastructure-building efforts to help narrow the $40+ trillion infrastructure need in the developing world," with "health and health security" as a major cornerstone (United States, Office of the Press Secretary, 2021; Zhao M. , 2021). Though the details, implementation methods, and results are yet inconclusive, this broad infrastructure and development initiative places health in a prioritized position, meaning that U.S. and global pharmaceuticals may find opportunity to work in cooperation with government initiatives, in a way similar to that seen through the Belt and Road Initiative's use of the private sector. It should be noted that international development should not be a zero-sum game – a perspective maintained by European countries and Japan (Zhao M. , 2021).

Market and Competitive Environment

Market Size and Growth

Entrenched in a long history as a major player in the creation of the modern pharmaceutical industry, the United States enjoys a flourishing economic environment for the pharmaceutical industry. Characterized as the current largest single pharmaceutical market (a demand that far exceeds population size), as having near no regulation for prices of goods sold to the average consumer, the market is predictably large. However, market growth in this mature sector has slowed significantly.

In an analysis by Fitch Solutions, the U.S. pharmaceutical industry was valued at 369 bn USD in 2019, with projections putting the value at 420.299 bn USD by the end of 2024, yielding a compound annual growth rate of 2.6%, calculated in USD terms. The current pharmaceutical spending as a percentage of GDP is 1.72%, which is compared to a global average of 1.5% and 1.05% in China (2019), meaning that although the U.S. market's spending is predicted to reduce by 5 points to 1.67% by 2029, above average spending is expected to persist (Fitch Solutions, 2020; Fitch Solutions, 2020).

As for segments constituting the pharmaceutical industry, Fitch Solutions values the patent drug market as being 279.91 bn USD in 2019 with projections of growth to 325.682 bn USD by 2024. The generic drug market reached a value of 68.18 bn USD in 2019 and is predicted to reach a value of 71.751 bn by 2024. The over-the-counter (OTC) drug market segment is valued at 20.91 bn in 2019 and is predicted to reach 22.866 by 2024 (Figure 23) (Fitch Solutions, 2020).

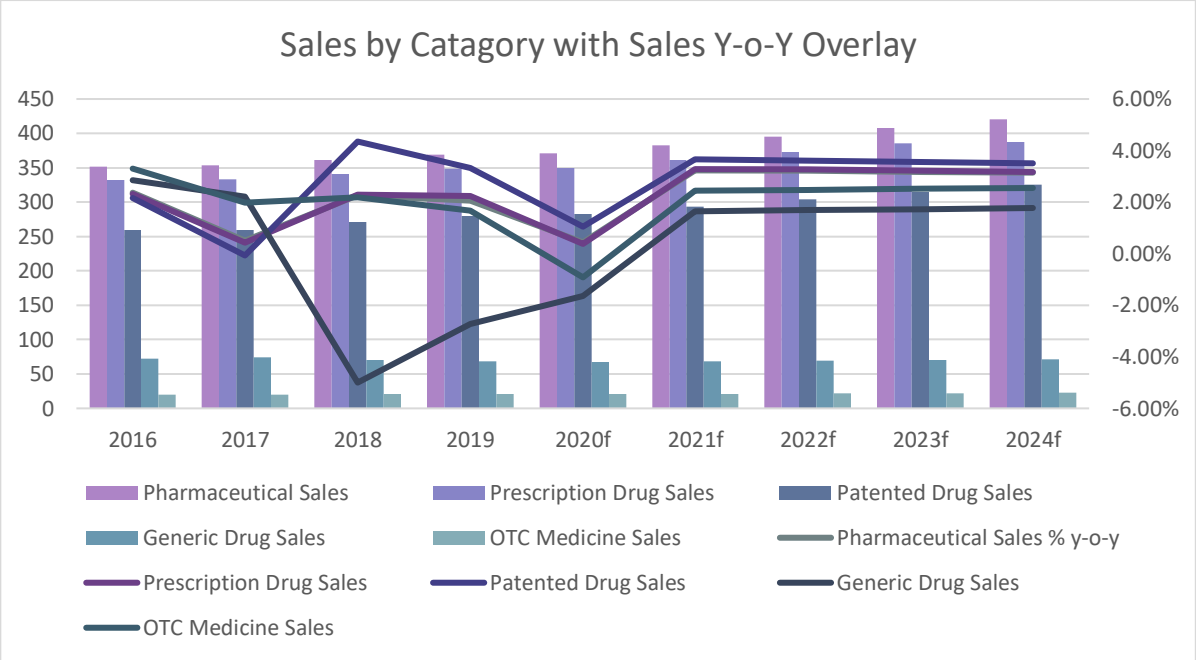


Figure 23 Pharmaceutical segmental sales by category and annual growth rate, data from FitchSolutions

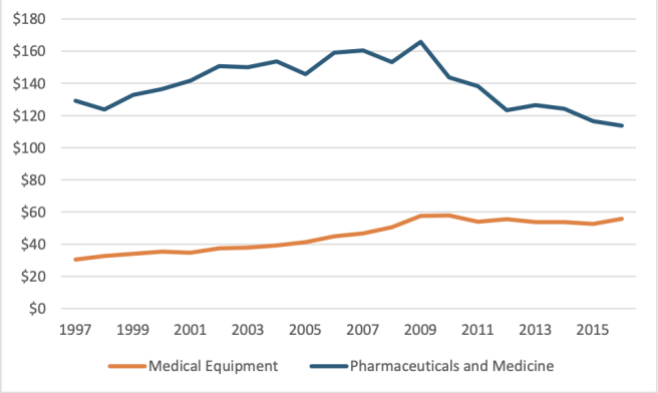


Figure 24 Real Value Added in Pharmaceuticals and Medical Equipment Manufacturing (Billions of 2012 Dollars), from Information Technology and Innovation Foundation

Market Organization and Composition

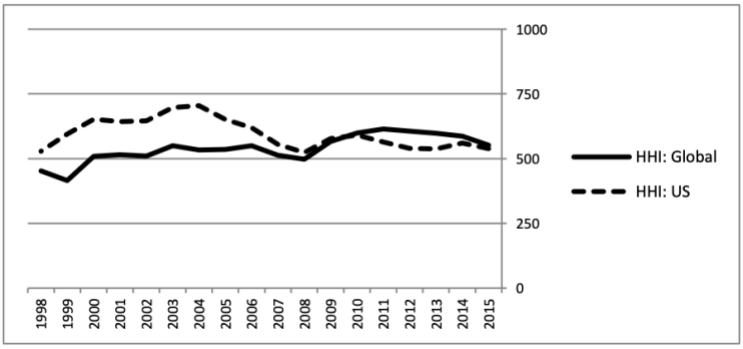
Market Organization. The United States is an "old guard" of the pharmaceutical industry, with healthy competition dating back to the mid-1900s, when the industry truly began to take root and enter the "Golden Age" of pharmaceuticals. This continuity of industry gives it a distinct advantage when compared to countries with emerging pharmaceutical industries ("pharmerging" countries), such as China, or industrialized countries that do not benefit from the same historical connection with pharmaceuticals.

Perhaps one of the most distributed sectors in the American pharmaceuticals industry is the generic pharmaceutical manufacturing sector (in part due to the low profit margins incurred by manufacturing off-patent drugs), which had 448 firms in 2021 according to IBISWorld (IBISWorld, 2021), largely remaining steady since 2016, with the top 4 companies constituting 22.3% of the total industry revenue (Kennedy K. , 2021). Interestingly, the brand name segment had 1,982 firms in the U.S., an increase of 7.4% as compared to 2016 (IBISWorld, 2021), with the largest four firms accounting for 50% of the total industry revenue, indicating the U.S. brand name segment has a moderate to high level of market concentration. Overall, the United States' pharmaceutical industry was measured by Barbieri to be 74.07% in 2011, found by comparing the annual cumulative revenues of the top ten listed American companies to the total revenue of all listed companies (Barbieri, Huang, Pi, & Tassinari, 2017); the industry was also found to have a CR4 of 33.5%, CR8 of 49.6%, and CR20 of 71.8% in 2002 according to Zhang and Ni (张晓燕 & 倪春霞, 2017), proving to have a far greater market concentration than China or Japan during Zhang and Ni's study period (CR5 8.82 and CR5 25.1%, respectively), which as of 2002 did not yet classify the American industry as an oligopoly (CR5 = 60%). Segment variation exists in the market, with IBISWorld stating that 72% of brand name pharmaceutical manufacturing market share was occupied by "major players," with "some major players" including Pfizer Inc, Wyeth, Merck & Co. Inc., Schering-Plought, AbbVie Inc. and Allergan - characterizing the industry's level of consolidation as being "extreme." This concentration ratio is also expected to increase by 2026 due to small-scale brand name manufacturers being crowded out by competition (see Figure 26) (IBISWorld, 2021). This data shows that, though the U.S. pharmaceutical industry is typically perceived as being a static entity, it has in fact undergone

large reorganization and consolidation over the past few decades that have enabled significant strengthening in market concentration. The impact of the degree of industry concentration is currently in debate, in part due to the use of census data for market concentration measures (OECD Competition Division, 2018); however, a recent OECD discussion suggests that, though not the only cause at play, this increased market concentration may be leading to a reduction in competition, partially reflected through an increase in average profitability and mark-ups (OECD, 2019). If this association between concentration and decreased competition is indeed valid, it has negative implications for the consumer's ability to access medicine, as well as the firm's willingness to efficiently conduct R&D.

The generic manufacturing segment predictably functions in a decentralized environment due to lower entry barriers and higher cost pressure, yielding concentration of the top four generic companies accounting for only 22.3% of total industry revenue (IBISWorld, 2021) (see Figure 27).

Figure 25 Pharmaceutical Industry Concentration, Measured by HHI, 1998-2015, from Richman et al.



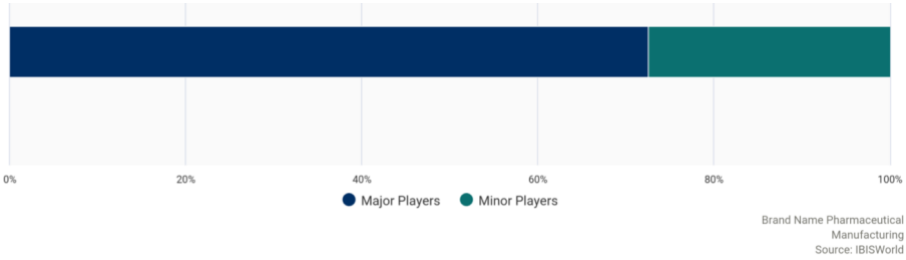


Figure 26 Brand Name US Pharmaceutical Manufacturing Market Share Concentration, from Kennedy, K.

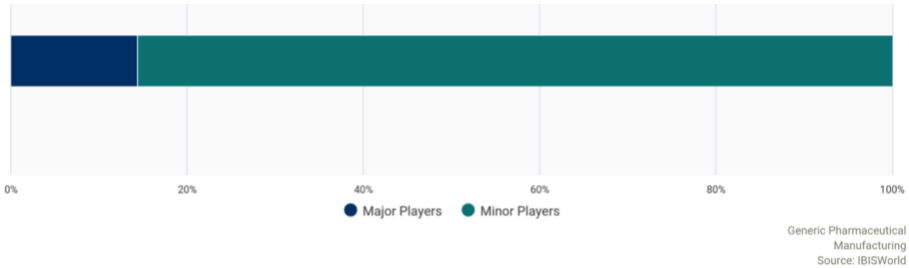


Figure 27 US Generic Pharmaceutical Manufacturing Market Share Concentration, from Kennedy, K.

Market Reorganization. The U.S. pharmaceutical industry, often used to represent the wider pharmaceutical industry, is a space which traditionally experiences a greater number of mergers and acquisitions than other industries (Congressional Budget Office, 2021). As we will see, M&A is a major driver in the Chinese industry as highly homogeneous firms attempt to consolidate into larger firms, yielding a "national champion" (Barbieri, Huang, Pi, & Tassinari, 2017). Though China is experiencing significant M&A activity within the context of the pharmaceutical industry, the U.S. pharmaceutical industry has begun to experience notable rates of M&As particularly in the biotechnology sector during the past 20-30 years, termed by some to be the "biological revolution." In the 1990s, six of the Big Pharma firms (Johnson & Johnson, Merck, Eli Lilly, Roche, Novartis, and GSK) were early investors in biotechnologies, largely via. M&As and alliances, with other large firms joining in the investment trend in the late 1990s. Despite this investment trend, the pattern of results for those investing in biologics began materializing in the 2010s, with early movers clearly outperforming their later counterparts (Figure 28 and Figure 29).

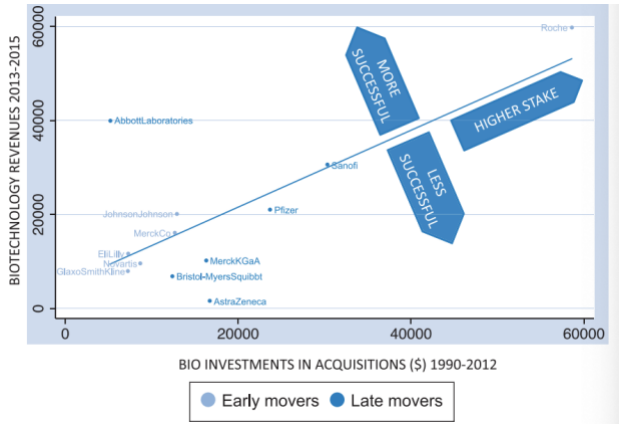


Figure 28 Biotech Revenues (2013-2015) versus biotech acquisitions (1990-2012), from Birkinshaw et al.

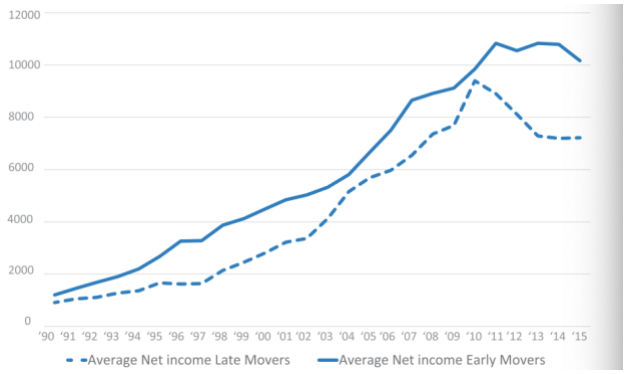


Figure 29 Net income over time - early movers versus late movers, from Birkinshaw et al.

IBISWorld Analysis laments biotechnology and bioinformatics as a gradual, yet fundamentally altering change currently experienced by the global pharmaceutical industry, with an especially large impact on the R&D process by allowing firms to cut costs by closing research facilities and outsourcing functions or research to biotechnology firms who have been acquired or closely partnered firms (joint ventures, licensing agreements, etc.) (Koronios, 2021). The aim of this is to be able to reduce the cost of highly innovative R&D by shifting away from the traditional form of in-house volume-based chemical development which hopes to identify the "next drug" (e.g. "blockbuster model"), to a more risk-sharing model characterized by the creation and strengthening of a supply-web for knowledge networks. In other words, greater decentralization of the highly innovative processes involved in new drug conceptualization, design, and implementation, allowing for greater collaboration and reduced risk experienced by all firms (ex. biotech firms since Genentech's initiation in 1979 generally lack vertical integration capabilities allowing the full marketization of highly innovative methods, thus are able to benefit from a biotech/pharmaceutical relationship by utilizing pharmaceutical's commercialization capabilities). Biotechnology has progressed by leaps and bounds in the U.S.,

but this has largely been unable to be replicated in other settings – two factors are theorized for this: scale of research depending on the American university system and skilled labor market, and uniquely beneficial financial institutions which have all contributed to American superiority in the life sciences (Malerba & Orsenigo, 2015).

It should be pointed out that although many herald the biotechnology revolution in pharmaceuticals as a boon to the innovative capabilities of the industry, some believe the biotechnology sector may drag down pharmaceutical's productivity: "decline in productivity could be the outcome of an intrinsic difficulty in discovering new drugs for increasingly complex pathogens," suggesting that biotech has not increased innovation productivity (Hopkins, Martin, Nightingale, Kraft, & Mahdi, 2007) due to more deep rooted productivity issues.

Outside of this continual incorporation or biotechnology, the U.S. industry seems to maintain an expected, if increasing, rate of market reorganization through the use of M&A.

Pricing

The traditional pharmaceutical supply chain does not transfer the flow of money through the same supply chain as the final goods. In fact, due to the interplay between the manufacturer (branded or generic), the wholesaler, the pharmacy, the pharmacy benefit manager (PBM), the insurer and the final consumer, the pricing system is quite complex, with aspects of pricing agreements being fully confidential from the public. This largely decentralized pharmaceutical pricing system stands in contrast to most other countries who use reference pricing or other forms of government price control by allowing the free market to determine the price paid by the consumer and the insurer – hence we revisit the subject of drug pricing from a market perspective rather than a government regulation perspective in an attempt to understand how the above-mentioned players contribute to the cost borne by consumers and insurers. We focus on the three notable players: branded drug manufacturers, generic drug manufacturers, and pharmaceutical benefit managers (as wholesalers retain little profit and are a passive market player (Lakdawalla, 2018); and insurers are downstream to PBMs and reliant on PBMs for administrative service, formularies, etc. (Kouvelis, Xiao, & Yang, 2015) and fall outside the scope of this research).

Branded Drug Manufacturers. Given the market exclusivity period granted to branded drugs, the innovator entity is able to price the medicine to the general public at any price that the firm deems the market will bear (as mentioned, selling to government via. Medicare or Medicaid reduces ability to freely price due to buyer power, but here we discuss the non-publicly insured consumer). These prices, manufacturer "list prices," are freely set and have been increasing at a rate of roughly 9.1% per year from 2007 to 2018 - although Rome et al.'s study notably identified an average of a 16.7% increase in list price of 79 drugs between 2015 and 2016, with the drug with the smallest change being +13.6% when weighted by usage (Rome, Feldman, Desai, & Kesselheim, 2021). However, the list price is not the final amount paid – PBMs negotiate a highly confidential rebate deal with the branded drug manufacturer yielding the net price of the drug. Interestingly this net price has remained relatively steady *when compared to the list price change* at an average increase of 5.4% per year between 2015 and 2017 (Rome, Feldman, Desai, & Kesselheim, 2021). This shows that, though branded drug manufacturers are steadily increasing their prices, the *value* of the drugs have lagged behind, with nearly 2/3rds of the change in list price being absorbed by the PBM. At the consumer level, higher insurance deductibles are predictably associated with higher out-of-pocket payment prices, while lower

deductibles have lower out-of-pocket payment prices (Rome, Feldman, Desai, & Kesselheim, 2021). We therefore see that branded drug manufacturers are not directed by any government regulation to limit prices to the average non-government insured consumer but are impacted by confidential rebate negotiations in relation to PBMs.

Once the patent exclusivity period comes to an end, a shift in branded drug manufacturer pricing behavior is noted. Before generic drug manufacturers enter the market, anticompetitive behavior outside of secondary patenting/evergreening by the innovator begins with an intent to delay generic competition's market entrance. One such practice is the use of "pay-for-delay" settlements, in which the brand name drug manufacturer's claim to the patent is untouched and the generic drug manufacturer delays market entry in exchange for monetary compensation (Gupta, Shah, & Ross, 2019). The strategy allows the branded drug manufacturer to lengthen the amount of time for which it holds market exclusivity. Yet another strategy impacting the pricing of drugs is an "authorized generic," or a generic drug released by the branded drug manufacturer to compete with generic drug manufacturers – in this way the branded drug manufacturer may make profit from the brand loyal customer segment while increasing competitive pressure in the generic market to prevent non brand-associated drugs from entering the market (Gupta, Shah, & Ross, 2019). Both of these practices reduce the substitutability of the branded drug by reducing the amount of competition.

Finally, once generic drug manufacturers are successful in penetrating the market, branded drug manufacturers again alter pricing behavior in accordance with the theory of market segmentation to maximize profitability and fully utilize consumer segment loyalty.

Once generic drugs successfully enter the market and market exclusivity is lost, it is to the branded drug's benefit to increase prices in order to take advantage of brand-loyal segment's price insensitivity. Regan found that branded drugs maintain or even increase prices after generic entry, with each generic entrant being associated with a 1% increase in the price of the branded drug, though other research has indicated that price increases per generic entrant could be as high as 2.4% to 5.5%, depending on the assumption of exogenous generic entry (Frank & Salkever, 1997) (the variance between Regan and Falkner and Salkever could also be explained by the 10 year difference between the two publish dates, indicating that branded drug manufacturers have tempered their post-generic entrant price increases).

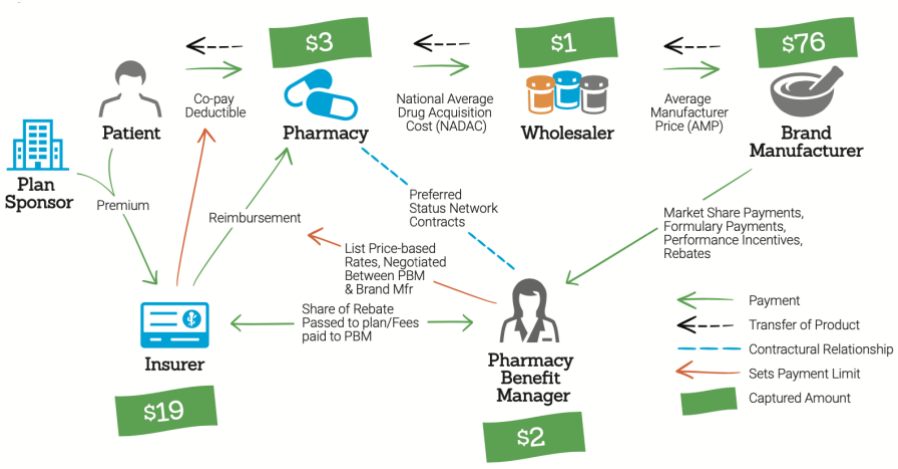


Figure 30 Spread of $100 Across Various Channels in the Branded Drug Supply Chain, from AAM

Generic Drug Manufacturers. In the generic drug market, the generic drug manufacturer's revenues play a far reduced role in the final cost of the drug, accounting for only 36% of the final drug cost compared to 76% for the branded drug manufacturers (Association for Accessible Medicine). This is due to a highly populated, homogenous market consisting of price sensitive, nonloyal consumers. This market's high supplier population results in weakened firm position in negotiations with wholesalers, pharmacies, and PBMs. As additional generic market entrants arrive, this weakened position is reflected in the generic-to-brand price ratio. Data shows that once a single generic drug manufacturer enters the market, it sells at a price that is about 60% of the branded drug. Once 10 generic manufacturers join the market drugs are sold at nearly 1% of the original brand price (Figure 32). Though the Association for Affordable Medicine proposes price volatility in the generic drug market "tends to be downward" due to high competition in pricing pressure (Association for Accessible Medicine), generic drug prices are actually increasing in the long-term. In a price analysis of topical generic drug prices between 2005 and 2016, wholesale prices increased from $0.85/unit in 2005 to $3.17/unit in 2016, yielding a 273% price increase, while some generic medicine (ex. nystatin-triamcinolone acetonide cream) increased by 2,529% (Bhatt, Bhatt, Dorrian, & McLellan, 2019). This is perhaps due to decreasing competition in the generic sector caused by increasing concentration (a result of the steady rate of generic M&As) (Gupta, Shah, & Ross, 2019). In summation, it appears that generic competition does indeed have a positive impact to consumer-price with pharmacies, wholesalers, and PBMs having increased leverage to raise their share of the supply chain profit in comparison with the manufacturer; yet generic prices are still increasing at a significant rate.

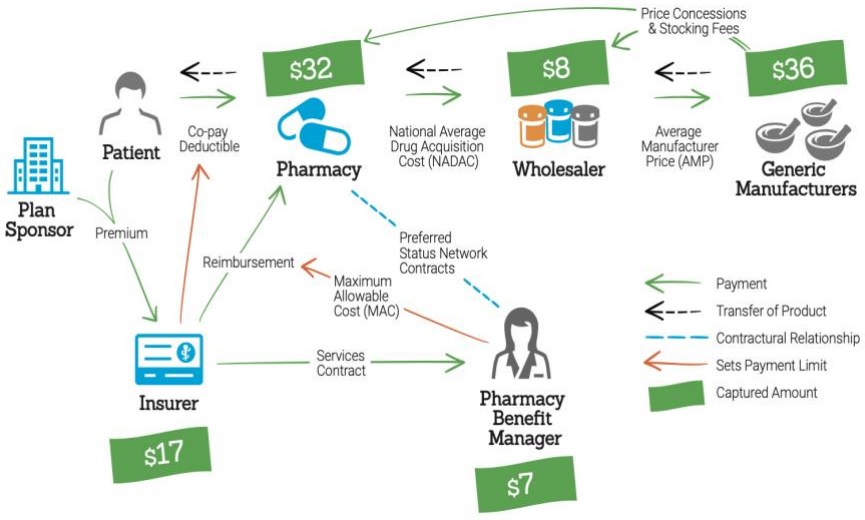


Figure 31 Spread of $100 Across Various Channels in the Generic Drug Supply Chain, from AAM

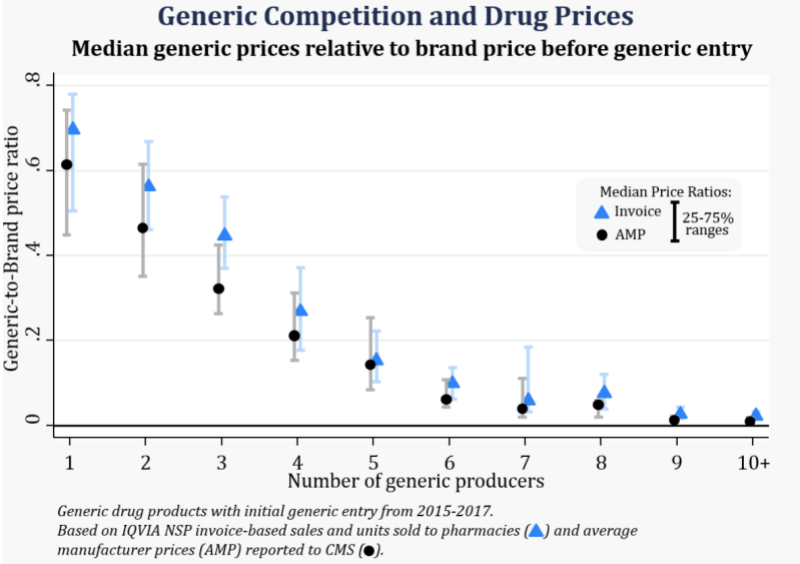


Figure 32 Generic Competition and Drug Prices, from Conrad and Lutter (FDA)

Pharmacy Benefit Managers (PBMs). PBMs are a relatively new entity, springing up in the 1960s to their current central position in the financing of pharmaceuticals. Their original intention was to help insurers better manage the cost of creating and administering insurance benefits, and thus play an intermediary role between insurers, pharmacies, and manufacturers (see Figure 33 for the drug supply chain with an emphasis on the financing activity of PBMs). Their value is threefold: they provide administrative services, processing, and claim payment; they are large purchasing organizations that leverage size in private price negotiations with manufacturers and pharmacies; and they design insurance formularies that organizes drugs to levels of varying copayment size – in essence they have an indisputably large contribution to the determination of drug prices paid by the patient (Kouvelis, Xiao, & Yang, 2015). They perform a balancing act between ensuring patients have access to innovative new drug therapies while keeping insurance spending from growing too quickly by using five key tools:

> *(1) Higher cost sharing tiers, shifting more of the cost from the insurance company to the patient (2) step therapy, creating the requirement that patients try drug x and show it to be insufficient before being eligible for drug y; (3) prior authorization, which essentially creates administrative red tape as a way of discouraging physicians from prescribing more expensive drugs (4) indication restriction, which sets narrow limits on which patient can receive which drug; and (5) completely excluding drugs from the formulary, particularly expensive new drugs (Schulman & Dabora, 2018).*

Despite not bearing financial risk, their intermediary role in price negotiations and formulary negotiations positions them favorably. The opaqueness of PBM practices and the low understanding of the role PBMs play in the market has created various claims of PBM-nonimpact, price gouging, and artificial price increase. For one, by setting formularies on behalf of insurers, these PBMs can influence manufactures to increase the list price of drugs in response to anticipated aggressive price concessions in the rebate negotiations (Schulman & Dabora, 2018) – in some cases manufactures have "tried to provide low prices and were faced with a situation that if they did not raise the cost of the drug, therefore giving a larger rebate to the PBMs, they did not appear on the formulary" (Patel, Bhatia, & Kaufmann, 2020). PBMs have also been accused of copay clawbacks because when the negotiated price is less than the copay, the difference is passed to the PBM, i.e. if a pharmacy acquires medication for $1.50 (that would normally self for $2.50), it must sell for $11.00 to maintain a $2.00 profit after the PBM removes its $9.00 clawback (Patel, Bhatia, & Kaufmann, 2020; Van Nuys, Joyce, Ribero, & Goldman, 2018)

These relatively new entities to the pharmaceutical industry, wholly unique to the United States, are not well understood. It is generally believed that they have a significant impact on the cost of drugs, but it is not yet well understood if they are successful in shifting cost away from the end consumer. More research must be done on PBM's and their role in orchestrating the finances of the pharmaceutical industry.

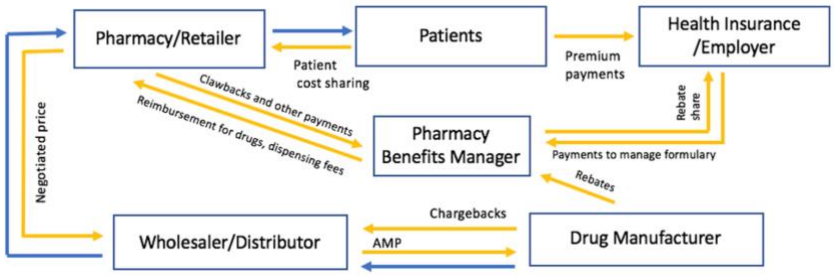


Figure 33 Central Role of PBMs in the Pharmaceutical Supply Chain, from Schulman and Dabora Blue Indicates the flow of goods, yellow indicates the flow of money

Industry Focus and Research and Development Focus

The United States of America has a significant, high value-added role in the pharmaceutical industry due to notable environmental factors such as the relatively low level of regulation, little price regulation, and the refined higher education system that ranks the U.S. consistently in a top position (Quacquarelli Symonds Limited, 2019). The U.S. participates to a high degree in the R&D functions, and participates to a lesser degree in the manufacturing of API or final product, which has over the years been exported to countries in which the cost of production is more affordable (Cohle, 2019; Sardella, 2021). In fact, "for a long time the U.S. constituted the only hub in the network of pharmaceutical innovation" (Jiang & Luan, 2018). Figure 34 displays the pharmaceutical industry's current specialties, which should give a degree of insight to the areas in which the U.S. focuses. An over approximation is necessary due to lack of US-specific information, a result of the U.S.' intimate identification with Big Pharma. We see that the small molecule subsector holds the greatest share at 58%, while biologics hold the

second greatest share at 32%. The strength of pharmaceutical R&D capital funding was measured at 15-18% in 2016 (赵娜娜 & 孙利华, 2018), meaning that significant emphasis is placed on the continuance of R&D innovation in this industry. As can be expected, the focus on R&D in U.S.-based generics firms is more limited than that of brand name pharmaceuticals, with approximately 4.5% of generic cost structure being focused on R&D activity (Figure 35 and 36). Brand name pharmaceutical manufacturing firms spend more on R&D activities, with 15 to 25% of total revenue going to these activities (Figures 37 and 38).

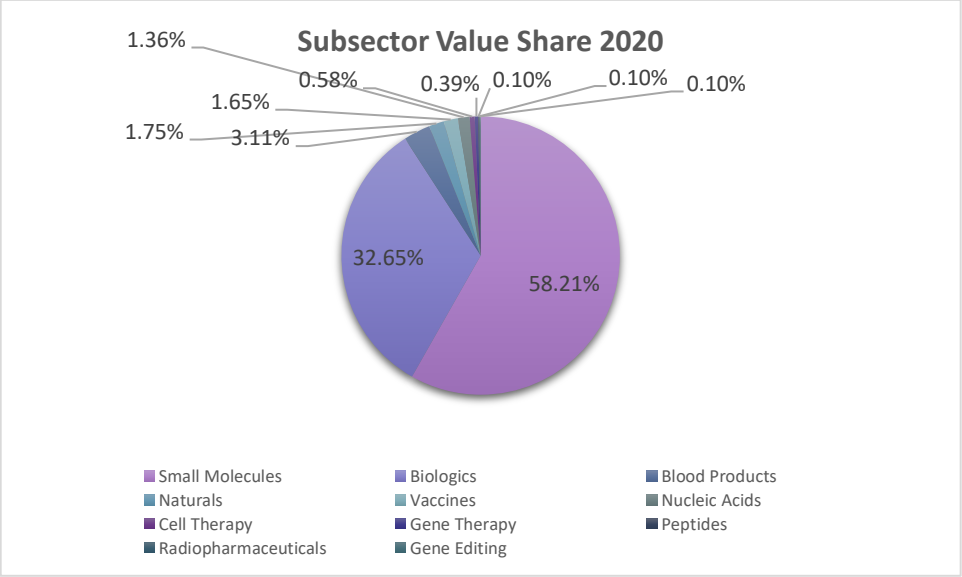


Figure 34 Pharmaceutical Value by Modality, from Torreya

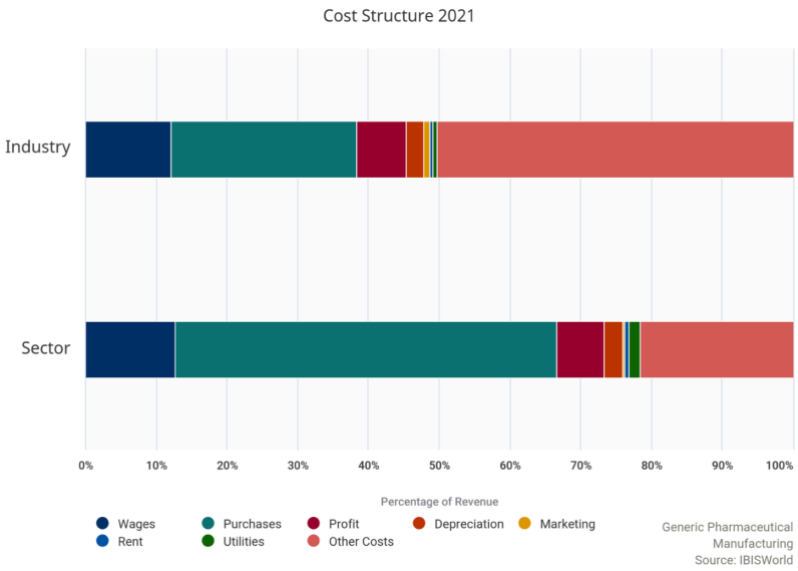


Figure 35 Generic Pharmaceutical Manufacturing Cost Structure, from Kennedy, K.

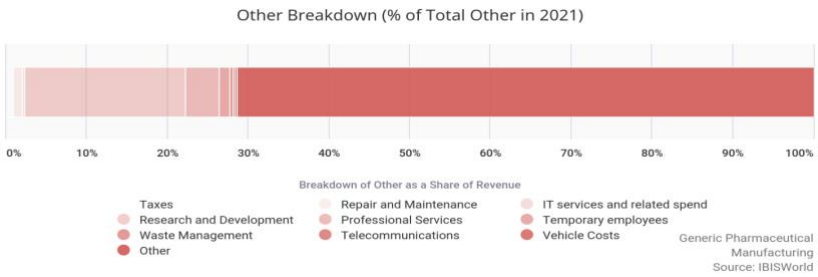


Figure 36 Generic Pharmaceutical Manufacturing Cost Structure "Other Costs" Breakdown, from Kennedy, K.

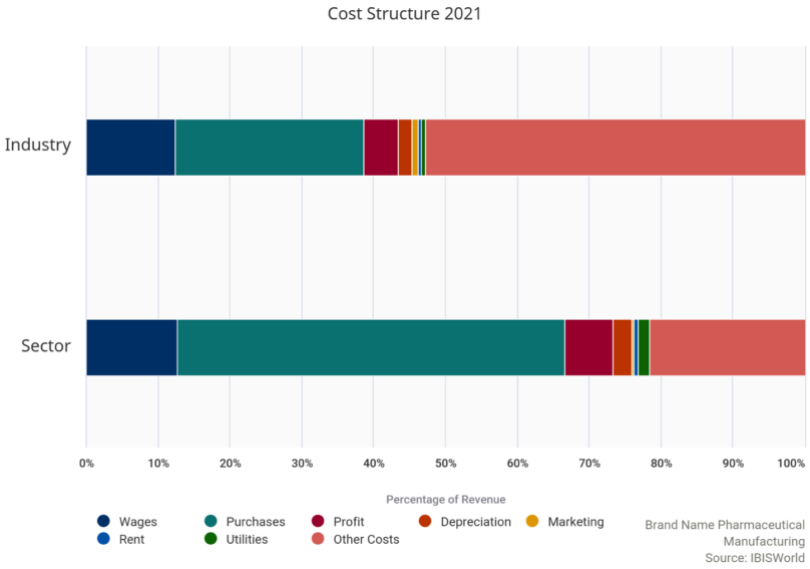


Figure 37 Brand Name Pharmaceutical Manufacturer Cost Structure, from Kennedy, K.

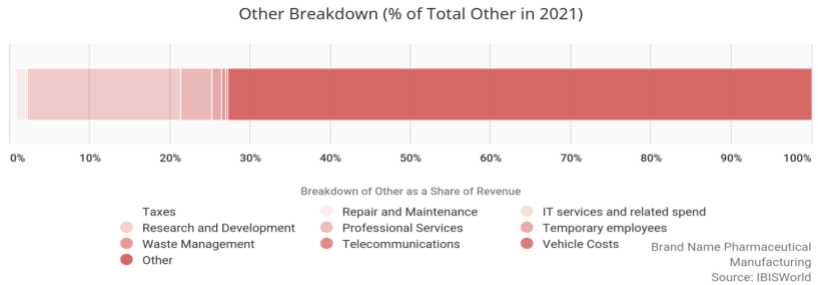


Figure 38 Brand Name Pharmaceutical "Other Costs" Breakdown, from Kennedy, K.

It is of significance to note that the structure of R&D in the pharmaceutical industry is itself being changed. In the face of increasing R&D cost pressure on large pharmaceutical firms, lowering R&D success (Figure 39), and the patent cliff[2], the traditional model for R&D that

[2] The Patent Cliff refers to many patent expiration dates passing in quick succession, resulting in dropping sales as generic drug substitutes enter the market, taking the innovator's market share. Due to the success of pharmaceutical development in the 1990s, a number of blockbuster drug patents are ending resulting in an industry-wide reduction of revenue. The flattening of new R&D productivity has confounded with these expirations, resulting in a phenomenon in which firms fail to make up the revenue lost by expirations (Song & Han, 2016).

brought U.S.' pharmaceutical innovation to the forefront during the span of the 20th century (e.g. the "blockbuster" "in-house" R&D mode, featuring large investment by a firm to nurture internal innovative ability) is in flux. A new tendency to outsource R&D using external collaborations with biotech firms, has resulted in an overall decrease in the number of publications led by pharmaceutical firms but has also resulted in an increase in collaborative publications (Rafols, et al., 2014). In an increasingly outsourced R&D model, contract research organizations (CROs) have seen their role develop from clinical development-focused to a therapeutic area-specialized R&D role; from routine science activities to increasingly complex R&D capabilities (DeCorte, 2020). In addition to outsourcing aspects of the R&D function, pharmaceutical firms are also externally sourcing innovative ideas to supplement their existing R&D pipelines. This external sourcing includes "new models for open innovation such as open-sourcing, crowd-sourcing, public-private partnerships, innovation centers, Science Parks, and the wholesale outsourcing of pharmaceutical R&D" (McMeekin, et al., 2020). Biotech seems to play a particularly key role in the external sourcing of ideas (Figures 40 and 41), supporting the perception that pharmaceuticals are heavily investing in biotech following its investment success in the 1990s and 2000s. Yet despite this heavy emphasis in biotech as a key source of knowledge to fill R&D pipeline gaps and improve R&D effectiveness, Fernald et al. finds the acquisition of biotech has had a negative impact on Big Pharma firms' innovation performance - largely due to limited absorptive capacity (Fernald, Pennings, Bosch, Commandeur, & Claassen, 2017).

It seems as though Big Pharma, in the search to reduce financial risk caused by the high and growing cost of pharmaceutical R&D, lowering R&D productivity, cost pressure caused by the patent cliff, growing regulatory attention, etc., has neglected internal R&D in favor of the 'biotech revolution' which may ultimately have negatively impacted firm capabilities and absorptive capacity (Fernald, Pennings, Bosch, Commandeur, & Claassen, 2017), shifting pharmaceutical's long term competency from comprehensive R&D activity more towards the 'D,' wherein biotech and other external knowledge sources are the locus of innovation and creativity while pharmaceuticals serve in a network orchestrator role by capitalizing on its regulatory, political, and financial capabilities to successfully commercialize innovation (Rafols, et al., 2014) (supported by Gleadle et al., 2012); however, other literature points to a more moderated view of pharmaceutical's ongoing externalization of knowledge, believing that "externalized or acquired R&D appears to complement, rather than substitute, internal R&D" though "distancing the capability for innovation (associated with the transition to biotech) from the resources for innovation (concentrated in Big Pharma due to their size, profitability and experience) is a real phenomenon that is creating a fragmentation of knowledge, knowledge sharing and other structural inefficiencies (Gleadle, Parris, Shipman, & Simonetti, 2012).

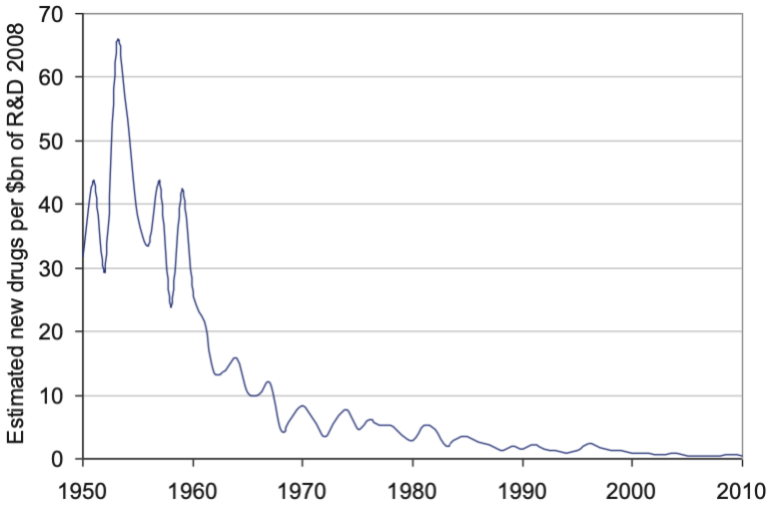


Figure 39 The decline in R&D Productivity of US Big Pharma, from Scannell et al., 2012, via. Gleadle et al.

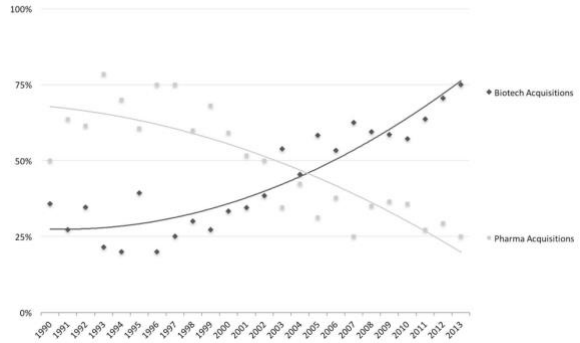


Figure 40 Trends in externally acquired knowledge and assets through acquisitions by big pharma firms between 1990 and 2013. Showing the acquisitions of "Pharma" targets and "Biotech" targets as a percentage of included acquisitions. From Fernald et al.

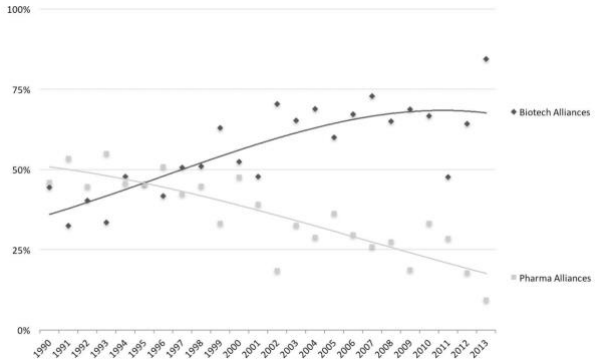


Figure 41 Trends in externally acquired knowledge and assets through alliances of big pharma firms between 1990 and 2013. Showing access to knowledge/assets in alliances with "Pharma" companies and "Biotech" companies as a percentage of all studies alliances. From Fernald et al.

Under the changing R&D environment of U.S.-based pharmaceutical trends, it is critical to not only understand changes that have happened recently (e.g., biotech innovation and external knowledge sourcing). It is just as critical to understand the current orientation of pharmaceutical R&D development: where is the industry focused right now? What are the current prospects for the future of pharmaceuticals?

In order to understand the current orientation of the pharmaceutical industry, we first refer to the FDA CDER's new drug approvals according to therapeutic area, including both NMEs and BLAs (biologics license applications) (Figure 42). This data displays that oncology continues its 4-year trend as the leading therapeutic area for drug approval, with high growth substituting its primary position. Neurology grew to become the second largest therapeutic area for R&D activity, surpassing infectious diseases which experienced slight shrinkage to third place. A diversification of therapeutic area also seems to be occurring in 2020 drug R&D activity, with areas previously without much R&D activity gaining FDA approval such as allergy, anesthesia, medical genetics, and urology, potentially indicating therapeutic area scope

to capture the 'low hanging fruit' available with minimal investment. Though this information is helpful in understanding the make-up of current R&D activity, research should be conducted from a historical development perspective to identify drugs' FDA approval trends. It should be noted this data only examines FDA approvals and, in doing so, it is a reflective look at R&D which adds approval bias that serves to minimize the impact of failed or unapproved drugs.

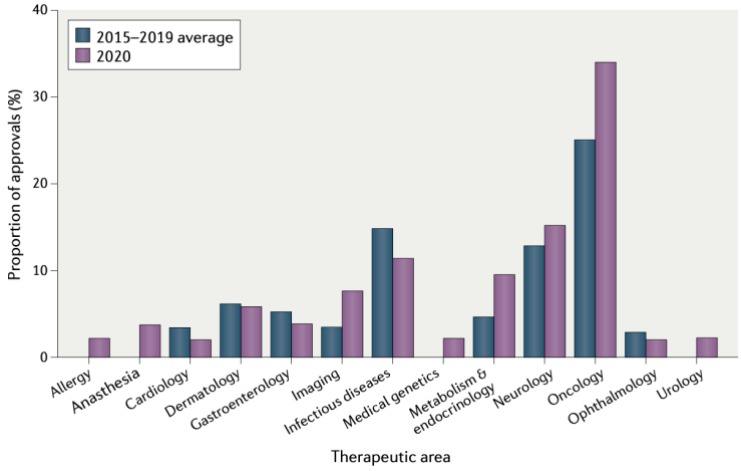


Figure 42 CDER approvals by selected therapeutic areas. From Mullard

Jiang and Luan examined both the impact and the diffusion of U.S.-based pharmaceutical patents by analyzing which pharmaceutical patents received the most references, and to which therapeutic area those referencing-papers belonged (Jiang & Luan, 2018). This research shows the *impact* of current research in the broader scientific and academic communities to show the competencies of U.S. pharmaceutical research in the eyes of others. Jiang and Luan identified 28,075 patents citing U.S. pharmaceutical patents registered in the State Intellectual Property Office of the P.R.C, in the U.S. Patent and Trademark Office (U.S.), or both for the 2014-2015 period. In a U.S.-China comparison, the U.S. had a significant lead in the widespreadness of pharmaceutical patents, though the growth rate of patent influence falls behind that of the Chinese pharmaceutical patents. The top 10 assignees referencing U.S. patents (F. Hoffmann-La Roche Ltd., 1.75%; University of California, 1.03%; Merck Sharp & Dohme Corp., 0.88%; Institut National de la Santé et de la Recherche Médicale (INSERM), 0.53%; Novatis AG, 0.50%; Sanofi-Aventis Deutschland GmbH, 0.49%; Harvard College, 0.47%; University of Texas System, 0.47%; Roche Diagnostics GmbH, 0.46%; John Hopkins University, 0.45%) (including five pharmaceutical firms, four universities) accounted for 7.03% of patent filing citing U.S. pharmaceutical patents, showing a degree of convergence that was significantly higher than China's 3.84%. By analyzing data in this way, Jiang and Luan were able to identify "possible cutting-edge frontiers towards which the industry is advancing," by finding which U.S. patents have gained the most traction, then developing a representative measure of the degree to which an innovation is adopted.

The data seems to indicate that pharmaceutical composition maintains the highest degree of convergence, indicating that the U.S. is perceived to be a leader in this subject. Due to the degree of integration between the U.S. and Big Pharma, it is also safe to say that the high degree of patents citing pharmaceutical composition patents (ct. 1049) indicates that this is a subject of importance in the wider 2014-2015 pharmaceutical industry. The U.S. convergence map (Figure 43) shows a great number of prominent subjects, which stands at a contrast with that of the

Chinese convergence (Figure 66), indicating that the *perception* of the U.S. pharmaceutical knowledge expertise is far wider than the perception of the Chinese's. This is most likely due to the long-established prominence of the U.S. as a pharmaceutical innovation hotspot, while China is a relative newcomer to the chemical and biological pharmaceutical innovation scene.

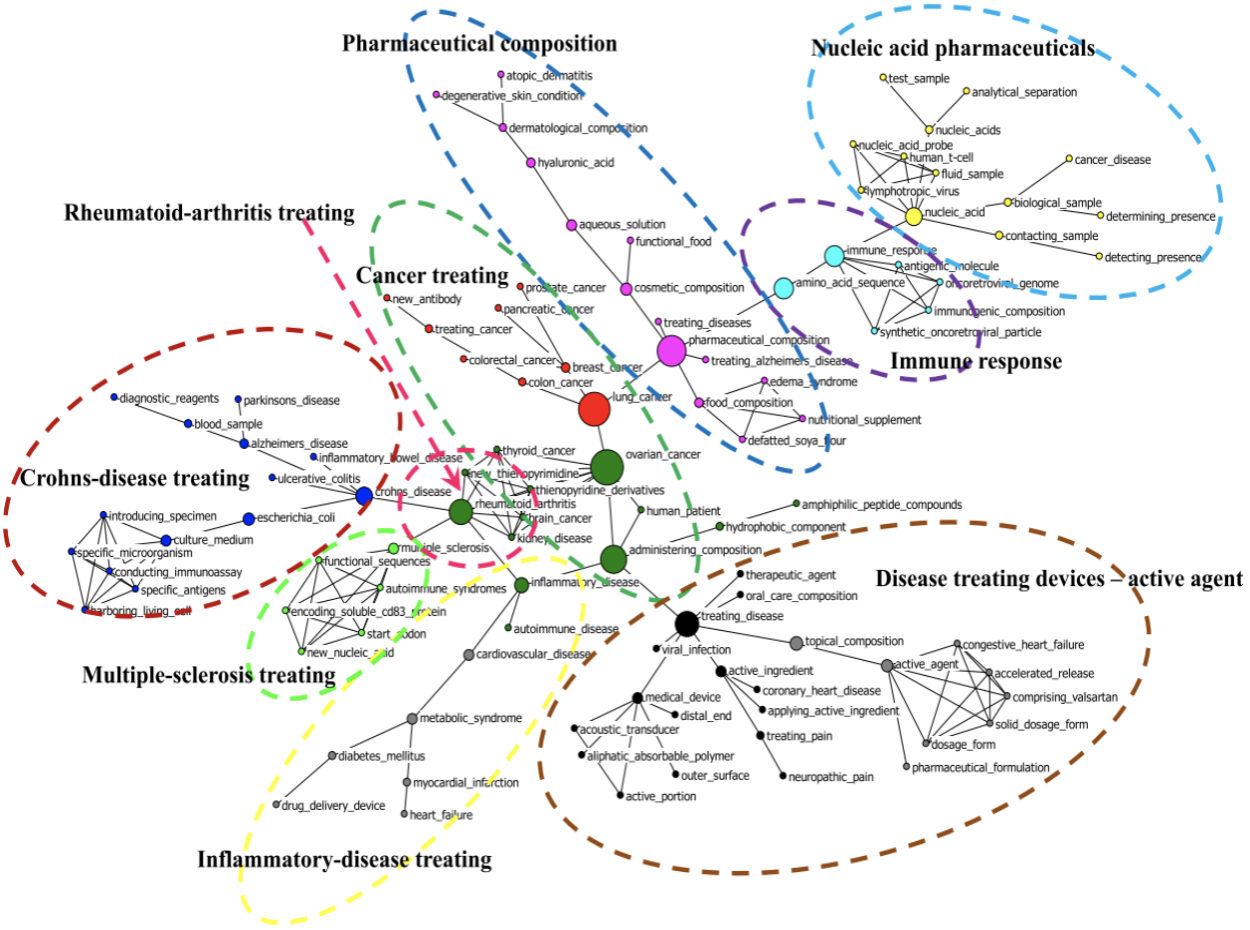


Figure 43 Convergence of U.S. Pharmaceutical Innovations in the Global Pharmaceutical Industry; from Jiang, Q. and Luan, C.

For pharmaceuticals, "the way forward," as the former director of the NIH Elias Zerhouni, said "is to engage in predictive, personalized, preemptive and participatory medicine" (de Vrueh & Crommelin, 2017). Literature, industry, and the broader community seem to be waiting in anticipation for the arrival of "personalized" pharmaceuticals. Cumulating all previously acquired pharmaceutical and biological knowledge, personalized medicine comes in the wake of intimate understanding of genomic and proteomic technologies and biologic properties, and will take advantage of growing biomarker technology (NIH on biomarkers: "A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" (National Academies Press, 2009)) to develop more sophisticated diagnostic and monitoring tools for medical treatment (Amir-Aslani & Mangematin, 2010). This shift to personalized medicine is aided by a failure of the "blockbuster" system of R&D to effectively treat patients regardless of disease subtype and individual differences from the population average and seems

to have positive prospects for more effective treatment, earlier diagnosis, and lower drug development cost (Amir-Aslani & Mangematin, 2010).

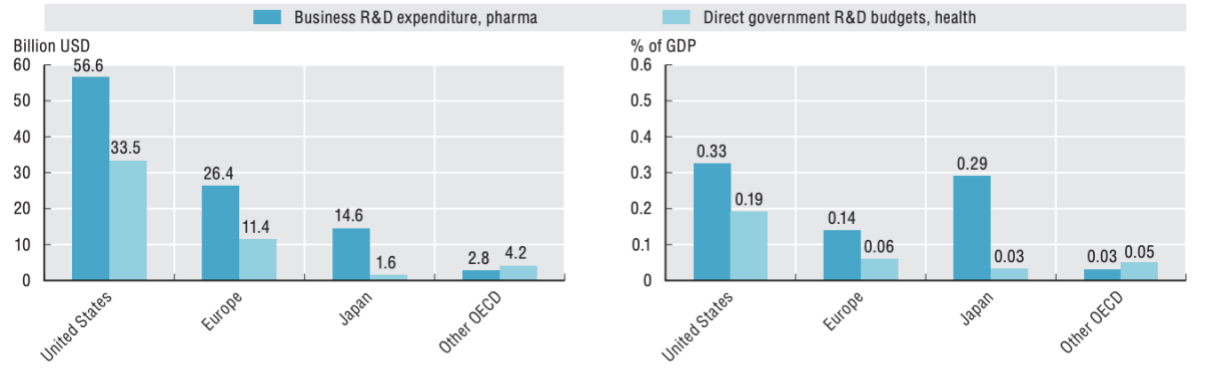
Financial Environment

Pharmaceuticals is a capital-intensive industry with extensive funding necessary to push a potential drug through the long process of research to breakthrough, which is then followed by years of efficacy and safety testing in clinical trials and other regulatory procedures, often taking up to 13.5 years and 1.78 billion USD for a drug to finally enter the market (Paul, et al., 2010). Under such an investment heavy environment, it is necessary for pharmaceutical firms to mitigate financial risk throughout the drug supply chain in order to ensure financial stability in the face of high drug attrition during the research and regulatory process. Though the financing system in the pharmaceutical supply chain is quite unique and complex in the U.S., we examine the financial environment of pharmaceutical firms in the U.S., paying greatest attention to private investment and public funding received by pharmaceutical firms.

Public Funding

The largest Federal government source of investment for pharmaceutical drug discovery research is through the National Institutes of Health (NIH) (National Academies Press, 2010). Recently, political attention has shifted to the perception of government funding in pharmaceutical research as "paying twice," in connection with current discussion of lowering consumer prices; however, despite the NIH financial and practical contributions to all stages of research, the main role of NIH funding has been oriented towards early scientific findings which form the foundation of research, rather than the actual content that private firms will later commercialize (Conti & David, 2020). Though NIH funded research was used in over 90% of new privately held and developed pharmaceutical products between 2010 and 2016, they were not found when examining the actual drug itself, indicating that the research was basal, and was better attributed as a result of knowledge spillover effect from basic research on things such as drug targets (Cleary, Beierlein, Surjit, McNamee, & Ledley, 2018).

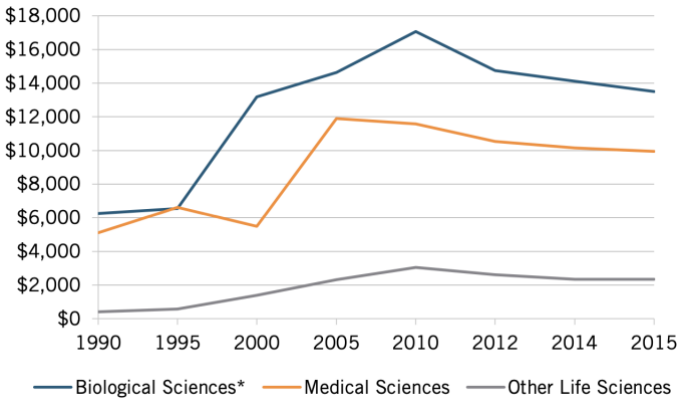
However, despite 33.5 billion USD invested into direct government R&D in 2014 (OECD, 2017) (Figure 44), federal obligations for R&D has steadily decreased across the life sciences since at least 2010, which some argue is damaging to the U.S.' position as a rich knowledge base for life-science innovation (Kennedy J. , 2018) (Figure 45).



Note: 2012 BERD data for Switzerland and 2011 GBARD data for Mexico; all other countries 2014 or 2013. Europe includes 21 EU member countries that are also members of the OECD, Iceland, Norway and Switzerland; no BERD data available for Luxembourg and no GBARD data for Latvia.
Source: OECD Main Science and Technology Indicators and Research and Development Statistics Databases.
StatLink http://dx.doi.org/10.1787/888933605597

Figure 44 Business R&D Expenditure for Pharma R&D and Government Budgets for Health-Related R&D, 2014 or nearest year, from OECD

Figure 45 U.S. Federal Obligations for Research (Millions, 2009 Dollars), from Kennedy



Though there has been support for a new innovation financing system using motivators tools such as prizes, government contracting, government R&D, etc., the current system of government support for pharmaceutical R&D largely stems from exclusivity-based incentives (Cutler, Kirson, & Long, 2020). This would indicate that the government relies more on passive financial support for the pharmaceutical industry rather than the aggressive use of direct funding for commercial products. However, this does not consider the criticality of industry-academia interaction that indirectly uses government money to support industry-based research, which we will examine under the Knowledge Environment section.

Private investment

Funding for late-stage development of pharmaceutical products (non-basal research) is typically sourced from private financial sources such as the pharmaceutical company itself, venture capitalists, or other forms of private investment (National Academies Press, 2010). According to biopharmaceutical trends of the 1990s, “10% of a biopharmaceutical firm’s funding c[a]me from venture capital, 50% form R&D alliances with established pharmaceutical companies, and 40% from public equity markets (Lazonick & Tulum, 2011). Figure 46 displays venture capital invested in biopharmaceuticals until 2009.

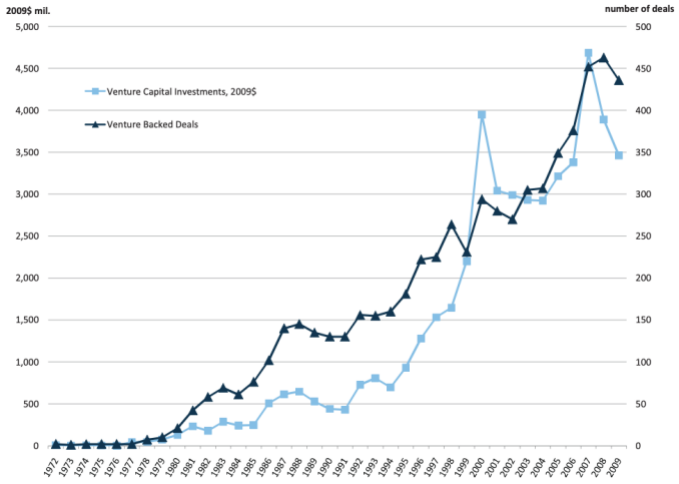


Figure 46 venture-Backed deals and venture-capital investments (if known) (2009 dollars) in US Biotech 1978-2009, from Lazonick and Tulum

Knowledge Environment

A common theme through this section: tides have turned (to an extent) for the pharmaceutical industry, ushering along the need for adaptive approaches to innovation and drug development – the golden age of pharmaceutical discovery, characterized by extremely high R&D productivity has come to an end; in response, firms are needing to create and maintain greater levels of knowledge synergy to achieve comparable levels of productivity. One critical way in which pharmaceuticals have adapted to these R&D pressures is by altering the innovation method. Rather than a fully in-house R&D system as was characteristic to the pharmaceutical industry's golden years, an outward-facing innovation strategy is being implemented in which external sources of knowledge are accessed and combined with internal knowledge (McMeekin, et al., 2020). We simplify the direction of this external shift in the R&D knowledge environment to two classifications: inter-firm collaboration and industry-academia collaboration - as partnership along these two classifications represent the two different types of benefit gained by the pharmaceutical company. Under industry-academia collaboration, the pharmaceutical firms that work with an academic (or university) dominant portfolio of partnership have high rates of breakthrough patents when the centrality of the firm is low. However, when functioning under an inter-firm collaboration style, the pharmaceutical firm works with an industry dominant portfolio of partnerships having a greater breakthrough patent rate if the centrality of the firm is high (Dong & McCarthy, 2019).

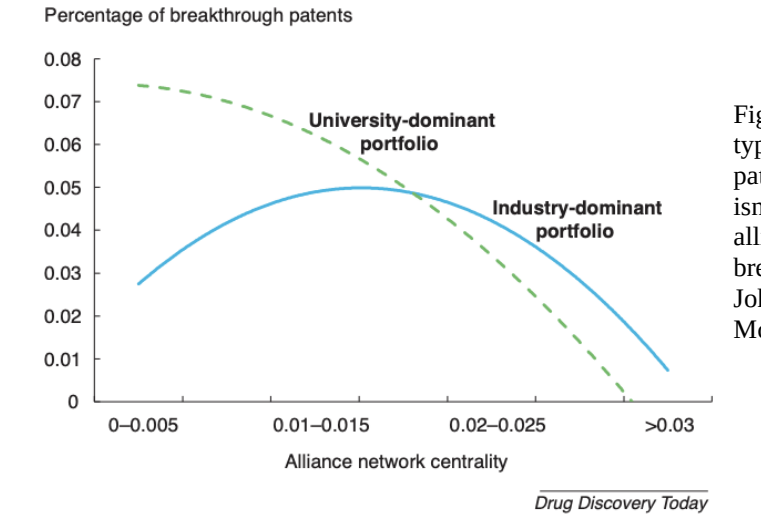


Figure 47 Alliance partner type and breakthrough patents, from When more isn't merrier: pharmaceutical alliance networks and breakthrough innovation by John Qi Dong and Killian J. McCarthy

When facing high rates of external knowledge sourcing, one of the main difficulties for a firm is core rigidity and limited absorptive capacity. Absorptive capacity is the ability of a firm "to recognize the value of new, external information, assimilate it, and apply it to commercial ends," which takes a central role in the ability of a pharmaceutical firm to incorporate external knowledge and synergistically innovate (Cohen & Levinthal, 1990). Core rigidities are distinct and embedded technical systems and skills that may conflict with innovation or expansion to nontraditional knowledge areas (Leonard-Barton, 1992).

Inter-Industry Collaboration

The collaboration between two firms in the industrial sector is a form of market-prioritized partnership that places commercial application of a product as a central goal (Dong & McCarthy, 2019), i.e. focusing on market pull (de Vrueh & Crommelin, 2017). In this type of partnership, data is often less visible to the public. When this form of alliance is used, the distance between partner goals is far less than in industry-academia collaboration (with both orienting innovation toward commercialization), allowing firms to participate in knowledge sharing to a greater extent due to increased knowledge digestibility, preventing absorptive capacity from severely limiting the benefit external collaboration brings to both of the firms; yet this reduced diversity of knowledge reduces the likelihood of the resulting innovation being a breakthrough (Figure 47).

Industry-Academia Collaboration

As humanity's understanding about the human body has developed, a growing breadth and depth of knowledge has allowed development in novel therapeutic areas, a significant driver for the collaboration between industry and academia (Rose, Marshall, & Surber, 2015). Academics have long been "identifying targets, molecules and disease models," directly contributing to the knowledge base of the industry (Hughes, 2008). It is then only logical that industry-academia collaboration is an advantageous way for firms to have greater access to critical knowledge and achieve synergy. Though the pharmaceuticals of the past focused on

academic collaboration from a position of arrogance, creating a one-way flow of information (DeCorte, 2020), recent decades have seen this collaboration shift to a "horizontal, multi-stakeholder public-private partnership" model, in which the two parties have more equal footing, allowing collaboration in areas of mutual interest for innovation (de Vrueh & Crommelin, 2017). Though pharmaceutical firms often focus on commercialization and market *pull*, academia focuses on technology *push* by providing development to fundamental scientific concepts (de Vrueh & Crommelin, 2017).

The interaction between industry and academic research organizations is quite strong in the U.S., surpassing the rates seen in China. In an analysis of university-industry collaboration, Zhou et al. found that the U.S. university with the highest degree of university-industry collaboration (UIC) productivity for all sciences, as measured through publication utilization, was Harvard University, with a UIC productivity of 3,756. The 10th top ranked university was Columbia University at a UIC productivity of 1,646 (6x and 5x China's top-ranking university, respectively) (see Figure 48, 74-75).

Rank	China		UIC(USA)/UIC(China)	USA	
	University	UIC(China)		UIC(USA)	University
1	Shanghai Jiao Tong Univ	651	5.8	3756	Harvard Univ
2	Tsinghua Univ	636	3.8	2429	Stanford Univ
3	Zhejiang Univ	547	3.8	2101	Univ Calif—Los Angeles
4	Peking Univ	494	4.0	1998	Univ Washington—Seattle
5	Fudan Univ	442	4.5	1989	Johns Hopkins Univ
6	Univ Hong Kong	302	6.6	1989	Univ Calif—San Diego
7	**Chinese Univ Hong Kong**	291	6.0	1732	Univ Calif—San Francisco
8	**Peking Union Med Coll**	285	6.0	1709	Univ Michigan
9	**Huazhong Univ Sci & Technol**	255	6.6	1691	**Duke Univ**
10	**Xi'an Jiaotong Univ**	251	6.6	1646	**Columbia Univ**

Figure 48 Top-10 Universities in Domestic Ranking in UIC productivity in "All Sciences" (2009-2012), from Zhou et al.

It is of note that this industry-academia partnership is frequently focused on for clinical research, which has been shown to introduce a pro-industry result (de Vrueh & Crommelin, 2017); however, due to the basal nature of academic research in the pharmaceutical field (the "basic science stage") it is largely concept-driven research which reduces negative impact of this relationship.

The People's Republic of China

Historical Background

Since China's Reform and Opening Up period which spanned the five-years between 1979 and 1984, the pharmaceutical industry lagged the development of the heavy industries, which were being used by the government as a key tool to develop the economy (Park, 2002). The knowledge-heavy characteristics of the pharmaceutical industry indeed requires an advanced education system to function. Instead, the industry naturally developed into generic pharmaceutical manufacturing, taking advantage of early capabilities in manufacturing to focus on the production of off-brand versions of drugs already developed by major pharmaceutical companies.

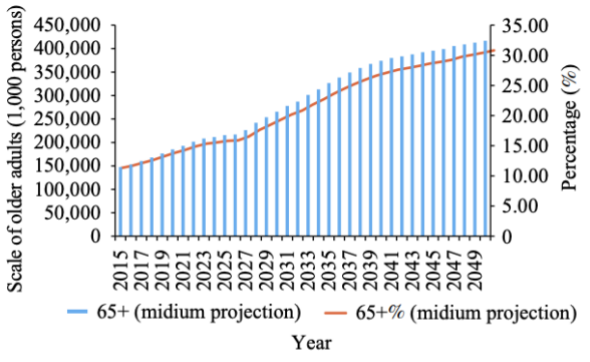
It is through this early focus on the manufacturing of off-patent drugs that gave the PRC a competitive advantage based on the price of medicine rather than technical innovation or product differentiation as is common in developed pharmaceutical markets. This had the effect of creating a strong generics sector, while simultaneously holding the industry back from expanding into the international market where greater differentiation (i.e. innovation) and profit is accessible (Li, Lian, & Zhao, 2013) - a decision in part motivated by the Drug Administration Law of 1984, leading to an early prioritization of producing *enough* medicine to supply the massive domestic population (Mao & Zheng, 2009). In addition to gaining competencies in the production of generic drugs, Chinese heavy industry's manufacturing capabilities were used as suppliers to others.

Since, the PRC has become the world's largest FDI recipient for a period of more than twenty years, allowing mass inflow of capital and, more importantly, tacit knowledge and technology (Jakubczak, 2020). This slow intake allowed the industry to progress through four different stages of intellectual independence: *pure imitation* (1949-1984) by small pharmaceutical factories with no patent law protection; *innovative imitation* (1985-1993) marked by weak patent protection to encourage innovation while slightly modifying existing drugs to avoid directly imitating the original drug while not developing significant innovative alterations; *imitative innovation* (1993-2008) with patent law adhering to TRIPS standards, marked by an increasing volume of new drug approvals (NDAs) showing the increasing awareness of the importance of innovation in the pharmaceutical industry but still with limitations to innovation capabilities and to the regulatory infrastructure; and finally *independent innovation* (2008-current) with increasing R&D expenditure and increasing volume of new drug applications (Ding, Xue, Liang, Shao, & Chen, 2011). This progression in capability can be observed in China's pharmaceutical output –the industry's output increased from a mere 2.5% to 18.3% from 1995 to 2010 (Ni, et al., 2017).

Modern Background

The modern pharmaceutical industry is not a static and unmoving entity. It is constantly evolving in response to opportunities and challenges. This applies not only to the global pharmaceutical industry, but equally to China's domestic pharmaceutical industry. The PRC's demographic and economic trends present opportunity to firms operating within the scope of the pharmaceutical industry and provide opportunity for international firms hoping to gain access to the Chinese market.

One important factor favorable to the growth of the domestic pharmaceutical industry are population megatrends. In 2020, the World Bank reported that the Chinese Mainland population had reached 1,402,112,000 citizens (World Bank, 2019) making it the most populated country in the world, followed by India at 1,380,004,000 citizens. In combination with a growing economy and continuing liberalization of the healthcare sector, a massive market for the purchase and distribution of pharmaceuticals in China continues to grow (Fitch Solutions, 2020). It should be noted that, due to a declining birth rate, the population is forecasted to undergo slight decrease in population after 2030, though it will largely remain at the same level (Fitch Solutions, 2020). Within this population, large structural changes are occurring, such as rapid population aging. Luo et al. forecasts the percent of the population 65+ years old will increase from 14% in 2022 to 21% in 2033 (Luo, Su, & Zheng, 2021) (Figure 49), indicating a need for a more robust pharmaceutical industry. Anderson emphasizes this critical link in his findings that between one-third and one-half of total health care spending goes to a country's elderly population (Anderson & Hussey, 2000).



Aging society	Aged society	Super aged society	Years of transition	
>7%	>14%	>21%	7% to 14%	14% to 21%
2000	2022	2033	22	11

Figure 49 The Predicted Proportion and Prevalence of Older Adults in China 2015-2050. Luo et al.

Besides a high and growing net demand for drugs and medicine, other factors such as traditional medicine and natural resources provide significant opportunity for the pharmaceutical industry. Containing 10% of the world's biological resources, firms hope to have better access to resources and discoverable compounds (Ni, et al., 2017). As American and other western firms constituting "Big Pharma" experience slowing R&D outcomes, companies seek new means of

drug discovery, with some companies turning attention to traditional Chinese medicine (TCM) as a tool for drug discovery. TCM-based novel drug discovery is benefitted by advances in chemical, biological, pharmacological, and other schools of technology, allowing the "rediscovery" of active compounds every year. Nagai and Hori were one of the early identifiers of TCM as a tool to identify and isolate naturally occurring compounds at the turn of the twentieth century, ultimately isolating ephedrine, an involuntary nervous system stimulant (Chen & Kao, 1912).

These trends all influence global and local industry movement and development. Both Chinese domestic and foreign firms see opportunity to access a growing market and valuable resource and knowledge-sourcing potential. As money and resources are being invested in the Chinese pharmaceutical market and western companies partner with local companies to research, develop, manufacture, and distribute pharmaceuticals, the impact is seen on an international level.

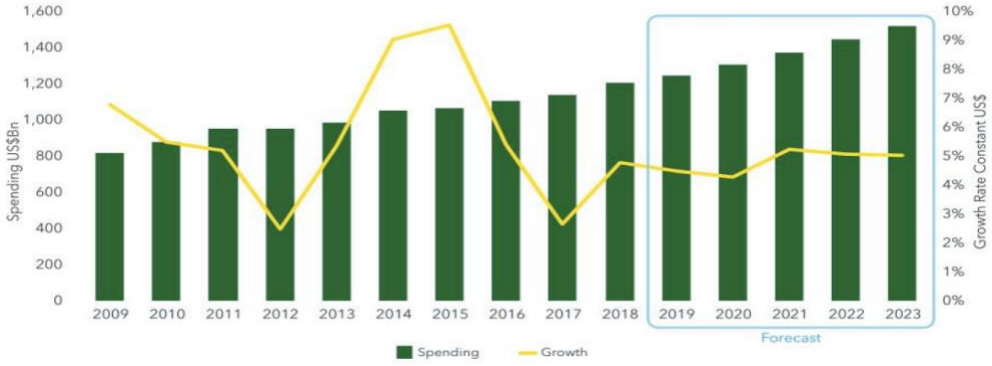


Figure 50 Chinese National Pharmaceutical Market Size and Growth, from the Ministry of Industry and Information

Policy and Regulatory Environment

When it comes the regulation of the pharmaceutical industry, governments must balance implementing price control to enable medicine to be widely available to the population (thus improving public health) and encouraging and incentivizing firms to innovate through profit, often using tools such as market-exclusivity periods, freedom in price-setting, or delayed market access to competitors. Though regulation is often seen as negatively impacting industry efficiency by reducing R&D ability, reducing drug access, and reducing competition, Zhao and Wu assert that regulation is necessary due to the assumption of weak competition relating to "patent monopoly, insurance that seems to be insensitive to prices, and physicians who may act as imperfect agents" (Zhao & Wu, 2017).

Regulation of this industry is complex, nuanced, and highly impactful to the performance of the industry. Focusing on important factors of the industry and its performance, we examine the current use of price control, patent rights, quality control, and corruption policy directed at

the pharmaceutical industry by the PRC. We then examine the strategies being implemented in the industry through the use of initiatives and policy used to guide the industry to growth.

Price Control

Pricing is a constantly and rapidly evolving area in the PRC regulatory sphere, as the government attempts to balance firm innovation and expanding the affordability of drug prices, particularly after price-targeted reform began in 2015.

Understanding it's two major reimbursement lists is vital to understanding the pricing and reimbursement system used by the PRC, as these lists express which drugs the government sees as of foremost importance, and which drugs are funded by the Basic Medical Insurance (BMI): the Essential Drug List (EDL, established 2009) and the National Reimbursement Drug List (NRDL, established 2000). These two schemes, managed by the central government, are aimed at providing basic medical coverage and selecting drugs with the highest therapeutic value and the greatest cost-effectiveness. These are important tools for price control in China (Shi, et al., 2018). Furthermore, recent adjustments by the NHSA ensures new drugs can be entered to these BMI-covered drugs and older drugs are removed on a more regular basis (Deloitte, 2020).

From 1997 to 2013, price ceilings were applied more than 30 times to drugs, but this system failed to achieve the anticipated reduction in medicine price and expenditure – only temporarily reducing medicine prices by 0.5% (Wu, Zhang, & Qiao, 2015). Since ending the use of price ceilings in 2015, the PRC has implemented different ways to regulate pricing. Mossialos et al. describes the present pricing and reimbursement system to be separated into three parts: supply-side policy, proxy-demand policy, and demand-side policy (Mossialos, Mrazek, & Walley, 2004).

Supply-Side Policy. Supply-side policy is a form of pricing policy dealing with the ability of the drug or firm to access the market. It includes the use of direct price controls, as well as quality regulations. As mentioned above, one early adoption of supply-side pricing policy was seen through the application of price ceilings (specifically to NRDL medicines); however, this policy reduced price marginally in the short term, and was easy for physicians to work around by using expensive and often off-list foreign drugs to maximize the use of the profit gained from the 15% mark-up allowed on non-EDL listed drugs (hence EDL's intended function in reducing medical corruption) (Shi, et al., 2018).

After ending the price ceiling method of price regulation in 2015, tendering became a main strategy for the pricing of off-patent drugs (Mossialos, Ge, Hu, & Wang, 2016). Used for the acquisition of most EDL drugs and many NRDL drugs, firms are invited to submit a competitive proposal to provincial level governments. The winner of the tender was able to sell the drug inner-provincially, with healthcare institutions guaranteed to purchase 80% of the tender by value. This policy reduced EDL drug prices by an average of 25% (Mossialos, Ge, Hu, & Wang, 2016).

It should be noted that, because tendering is executed at the provincial level, there is variation in how it is conducted. Effects of this include increased savings in some provinces, while others may decide on a non-scientific basis leading to opportunity for corruption. Due to a non-standardized tendering system at the provincial level, a lack of "scientific process and criteria for effective supervision" created opportunity for decisions to be made solely on price factors without consideration of quality or opportunity for firms to interfere with the selection

process via bribes or illegal alliances. Another unintended result of this policy was that companies bid at prices below their production cost, leading to a failure to follow through on production. Due to the often-exclusive right of the tender-winner to the production of the drug, shortages result (Hu, et al., 2015; Shi, et al., 2018).

Drug reference pricing (RP) is an emerging idea in supply-side price regulation as an alternative method to the EDL tendering method for generic drugs. Though not implemented at significant scale, the government ran a pilot program for the RP system in Sanming City, Zhejiang, China from 2014 to 2016 intended to replace the tender system in controlling health insurance's reimbursement and reduce the use of originator drugs. The RP system was associated with a 25.9% decrease in total monthly volumes for the 14 EDL-drug sample (including originator volume decreasing 56.8% and generic version volume increasing by 98.6%). The RP pilot was associated with a 47.7% decrease in cost for the 14 drug substances analyzed (USD 46,280.05, CNY 295,600). The combination of a decrease in the purchase volume of originator drugs and the increased volume of generics purchased can be understood as resulting from "dis-incentivizing physicians' preference of patients' acceptance of high-priced drugs. Since RP can direct patient demand to low-priced counterparts of drug substances with low profit margin, the rebate for physicians decreases, which in turn eliminates their financial incentives to prescribe high-priced drugs, " reducing excess expenditure by the patient (Jiang, Feng, & Zhou, 2022). These results may lead to further piloting of the RP system by the government. Though tested at small scale and so using intraprovince procurement carried out by Zhejiang Provincial Government using China's Essential Medicines Program, if applied to the national scale, the use of international and interprovincial reference points may help to address MNC drug prices being in the upper half of the international price range, with 20% of drugs being more expensive in China than elsewhere (Hu & Mossialos, 2016; Mossialos, Ge, Hu, & Wang, 2016).

When discussing tendering and RP as it relates to the pricing system of off-patent (generic) drugs, it is relevant to mention that noninnovative, pure product imitation, such as that seen in generic competition once the originator's market exclusivity period expires, moves approximately 98% of the drug's market value from the innovator (originator) and redistributes the value among the imitators (generics), as estimated by senior and middle managers from 149 pharmaceutical firms in China (Wang, Li, & Chen, 2020). By implementing policy promoting off-brand drugs as seen in the tendering system and, to a greater extent, the proposed RP system, the originator's post-market exclusivity period revenue will heuristically reduce on-brand pharmaceutical profit. Further reduction of post-exclusivity originator market share may have effects reducing the innovative ability of the originator firm.

Price control for on-patent drugs is an area recently experiencing change due to a shift to a national bulk purchase program (Xinhua, 2021; Reuters, 2019). This program was first tested in January 2019 with the General Office of the State Council of the PRC starting the "4+7" Volume-Based Purchasing scheme (4+7 带量采购). Under this experiment, four key municipalities (Beijing, Tianjin, Shanghai, Chongqing) and seven key cities began using a centralized purchasing platform for the procurement of drugs to encourage local and foreign firms to submit competitive bids – this scheme has since been expanded nationwide (now named NVBP) (Reuters, 2019). These 11 test locations formed a purchasing alliance, increasing per-transaction volume. The effect of this program was a 52% average decrease in price of the 25 tested drugs (Tang, et al., 2019). The goal of this program is to use high-volume purchasing and a centralized rating system to choose the drug provider with the lowest price and highest value to use for the national medically insured drug lists (NRDL and EDL) (杨心悦, 李亦兵, & 海桑,

2019). Yet a few issues exist in the piloted version that may introduce challenges if changes are not made when applied at the national level. The first weakness of the piloted program is the use of a single-source supply method, meaning that the risk of supply shortages and the impact of supply chain issues are greatly increased (Tang, et al., 2019). In the nationwide implementation, the government chained this to allow for up to three suppliers to moderate single-supplier risk (Reuters, 2019). Another issue: Yang et al. proposes that in order to regain the ability to compete for the contract, companies who were not selected by the centralized decision makers will have an enormous pressure to spontaneously reduce their prices (杨心悦, 李亦兵, & 海桑, 2019). While this is true, the preface of the bulk-buying program is the use of economies of scale, most present in large firms who are able to afford such drastic price cuts and who are able to supply such a large volume of drugs. This policy may increase the industry entrance barriers, making it more difficult for small and midsize firms to enter the market, and thereby reducing net competitive force present in the industry – though allowing multi-firm alliances to participate in the bidding process may help to alleviate this effect.

Proxy-Demand Policy. Proxy-demand policies are policies that influence health care providers such as physicians and healthcare institutions, as these groups act as proxies for patients when making purchasing decisions. Previously, a national allowance of a 15% mark-up on pricing at medical institutions, established in the Policy on Drug Markups issued in 1954, aimed to increase medical institution income during declining government subsidies (Ni, Jia, Cui, Zhou, & Wang, 2021; Liu, et al., 2021). However, in response to issues such as over-prescribing and overuse of antibiotics, a new proxy-demand policy was adopted to all county-level hospitals (which don't receive full budgetary support from the government (Ni, Jia, Cui, Zhou, & Wang, 2021)): the Zero Markup Drug Policy. Scholarship examining the result of this policy has been mixed; although it seems that considerable decreases were achieved in drug costs and total expenditure per patient visit, an increase in the number of visits annually increased (Liu, et al., 2021).

Demand-Side Policy. Demand side policies are those that directly impact the patient demand. Most notably, this includes tools such as the NRDL and EDL. The EDL and NRDL work as the guide for the Basic Medical Insurance (BMI). The cost of medications listed in the NRDL must be in part (50% to 70%) paid by China's BMI, and thus uses price incentives to guide patients to cheaper medicines (as price negotiation is a prerequisite for joining NRDL and EDL) (Zhang, et al., 2021; Evidera, 2019).

Patent Rights

When it comes to intellectual property rights, the pharmaceutical industry presents special challenges. Governments often face the decision between allowing a long patent protection period (thereby ensuring the drug innovator is able to reclaim the high R&D and institutional costs necessary for a novel drug development and innovation) and a shorter patent protection period which reduces the amount of return a firm can attain before generic drug manufacturers remove most revenue streams (thereby ensuring that patients can have greater access to critical new medicines).

Initially adopted in 1985, the PRC's patent law has gone through four revisions, the most recent one going into effect June 1, 2021; however, pharmaceutical *data exclusivity* protection

did not exist until 2001 (as opposed to the U.S.'s implementation of data exclusivity protection via. the Hatch-Waxman Act in 1984, requestable in conjunct with a patent), after which data was protected for at least 6 years (People's Republic of China, 2002), with the scope of data exclusivity being extended for certain classifications of pharmaceutical data in 2018 (Hogan Lovells, 2018). The goal of the 2008 revision of the PRC Patent Law was to begin to shift China's economy from manufacturing towards technology and innovation, while also ensuring domestic law is consistent with the international Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) (Tang P. , 2020).

However, it should be noted that adherence to and consistency with TRIPS does not remove potential for international disagreement on patent rights. For instance, TRIPS states that if the pharmaceutical data submitted by a pharmaceutical company has been approved by one country, another country that accepts the drug listing application is not obliged to protect the pharmaceutical data, which may lead to conflict regarding differences in the implementation of TRIPS (Li, Yu, & Pecht, 2015).

The most recent revision of PRC Patent Law saw special protection enacted specifically for pharmaceutical patents. The first revision affecting pharmaceutical patents (Article 42) was an extension of term, allowing firms to apply for an extension to compensate for time spent on the review and approval of drugs – with the total patent period unable to exceed 14 years. This extension has long been requested by MNCs as well as domestic innovators. Article 76 now implements a pharmaceutical patent linkage system that pairs generic drug marketing application with the originator drug. This is designed to resolve patent infringement issues earlier and prior to the marketing of the generic drug. However, this function may delay the speed with which generics, if tied up in patent disputes, may enter the market - in effect adding to the market exclusivity period of the originator (Li, Yu, & Pecht, 2015). To complement this, Article 71 allows infringement claims to not be based on the infringer's financial data if such data is difficult to attain, while additionally increasing the severity of punishment for patent infringement, e.g., maximum statutory damages increased from 1 million RMB to 5 million RMB (Tang P. , 2020).

The 2020 revision of the PRC Patent Law comes in the wake of U.S./China tensions centered around Intellectual Property disagreements. January 15, 2020, an agreement between the two countries resulted in the "Economic and Trade Agreement Between the Government of the United States of America and the Government of the People's Republic of China" (People's Republic of China; United States of America, 2020).

Quality Control

The early history of the PRC pharmaceutical industry after the establishment of the Drug Administration Law of the PRC (1984) is characterized by a push for domestic generic drug producers to produce enough medicine to meet the country's demand – with focus not placed on quality and innovation (Mao & Zheng, 2009). Even in recent history, the 12th Five-Year Plan for Drug Safety (2011-2015) acknowledged quality gaps with international standards that had an effect on efficacy and safety (Hu, et al., 2015).

One continued barrier to the establishment of wholistic and consistent drug quality standards is pharmaceutical industry composition: many small firms with scattered distribution and high fragmentation ("小、多、散、乱") makes it difficult for government bodies to comprehensively certify that quality standards are being amply and consistently met (张晓燕 &

倪春霞, 2017). Though we will discuss this industry's composition when discussing the market environment, it is relevant to understand this composition as a backdrop to the state of quality in the pharmaceutical industry.

Good Manufacturing Practice (GMP) is a conceptual guideline oriented towards ensuring that the manufacturing and testing of certain consumer products (food and beverages, cosmetics, pharmaceuticals, medical devices) are up to standards accepted by international bodies. It focuses on quality management and assurance built into the manufacturing system through procedure, documentation, maintenance, etc. (International Society for Pharmaceutical Engineering, 2022). In the 2016 Guiding Opinions of the General Office of the State Council on the Promoting of the Sound Development of the Medical Industry (State Council of the People's Republic of China, 2016) new GMP practices are specifically highlighted as an area to "fully implement and carry out" to improve quality metrics.

Yet, despite the long-term commitment to the GMP guidelines, regulatory standards were inconsistent with the international standards (Ni, et al., 2017). Zhao Weihan in his 2015 Master's thesis noted that a WHO evaluation of China's drug inspection quality system revealed that it fell short of the Pharmaceutical Inspection Co-Operation Scheme (PIC/S), an international program implementing standardized GMP practices in the pharmaceutical industry. Zhao reports that to respond to PIC/S requirements for a centralized quality management system and WHO's evaluations, a nation-wide centralized quality management system is critical, as at the time every drug inspection organization had established their own inspection procedure documents, system management documents, and technical standards resulting in difficulty creating standardization in the industry (招伟汉, 2015).

The Handbook on Capacity Assessment of Drug Inspection Agencies established an earlier version of GMP as an encouraged standard practice; however, it did not have strong enough requirements enforcing the necessary measures to fully implement GMP practices.

Another issue in the ability of quality standardization was the nature of the inspectors. Most inspectors used to evaluate the quality of manufacturing practices were part-time workers. Due to this, it was difficult to advance the inspectors ability, resulting in inspections that were inadequate. The training of these workers was likewise variable based on location as training lacked a national standard. The Interim Provision on the Appointment and Evaluation of Inspections for Drug Production Quality Control Standards (National Medical Products Administration) allowed government departments and provincial drug oversight departments to have their own training and appointment systems (招伟汉, 2015). This staffing issue is not limited to the inspectors, but extended to how manufacturers dealt with inspections – in actuality, managers focused solely on profit maximization, and would temporarily hire professionals to deal with GMP/GSP inspections and certifications (周亚萍, 2019). Both practices can result in increasing the prevalence of unstandardized medicines, and both are highly impacted by the state of the industry composition as many, small and scattered (小、多、散、乱).

Among the quality issues apparent in the pharmaceutical system (excluding the preparation of various forms of TCM to fit within the scope of this research), the greatest volume of nonstandard quality in chemical medicines came from foreign material in injectables (particularly stemming from intravenous fluid packaging and butyl rubber stopper quality), making up 42.29% of all reported nonstandard batches of chemical medicines (周亚萍, 2019).

To take steps to solving these quality issues, literature widely encourages the strengthening of the standardization, transparency, and publication of quality data (Wu, Zhang, & Yang, 2015; Wu, Zhang, & Yang, 2015; Hon & Lee, 2016; 招伟汉, 2015; 周亚萍, 2019).

Corruption Policy

When discussing corruption, it is important to not only look at specific and notable cases that cause industry and policy change – it is also vital to examine the incentives for corruption enabled by institutional structure, while at the same time not removing responsibility and fault from those firms actively participating in corrupt practices.

Literature suggests that one aspect influencing the prevalence of corruption to the pharmaceutical industry and enabling corruption is information asymmetry of essential services – that is, patients do not know what they need, allowing professionals the opportunity to self-deal and create opportunity for personal- or localized-profit (Rose-Ackerman, 2014).

In developing countries, such as the PRC, addressing corruption in the pharmaceutical industry is of particular interest due to a greater scarcity of public resource availability - increasing cost of care and limiting who can afford treatments (Rose-Ackerman, 2014). Allegations of corruption have been levied against international firms such as the notable GSK case (2007-2013), as well as some domestic players. In these cases, bribes have been given to physicians in public hospitals in exchange for purchasing contracts and medical prescriptions. Rose-Ackerman and Tan's (2014) comprehensive breakdown of institutional factors enabling corruption offers a holistic and institutional-level view of contributing factors, discussing: information asymmetries, moral hazards, and adverse selection. It is of note that the referenced literature is published in 2014, as reform in Chinese regulation has continually been occurring through the Reform of the Medical and Health Sectors initiative, (医药卫生体制改革) (State Council of the People's Republic of China, 2021).

Information Asymmetry. In the pharmaceutical and healthcare industries patients rely in part or in whole on the assistance of doctors and professionals when diagnosing issues and recommending appropriate treatments. Patents must rely on doctor's credentials and the industry's behavioral norms, which may result in error on the doctors' parts, or a bias for or against certain medicines. Self-deal is also a potential result of such asymmetrical information. In the PRC, we specifically see the manifestation of self-deal in two distinct areas: overprescribing and increasing annual inpatient visits. Before the implementation of the Zero Markup Policy (ZMU), the 15% mark-up policy on all medicines sold offered an institutionalized incentive for doctors to consistently prescribe more medicine, and more expensive medicine, including those treatments which were not necessary to patient health (Hu & Mossialos, 2016) (Jiang, Zhou, & Feng, 2022). Later, the trend of the self-deal was shifted from the sale of high volume, high price drugs (i.e. taking advantage of the 15% mark-up policy before ZMU) to self-deal manifested in patient visit volume after ZMU. Though after the implementation of ZMU, both drug cost and total expenditure per visit decreased, the number of inpatient visits per year increased (Liu, et al., 2021). In townships analyzed before and after the implementation of ZMU, Yi et al. discovered townships that were previously reliant on drug sales saw the number of inpatients increase by 127%, suggesting an effort by professionals to regain revenue lost by ending the 15% markup policy (Yi, Miller, Zhang, Li, & Rozelle, 2015).

An existing pressure encouraging in the healthcare industry that enables corruption is the decoupling from government support. In recent decades, the public hospital sector's central government funding has been undergoing severe shrinkage, aimed at reducing public expenditure and allowing public hospitals more freedom in self-funding. In 1980, the government subsidies were 60% of total hospital revenue; in 2012 it was 10% with 40% revenue directly from pharmaceutical sales (Yi, Miller, Zhang, Li, & Rozelle, 2015). This decrease put many Chinese

public hospitals at financial risk (Shi, et al., 2018), leaving professionals to find ways to increase other streams of revenue in order to stay viable.

Adverse Selection. Adverse selection occurs when individuals don't purchase into the insurance scheme, and thereby remove the financial backing of those who do need to use the insurance. This can occur if insurance companies cannot charge high-risk individuals a higher rate resulting in an average price that a young or healthy individual may choose to opt out of, undermining the financing system of insurance. In the PRC, this issue is reduced due to the recent push for high and expanding enrollment of Chinese citizens into either the Employee BMI or the Residents BMI (non-working) programs, with an enrollment rate of over 95% of total population (1.35 billion people) (Yi B. , 2021).

Moral Hazard. Moral hazard is defined by Rose-Ackerman and Tan as when insured patients demand excessive care because they do not have to bear the cost of the treatment. Though there is literature examining the predominance of this issue, it may be a contributing factor increasing the willingness of patients to be prescribed more expensive drugs or to increase the number of visits made to inpatient care per year.

Bribery Schemes. Bribery schemes exist in multiple areas in the Chinese pharmaceutical system. We will discuss the interaction with pharmaceutical MNCs**,** the tendering and bidding system, and academic sponsorship.

Practices that have been defined as corruption on the part of pharmaceutical MNCs are commonly used to promote a firm's products. These strategies include seeking to influence practitioners to authenticate, approve, prescribe, and promote their products; fund medical research; shape medical knowledge and practice; support patient advocacy organizations; and marketing (David-Barrett, Yakis-Douglas, Moss-Cowan, & Nguyen, 2017). Such practices are also present in the United States, as previously mentioned, such as funding gifting trips, guest speaking, and heavy academic journal marketing efforts oriented at practitioners. Most pharmaceutical MNCs see the Chinese market as an extensive opportunity to grow their business and are therefore enthusiastic to enter and maintain a growing market share. One such notable example comes from the GSK. In 2013, GSK was a found guilty and fined for bribing officials, hospital employees, and doctors to promote or sell GSK drugs, often at a sizable price increase (Hvistendahl, 2013; 南方都市报, 2014). This form of bribery is often used as a means to establish and maintain favorable relationships with purchasers and doctors, ensuring favorable competitive positioning (Rose-Ackerman, 2014). These firms may use an intermediary to avoid the visibility and potential liability of such illegal interactions.

The tendering and bidding system was widely regarded as enabling potential corruption in the purchasing decision process. Though we outlined the faults of the tendering and bidding system under the pricing policy section, we can summarize it as provincial negotiations of price with no nationally standardized selection criteria, allowing opportunity for corporations to influence the process. Its replacement, the reference pricing system, promises to reduce potential opportunity for corrupt practices and emphasize off-patent generics firms operating in an atomistic market.

Information asymmetry extends beyond patients to the practitioners, who also operate with limited information of the upstream operations of pharmaceutical companies. Physicians rely greatly on personal reputation (Rose-Ackerman, 2014) for advancement, and thus are liable to be sponsored in academic studies, which will improve the physician's reputation through papers published while promoting a specific firm's products.

Strategic Approach

The government of the People's Republic of China is currently pursuing several strategic initiatives with the goal of advancing industry and international position of both its industry and economy. By attempting to advance the industry and the role of Chinese firms on the international stage, these strategic initiatives have a tangible impact on local pharmaceutical development. When comparing U.S. policy to Chinese policy, a stronger and more obvious central strategy is visible in the PRC's policy. The three initiatives discussed in this paper include Healthy China 2030, Made in China 2025 and the Belt and Road Initiative.

Healthy China 2030. The medium- to long-term Healthy China 2030 policy focuses on the improvement of the health of Chinese citizens by increasing health service capacity and capabilities, controlling health risk factors, enlarging the health industry, and improving the health service industry (Tan, Liu, & Shao, 2017). As it pertains to the support and development of the pharmaceutical industry, the Healthy China 2030 policy (健康中国 2030) seeks to emphasize the importance of technical pharmaceutical innovation, particularly emphasizing patented medicine, pharmaceutical preparations, high-end medical equipment and other areas. These areas should be developed with the aim of "vigorously developing" biologics, new chemical drugs, high-quality TCM, high performance medical devices, new materials and pharmaceutical equipment's (Central Committee of the Communist Party of China; State Council of the People's Republic of China, 2016). It additionally advocates for drug quality improvements and increased access to healthcare, bringing opportunity and support to the pharmaceutical industry.

The impact this policy has on the pharmaceutical industry is not to be understated. It represents a strategic intensifying of the "Reform of the Medical and Health Sectors," (刘会, 2017) oriented towards improving access to medicine domestically, and increasing industry competitiveness internationally.

Made in China 2025. In recent years, shifts in the economic competitive position of China have led to a redirection of strategy. Though a global leader in manufacturing operations, and an economic power by itself, China is no longer the lowest-cost labor market, losing that title to Southeast Asian countries such as Vietnam, Cambodia, and Laos. As of the start of this initiative, it was also not the strongest player in high-tech fields, falling behind the U.S., Germany, and Japan (Li L. , 2018). Given this position, as well as tightening access to resources, Made in China 2025 (中国制造 2025) was launched to advance China's position in the value chain and shift to a position as a world-class innovative power – a shift from labor intensive manufacturing to knowledge intensive manufacturing (State Council of the People's Republic of China, 2015). Relying on local-level implementation at the provincial-government level (Ma, et al., 2018), the plan is targeted at endogenous innovation (innovation based on internal forces like local human capital, local knowledge, etc.), achieving self-sufficiency, and reducing the Chinese economy's dependence on foreign nations for advanced technology (Honcharenko, 2020), ultimately hoping to be a front-runner in the integration of the fourth industrial revolution (technological revolution) into existing and developing infrastructure (Li L. , 2018), with one of the prioritized industries being biological medicine and high-end medical equipment.

However, the scope of Made in China 2025 is far more extensive than the 10-year developmental project. Phase One (2015-2025) has set the Made In China 2025 initiative to "join

the ranks of great powers of manufacturing;" Phase Two (2025-2035) seeks to substantially increase and lead in innovative capabilities; Phase Three (2035-2049) aims to consolidate its position as the dominant manufacturing industry, and establish the leading position in global technological and industrial systems (State Council of the People's Republic of China, 2015).

A comparison of the local implementation policies from Guangdong, Jiangsu, and Hubei (*Notice of the Guangdong Provincial People's Government on Implementing 'Made in China 2025*,' *Notice on 'Made in China 20205' Jiangsu Action Scheme*, and *Notice on '1+X Action Scheme or Implementation Plan of Hubei Province for 'Made in China 2025'* among subsequent policies in each of the three provinces), identified unifying tactics for achieving the goals of the Made in China 2025 plan, including government system reform, simplifying administration, accelerated finance and tax support and associated policies, growing middle- and large-scale firms, developing small-scale firms, providence intelligence support, ensuring market-wide fair play (Ma, et al., 2018) as well as increasing interaction with the external environment (Honcharenko, 2020). With this being said, and with biological medicine and high-end medical equipment as one of the major development areas, domestic pharmaceuticals stand to benefit from this initiative (Fitch Solutions, 2020).

The Belt and Road Initiative. *The Silk Road Economic Belt and the 21st Century Maritime Silk Road (丝绸之路经济带和 21 世纪海上丝绸之路)* (BRI), introduced in 2013 by Chairman Xi, is one of the largest infrastructure projects undertaken in the world. In 2015, the project began implementation via. the publishing of *Vision and Actions on Jointly Building the Silk Road Economic Belt and the 21st Century Maritime Silk Road*. By 2016, 38 large-scale transportation infrastructure projects had been carried out in 26 countries by Chinese firms, totaling USD 51.1 bn (Thürer, et al., 2020), with Morgan Stanley predicting that total investment could reach USD 1.2-1.3 trillion by 2027 (Morgan Stanley, 2022). Such large outward FDI flows have lasting impacts, specifically on those industries with high R&D intensity – such firms are more likely to strategically conduct FDI as a means to obtain advanced technology, acquire internationally competitive brands and attract human capital. Those in high R&D industries do not necessarily have a competitive advantage as compared to low R&D intensity industries, thus the use of FDI, mergers and acquisitions, or partnership is a strategic move allowing one to catch up with industry leaders, i.e. a means of knowledge acquisition and competitive growth (Lu, Liu, & Wang, 2011).

Thus, it is no surprise that the PRC is using the pharmaceutical industry as an industry whose participation in and use of the BRI is vital. The 2016 issuance of *The Guiding Opinions of the General Office of the State Council on Promoting the Sound Development of the Pharmaceutical Industry* (State Council of the People's Republic of China, 2016), a document guiding the strategic development of this industry, specifically indicates that the pharmaceutical industry should "implement BRI initiative, keep in mind the global allocation of resources, and speed up the outward pace of movement," using diverse forms cooperation, promotion and investment to conduct M&A. With this outward development, FDI, and expansion, there is much government-supported opportunity to create new sales channels and develop Chinese brands abroad (Honcharenko, 2020).

Market and Competitive Environment

Market Size and Growth

Due to the support from the government, initiatives, general economic growth, an aging population, and global R&D cost trends, the Chinese pharmaceutical industry's output has grown from a mere 2.5% in 1995 to 18.3% in 2010, becoming the world's second largest pharmaceutical market in 2017 (Ni, et al., 2017).

The Chinese pharmaceutical industry was measured by Fitch Solution's Industry Analysis as being valued at 149.8 bn USD in 2019, with projections putting the 2014 market at over 176.1 bn USD, constituting a 3.3% annual growth of value, calculated in USD terms. By 2029, drug sales are expected to reach 233.0 bn USD. In 2019, pharmaceutical sales were about 1.05% of GDP, as compared to 1.72% in the USA and a 1.5% global average (Fitch Solutions, 2020). Historically, the Chinese pharmaceutical industry has developed at a very quick pace – from 2006 to 2010, the industry experienced an average growth rate of 23.9%, the fastest pharmaceutical growth rate at the time (Liu & Racherla, 2019), becoming the second largest pharmaceutical market in the world by 2017, following the U.S. market (valued at 370.6 bn USD) (Fitch Solutions, 2020).

Per segment size, as analyzed by Fitch Solutions, found the Patented Drug segment has reached 36.7 bn USD in 2019, with projections to reach 43.1 bn by 2024. The Generic Drug segment reached 95.1 bn USD in 2019 and is predicted to reach 111.8 bn by 2024. The OTC (Over-the-counter) segment reached 18bn USD in 2019 and is projected to reach 21.2 bn by 2024 (Figure 51) (Fitch Solutions, 2020).

Due to its large size and pace of development over the past 20 years, the Chinese market has become a strategic priority for many international pharmaceutical firms - with all 20 top multinational pharmaceutical corporations setting up wholly or partially owned operations in China, including GSK, Pfizer, Novo Nordisk, AstraZeneca, Merck, and Roche all establishing R&D centers (respectively: 2007, 2005, 2002, 2007, 2011, 2004).

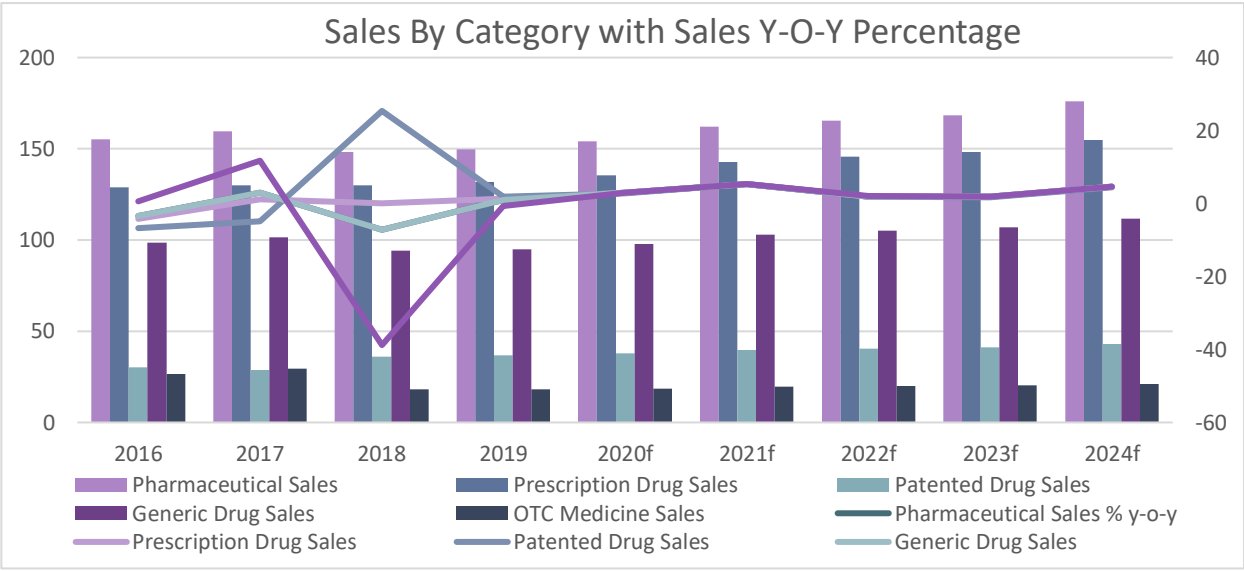


Figure 51 Sales By Category with Sales y-o-y Percentage, from FitchSolutions

Figure 52 Annual growth rate and proportion of added value of pharmaceutical industry, from the Ministry of Industry and Information. Blue Line represents "National Industrial Value-Added Growth Rate Above Designated Size." Orange Line represents "Growth Rate of Value-Added of the Pharmaceutical Industry"

Market Organization and Composition

Market Organization. Though growing in its size and power, the Chinese pharmaceutical industry is hindered by compositional factors that make international competition difficult and prevent continued development without alteration. The industry structure is well document as being scattered fragmented, and composed of many small firms (小、多、散、乱) (张晓燕 & 倪春霞, 2017; State Council of the People's Republic of China, 2016), even being criticized by the government in *Guiding Opinions of the General Office of the State Council on the Promoting of the Sound Development Of the Medical Industry* as an "irrational" industry structure with "irregular market order" (State Council of the People's Republic of China, 2016), ultimately weakening its profitability and innovative potential (马征, 2016).

In the pharmaceutical distribution sector, the Chinese market had over 13,000 firms in 2015, with the largest three firms in the sector having a total market share of only 25% of the market. This is compared to the top three firms in the U.S. having a total market share around 80%, and in Southeast Asia (Malaysia, Thailand, Philippines) of about 60% (Barbieri, Huang, Pi, & Tassinari, 2017). When compared to 2012, the distribution sector seems to be growing more concentrated with a total of 14,000 firms (Ni, et al., 2017) – a trend which displays that distributors are pushing to enter downstream activities to increase vertical integration and consolidate the supply chain.

Likewise, in the pharmaceutical manufacturing sector, the China Statistical Yearbook reflects the "Manufacture of Medicines" sector to contain 6,387 individual firms in 2012 (National Bureau of Statistics of China, 2014) (though notably at variance with Ni et al.'s reported 4,500 firms from the same source, it fits Zhang and Ni's estimate of 7000+ medicine

manufacturers for the 2005-2011 period (张晓燕 & 倪春霞, 2017) and 7,581 firms in 2018 (National Bureau of Statistics of China, 2020)). The pharmaceutical manufacturing sector has a CR_5 (concentration ratio of the largest 5 firms) of 8.82%. Because this is under 10%, this signifies the pharmaceutical manufacturing sector is characterized by near perfect competition (for reference, China had a CR_{20} = 25.64, while the USA's CR_{20} = 71.8%) (张晓燕 & 倪春霞, 2017). Of these pharmaceutical manufacturers, Ni et al. reports that 70% are small-scale operations with fewer than 300 employees, and less than 3 million USD in operating revenue (Figure 54) (Ni, et al., 2017).

IBISWorld provides a comparison between two market concentration indices of the Chinese pharmaceutical manufacturing sector and the United States' branded and generic manufacturing sectors. IBISWorld estimates the Chinese market as composed of 20% major players and 80% minor players (a measure parallel to other findings citing the relatively dispersed nature of the sector), distinctly at a variance with the United States' Branded manufacturing sector, which was composed of 75% major players and 15% minor players. In fact, the Chinese pharmaceutical manufacturing sector greatly resembled the United States' generic manufacturing sector, which had roughly 15% major players and 85% minor players. Though the Chinese market was not segmented to branded and generic markets, these measurements conducted by IBISWorld display the degree of industry decentralization, and the prominence of "minor players" in Chinese pharmaceutical manufacturing (Chen S. , 2021).

Due to the small scale of these operations, they are often low value-added operations such as generics manufacturing and packaging rather than the capital and resource intensive R&D and other high value-added activities that are better suited to creating and maintaining competitive advantage. Such a focus on non-innovative and homogeneous competition via generic drug manufacturing leads to an over-capacity in the generic drugs, which excessively increases competition to a level nonconductive to profit. In fact, many of these manufacturers were limited to slim to negative profit margins (Ni, et al., 2017). Under such intensive homogenous competition a vicious cycle is created – a "low-end lock in" phenomenon in which the adverse effects of such homogenous competition creates limiting effects through which an industry segment is contained to low-value added operations (韩兵, 刘芳名, & 匡海波, 2021), adding large barriers for innovative or differentiated competition needed for industry growth and development (马征, 2016).

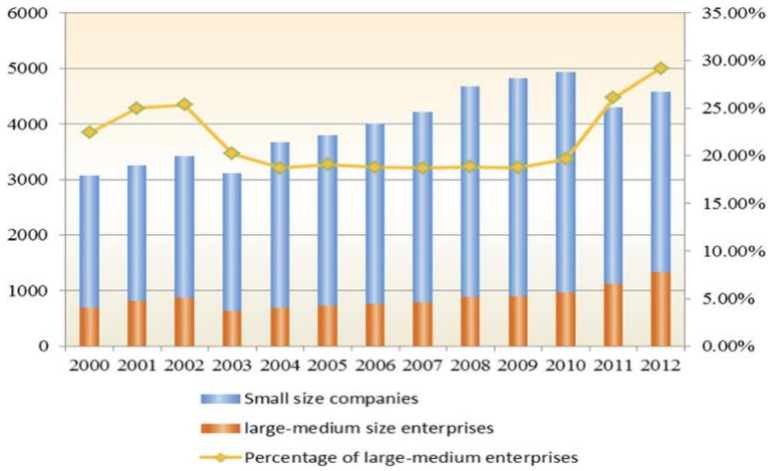


Figure 53 Number of Pharmaceutical Manufacture Firms and Percentage of Large-Medium Firms in China. Source: Ni et al. Data: China High-Tech Industry Statistical Yearbook

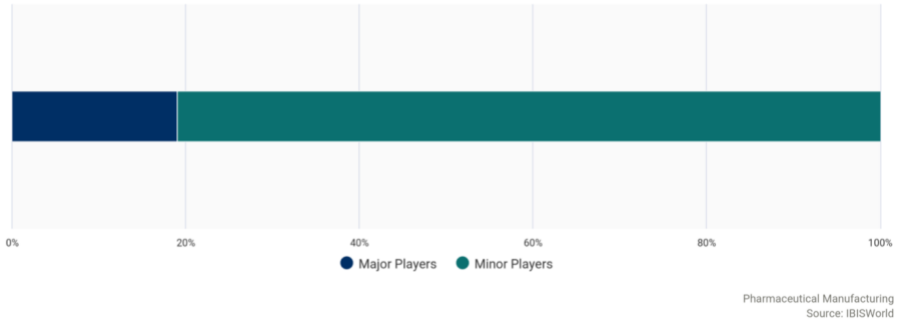


Figure 54 Chinese Pharmaceutical Manufacturing Market Concentration, from Chen, S.

Market Reorganization. As an identified issue, both the government and the industry itself are pushing for reorganization of the market space to increase the ability of the Chinese pharmaceutical industry to innovate and compete outside of the homogeneous generics and API manufacturing segments. There are two interconnected facets through which the industry is attempting to consolidate: mergers and acquisitions (M&A) and internationalization.

Mergers and acquisitions are the key tool through which the government encourages the industry to change its organizational structure from very dispersed with many small, homologous firms with limited access to capital and limited R&D ability into an industry with a greater degree of concentration that is more conductive to differentiated competition and innovation (Barbieri, Huang, Pi, & Tassinari, 2017). Some scholars have even directly tied growth of M&A in the Chinese pharmaceutical industry advancement with improvements in capital access and market efficiency (谢静妍, 2014). M&As serve to allow firms greater access to resource and brands which will not only lead to income and sales growth, but more importantly, will lead firms to expand their size, increase their production volume and capabilities, decrease and better distribute fixed costs, diversify product offerings to reduce firm risk, and gain greater market share (谢静妍, 2014) – i.e. begin to shift towards greater economies of scale (Figure 56).

Through policy and economic pressure for M&As, the government aims to create "national champions able to compete at the global level in the supply of pharmaceutical

products. (Barbieri, Huang, Pi, & Tassinari, 2017)" It should be noted that the pressure is not exclusively from government policy. In fact, at the global level, the pharmaceutical industry is quite active in M&As, partly due to the challenges intrinsic to the industry: enormous sunk costs and low R&A/drug pipeline success rates. Thus, by participating in M&A at a relatively higher level in comparison to other industries, firms hope to synergistically work with the strengths of small and innovative firms as a grassroots source for potential medications, theoretically reducing the R&D sunk cost while increasing the pharmaceutical firm's drug pipeline (Barbieri, Huang, Pi, & Tassinari, 2017).

Since policies to encourage consolidation of power in high-technology and strategic emerging sectors began in 2006, M&As in the pharmaceutical industry have been encourage to pursue higher R&D (刘会, 2017). With the exception of 2019, which Deloitte assigns to a combination between a slower GDP growth rate and unfavorable international conditions (particularly the US/China trade war and the EU's FDI framework changes) (Deloitte, 2020), M&A volume has been steadily increasing over time (Figure 57).

Note: The above deal count includes 271 deals with undisclosed deal value.
Source: MergerMarket, Deloitte analysis

Figure 55 Total Deal Value and Deal Count of China Life Sciences and Health Care M&A Transactions, via. Deloitte

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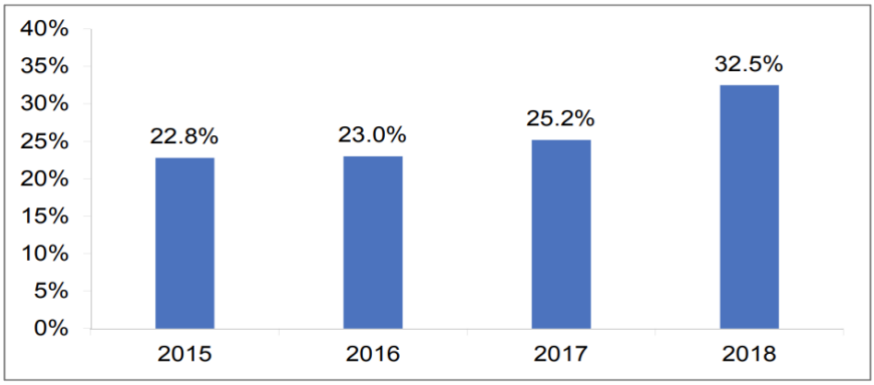
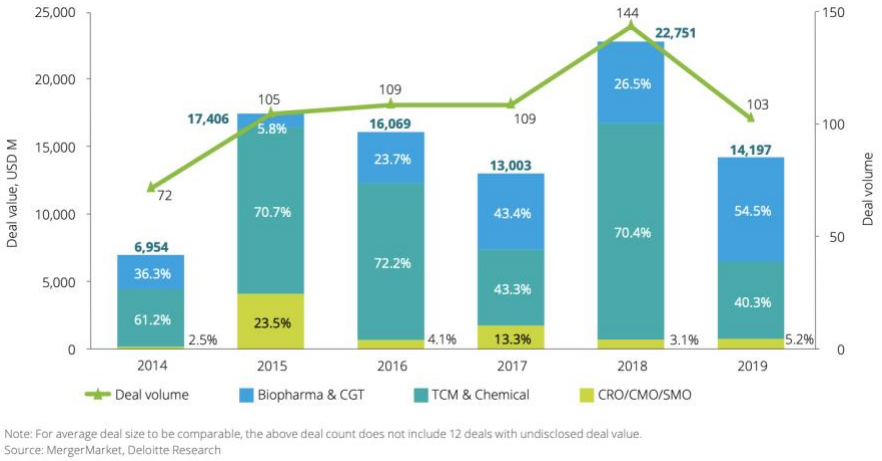


数据来源：中国医药工业信息中心

Figure 56 Concentration of main business income of the top 100 companies, years 2015-2018, from the Ministry of Industry and Information



Note: For average deal size to be comparable, the above deal count does not include 12 deals with undisclosed deal value.
Source: MergerMarket, Deloitte Research

Figure 57 Drug R&D and Manufacturing Companies M&A Trends, via. Deloitte

Current government policy encourages M&As in multiple ways. First, the government uses tax incentives and investment in research as incentives to encourage firms to shift to a more R&D-centric model, as displayed through the 12th and 13th Four Year Plans (People's Republic of China, 2016; People's Republic of China, 2011). It is critical to note that in the current low-levels of R&D and innovative capability are directly related to the pure-competitive, homogeneous composition of the industry. In prompting R&D, firms are incentivized to find ways to increase R&D capability, e.g., choosing to merge or acquire research-based firms to achieve these benefits.

Yet another policy pushing for a shift towards R&D, and consequently an increase in M&As, is the new shift to the volume-based pricing system for generic drugs. This new system puts large price pressure on the many generic manufacturers, particularly small- and medium-sized generic manufacturers who do not have the resources or scale to offer their products at competitive bid-price. This pressure has resulted in these small- to medium-sized generics manufacturers either being acquired by larger pharmaceutical companies, increasing their production capacity; or making these small- medium-firms strengthening their R&D capability and innovative drug portfolio by acquiring or merging with firms who already possess these capabilities (Deloitte, 2020).

Other policies seek to encourage M&A through means other than R&D incentives. GMP standardizations (both old and new) set criteria for participating in the manufacturing of pharmaceuticals. Barberi asserts that this policy's criteria "imply that only those firms qualified as GMP are allowed to produce," and that without such certification, the firm can "no longer operate." Barberi reports that the establishment of this implicit prerequisite for production caused small and medium sized firms to seek to merge with firms holding a GMP certification, ensuring the ability to continue production operations and gain faster market access (Barbieri, Huang, Pi, & Tassinari, 2017).

Despite the benefits of M&A to an industry characterized by many generic manufactures participating in homogenous competition, a nuanced policy approach must be adopted to ensure a beneficial result to industry from extensive M&A activity. Though they support M&As as a way to alter industry composition from largely generics with low gross profit margins and fierce competition to one characterized by innovative medicine, Xie argues "rushed M&A reorganization is actually not a good idea," due to the obstacles M&As bring to the newly merged organization, including having to merge two difference company cultures, two different

management and personnel structures, two different companies' finances, as well as their intangibles (licensing permits, GMP certifications, registration, etc.), all of which slow down the merging process and prevent continuous and rushed mergers at an industry-scale (谢静妍, 2014). Xie also proposes that, in some cases, the acquired firm may have an inflated or too high expected value of acquisition, causing the acquirer to encounter capital turnover difficulties, as in the case of China Resources Sanjiu (华润三九), Garden Pharmaceutical (花园药业), and Dongsheng Group (东盛集团) (谢静妍, 2014). Barberi et al. also proposes the *type* of merger as a critical factor in whether M&As benefit or harm the competitiveness of the Chinese pharmaceutical industry. Their data find that if horizontal mergers are occurring in a manner in which *large* firms increase their assets, sector performance will fall. However, if the M&A happens such that the M&A increases the number of large firms in the pharmaceuticals market, the sector performance increases (Barbieri, Huang, Pi, & Tassinari, 2017).

Through this nuanced view we understand that M&A is a strong and effective tool being used in China to consolidate industry power and allow greater differentiation among firms, but these effects are only realized if the proper pace is adopted (i.e. not pressuring M&As at too fast of a pace), the acquired firms are properly valued, and the M&A increases the *median size* of firms in the industry.

Internationalization is a large driver of industry growth, with incentives such as extended market access, market diversification, higher margins, and survival in a competitive environment as some of the greatest motivations (Dixit & Yadav, 2015). The PRC and its pharmaceutical industry are no exception to these. However, as an emerging economy, the pharmaceutical industry has traditionally had low exposure to the differentiation and competitive strategies used by pharmaceutical MNCs, rather than sticking to the traditional production of generics of APIs. The industry's current international movements firmly place it in the "second wave" of internationalization, in which emerging markets' MNCs are entering the world stage (Li, Lian, & Zhao, 2013).

As a member of the "second wave," more advanced strategies are necessary to enter an already competent, crowded, and competitive international market. Luo and Tung argue that these Emerging Market MNCs use a "springboard" behavior, meaning they overcome the latecomer disadvantage through a series of "aggressive, risk-taking measures," such as aggressive M&A activity, to gain tacit knowledge (Luo & Tung, 2007).

Primary tools used by Chinese pharmaceutical firms to internationalize include moving up the supply chain from a producer of generics/APIs; international certification and collaboration through standards such as the GMP; building international-scale capacity via. outsourcing functions for which firms do not have initial capability, i.e. contract research organizations (CRO) can be used to do research on behalf of the firm (ex. WuXi AppTec and CRO HD Biosciences), contract manufacture organization (CMO) firms may build capability in specific processes such as running clinical trials, API production, or preparation production (ex. Shandong Xinhua); and overseas M&As or listing (through which Chinese pharmaceutical firms attempt to gain access to foreign capital markets) may help to internationalize firms (Li, Lian, & Zhao, 2013).

Chinese industrial policy firmly pushes for the internationalization of the pharmaceutical industry, with a specific emphasis on M&A in its current-/late-stage of internationalization (as compared to serving as API manufacturers or other CMO roles) because, as Yu Zhang finds, cross-border acquisitions by Chinese firms have "significantly improved the acquirers'

innovation performance" by bringing scarce and valuable tacit knowledge to the acquiring firm – serving as a way to remove the latecomer disadvantage by accessing, studying, and absorbing innovative capabilities (Zhang, Wu, Zhang, & Lyu, 2018).

Thus, the separation of an internationalization strategy view from mergers and acquisitions serves to distinguish two main differences in motivations between domestic M&A and international M&A conducted by Chinese pharmaceutical firms. While domestic firms tend to conduct M&A as a strategy to gain capital resources, competitive strength, and begin conducting R&D at a level distinguished from the homogeneous industry composition, firms conducting outward international M&A are focused on gaining tacit knowledge from companies who may have more experience in the international or R&D arena.

Industry Focus and Research and Development Focus

Chinese pharmaceutical manufacturers have a large presence in low value-added activities. Its largest presence by revenue is in the field of pharmaceutical preparations manufacturing. As defined by the U.S. Department of Labor's Occupational Safety and Health Administration, pharmaceutical preparations firms are those who manufacture and process drugs for human use, with the end-product of these firms being drugs in a form ready for consumption (United States Department of Labor). Also notably active is the pharmaceutical ingredient (API) manufacturing segment. The U.S. FDA defines API as "any substance or mixture of substances intended to be used in the manufacturing of a drug product and that, when used in the production of a drug, becomes an active ingredient in the drug product," meaning that API is one of the necessary upstream materials needed for the production of pharmaceutical preparations (Food and Drug Administration). Though not China's second largest revenue stream, the API segment is notable due to its large presence on the world stage. Chinese API production accounts for 40% of total global production as found by the United Kingdom's Medicines and Healthcare Products Regulatory Agency (MHRA) in 2017 (Medicines and Healthcare Products Regulatory Agency, 2017).

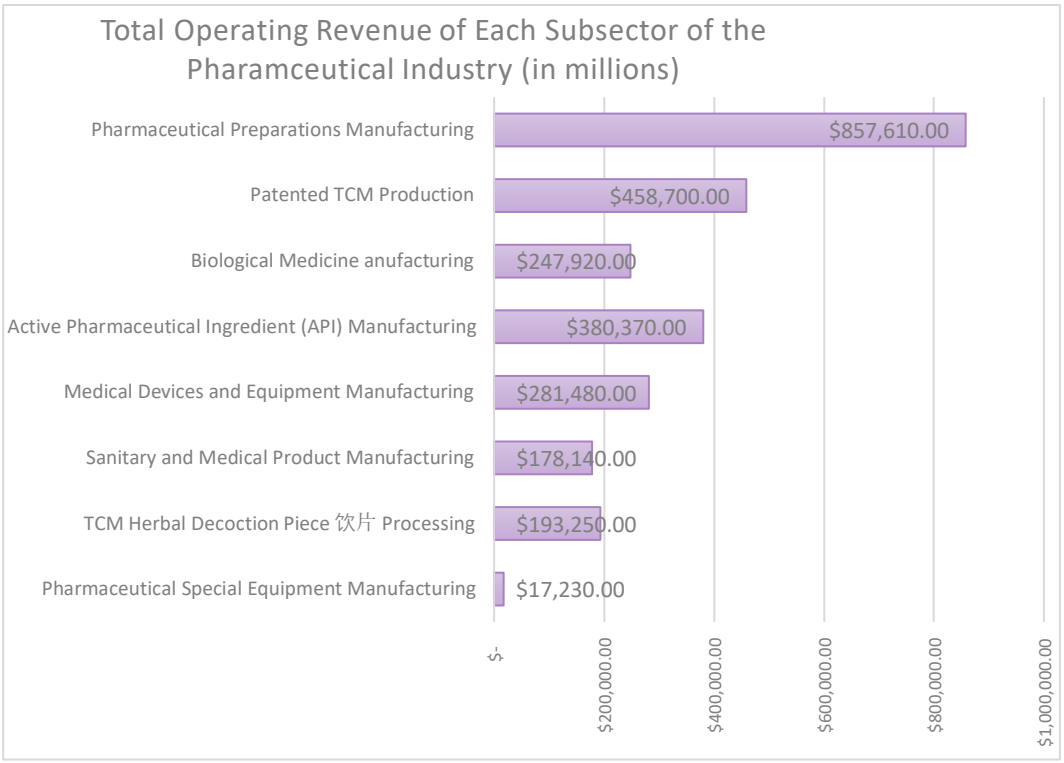


Figure 58 Total Operating Revenue of Each Subsector of the Pharmaceutical Industry, data from the Ministry of Industry and Information

As a separate measure of the focus of the Chinese pharmaceutical industry, cost structure provides a measure to help comparatively understand the financial inflow to R&D activity, and thereby the importance placed on R&D (or other functions) and the macro-level. When compared to the same measures from the U.S. industry (Figures 35-38), purchasing takes up a larger share of the cost structure, with the effect being that the investment in R&D and "other costs" in general have a far reduced role (Figure 59 and Figure 60) (Chen S. , 2021).

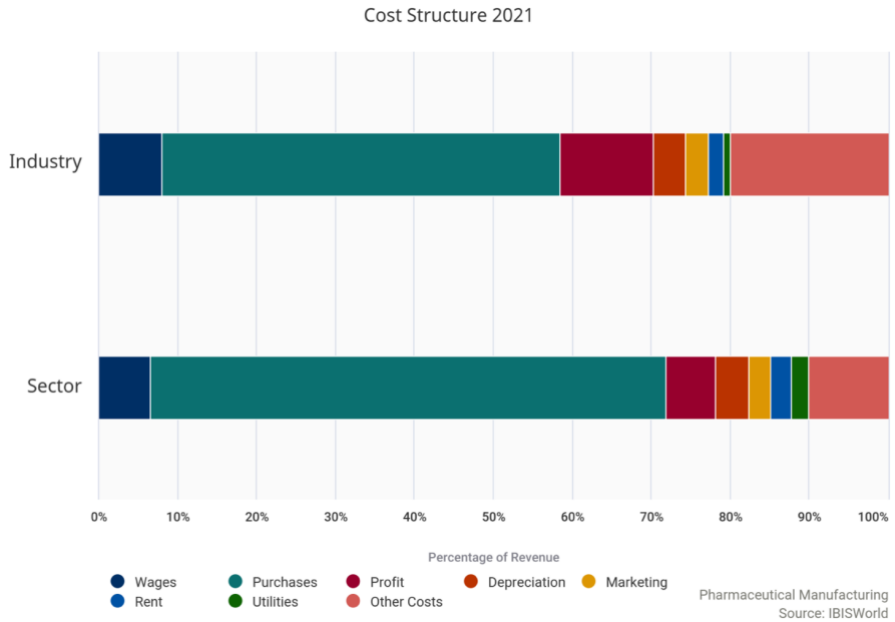


Figure 59 Chinese Pharmaceutical Manufacturing Cost Structure, from Chen, S.

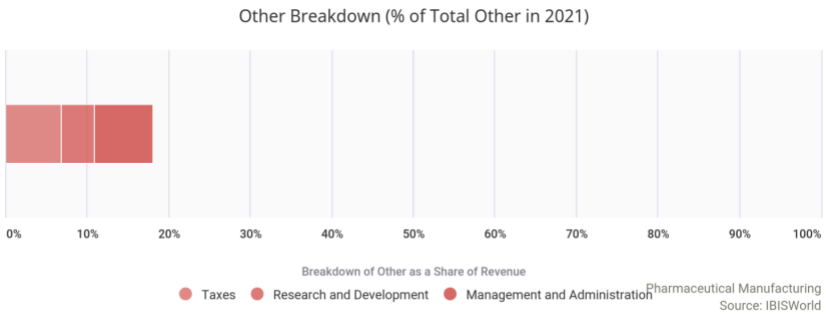


Figure 60 Chinese Pharmaceutical Manufacturing Cost Structure, "Other Costs" Breakdown, from Chen, S.

With an understanding of the current emphasis of the Chinese pharmaceutical market, it is now relevant to look into the drug-pipeline to understand the direction of R&D, as R&D is a critical aspect for the sustainability and growth of any pharmaceutical industry (Jiang & Luan, 2018).

The Chinese pharmaceutical market, as compared to those of other countries, is characterized by weak pharmaceutical R&D in terms of proportional investment, a low level of innovation, and a comparatively low volume of novel drugs – in fact, the market continues to have a high concentration of generic drugs with as many as 97% of drug production coming from generic drug manufacturing (赵娜娜 & 孙利华, 2018). Some factors leading to this low R&D/innovation include increasing regulatory oversight, continued development of science and technology, increasing expenditure for environmental conservation, increasing levels of competition (樊玉录, 2018), the industry structure, R&D professional amount and quality, and R&D capital investment (赵娜娜 & 孙利华, 2018). When examining the capital funding of pharmaceutical R&D activities, the strength of China's capital funding was measured as 1-2% in 2016, compared to a global average of 15-18% (赵娜娜 & 孙利华, 2018), meaning that significantly less funding is going to R&D activities in China than outside China, potentially due to the scattered and homogeneous composition of the industry which minimizes the size and capital power per firm, resulting in less capital available for R&D or other differentiated activities. In a scattered and fragmented industry made of many small firms (张晓燕 & 倪春霞, 2017; 赵娜娜 & 孙利华, 2018; State Council of the People's Republic of China, 2016) producing homogeneous generic drugs, the profitability and innovative ability of the sector is weakened (马征, 2016); in other words, in a market characterized to such a large degree by perfect competition, the ability to conduct R&D is limited. Zhao and Sun additionally found that the number of R&D professionals lagged behind that of developed countries: in 2014, the pharmaceutical manufacturing industry had 2,160,000 R&D professionals including 180,000 R&D personnel (8% of R&D professionals). This was approximately 30% of the number of R&D professionals in developed countries – meaning China has almost a quarter fewer R&D personnel (赵娜娜 & 孙利华, 2018).

As the government and the industry push for a transition to a more innovation-driven economy, industrial policies such as the "Made in China 2025" policy series, ongoing changes to the patent system, as well as increasing use of differentiation as a competitive advantage, R&D has increasingly become a focus. Here, it should be noted that the impact of industrial policies like Made in China 2025 and the Belt and Road Initiative on targeted industries' development and innovation is a debated subject, with some finding industrial policy can ease the high-risk

and high-input nature of related investment (via. subsidies, tax deductions, credit enhancement etc.), while others find that industrial policy may have a "significant negative moderate effect" on the innovative performance due to excessive incentives and preference leading to government "rent-seeking" behavior (Zhang, Wu, Zhang, & Lyu, 2018). Regardless of negative or positive impact from its industrial policies, in 2015 China accounted for 18% of worldwide R&D across all industries (Wu, Zhang, & Yang, 2015) – with pharmaceuticals, being one of the government's pillar industries, particularly encouraged to conduct R&D.

A changing environment is a contributing factor to the slow increase of R&D output in this industry. Figure 61 displays the China Drug Innovation Index (CII) for biopharmaceutical innovation, an index maintained by McKinsey & Company based on a poll of 129 industry experts. It displays that, since 2016, the innovation environment for Chinese biopharmaceuticals has had an all-around increase, lagging approximately two points (at 6/10) behind the U.S. (at 8/10) in 2020 as opposed to 4 points in 2016 (at 4/10). The change with the most significant impact on the industry innovation prospects has been a change in the regulatory environment, including staff size increase for the Center for Drug Evaluation and a streamlining of approval procedures (Han, Le Deu, Zhang, & Zhou, 2021). Though the index is crafted specifically toward the biopharmaceutical subsector, the essential factors ascribed by McKinsey & Company (including joining the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use, National Medical Products Administration approval streamlining, updates to the NRDL, tacit information gain via. CRO and CMO infrastructure, and a surge in cross-border partnerships) are also applicable to the broader pharmaceutical industry.

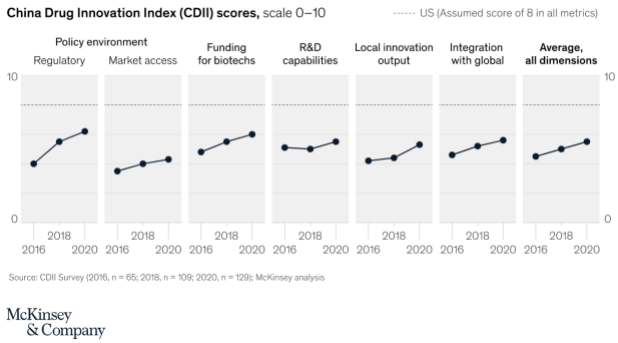


Figure 61 China Drug Innovation Index (CDII) scores for Biopharma Innovation, from McKinsey & Company

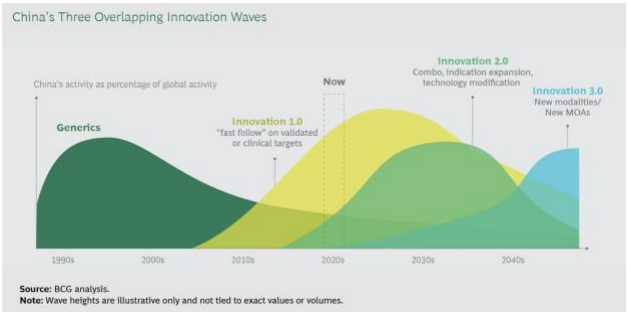


Figure 62 China's Three Overlapping Innovation Waves, via. Boston consulting Group

In an environment in which government processes are being smoothened and market concentration is slowly increasing through the use of M&As, the innovation model and orientation are changing. As Boston Consulting Group describes them, in the Innovation 1.0 phase, pharmaceuticals aimed to develop new molecules on already validated or late-stage clinical targets or therapies; in Innovation 2.0, pharmaceuticals saw greater original indication expansion, combo therapies, and novel antibodies; followed by Innovation 3.0, characterized by advanced and novel technologies and mechanisms of actions (currently mostly in cell therapies and gene editing fields) (Figure 62) (Wong, Wu, Xie, & Vaidyanathan, 2020).

With increasing emphasis and expenditure on R&D, it is vital to understand the strategic direction pharmaceutical companies are taking to increase their ability to both differentiate from domestic and international competitors, and to address the specific needs of the local consumer

market. In her Master's Thesis on Chinese novel drug R&D, Yulu Fan dissects new drug registration applications submitted to the CFDA (now MNPA) on two levels: the number of new class I drugs by type (type 1, 1.1, and 1.2 chemical drugs; type 1 biologics, and type 1 TCMs [as categorized by the 2007 publication of Measures for the Administration of Drug Registration]) and by the therapeutic field subclass (樊玉录, 2018). Such classification produces both a broad understanding of drug type being pursued by the pharmaceutical industry (chemical, biologics, TCM), and a narrow understanding of specific therapeutic fields being focused on by the industry. Figure 63 gives a preliminary understanding of the general direction of research and drug development: the industry's development is largely focused on chemical drugs (with such drugs taking up 60% of new drug applications from 2005 to 2016), followed by biological drugs with 34%, and TCMs at 6%.

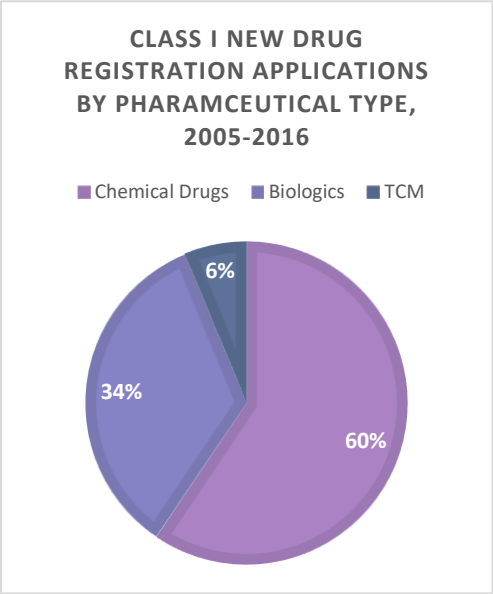


Figure 63 Class I New Drug Registration Applications 2005-2016 as identified by CFDA, data from Yulu Fan

Following this broad analysis, Fan subdivides these segments into their respective therapeutic segments to lend to an understanding of the fields and directions of the pharmaceutical industry's research and development.

From these CFDA (MNPA) drug registration records, anti-tumor drugs have a prominent position in the registration of chemical pharmaceuticals and biologics. In chemical pharmaceuticals, anti-tumor research and registration is far greater than the other 10 classifications. Based on an 11-year sum, digestive system drugs are the second strongest classification with 50 registrations (compared to 197 for anti-tumor). This compares to 44 anti-infective drug registrations, 34 endocrine and metabolic regulation drugs, 26 rheumatic disease and immune drugs, 25 nervous system drugs, 14 mental disorder drugs, etc. (Figure 64) (whole dataset available in additional resources Figure 79). Under the biologics classification, anti-infective drugs have held a long-term emphasis and have the period's greatest number of registrations at 89 new drugs. However, the emphasis on anti-infectives began decreasing after 2013, with anti-tumor drugs gaining a dominant position by 2016. Based on the 11-year sum totals, anti-tumor drugs follow anti-infectives with 62 registrations, immunomodulators at 47, blood and hematopoietic system drugs at 21, and endocrine and metabolic regulatory drugs at 20 registrations (Figure 65) (whole dataset available in additional resources Figure 80). Finally,

TCM, making up 6% of total new drug registrations from 2005-2016, seems to be far more dispersed in terms of development orientation – in part due to the low volume of new drugs being registered. Under the TCM classification, nervous system drugs have the greatest emphasis early in the examined period with a total of 19 registrations. Anti-infectives follow at 6 drug registrations. Other subclasses only have 1 or 2 new drug registrations (Figure 66) (whole dataset available in additional resources Figure 81).

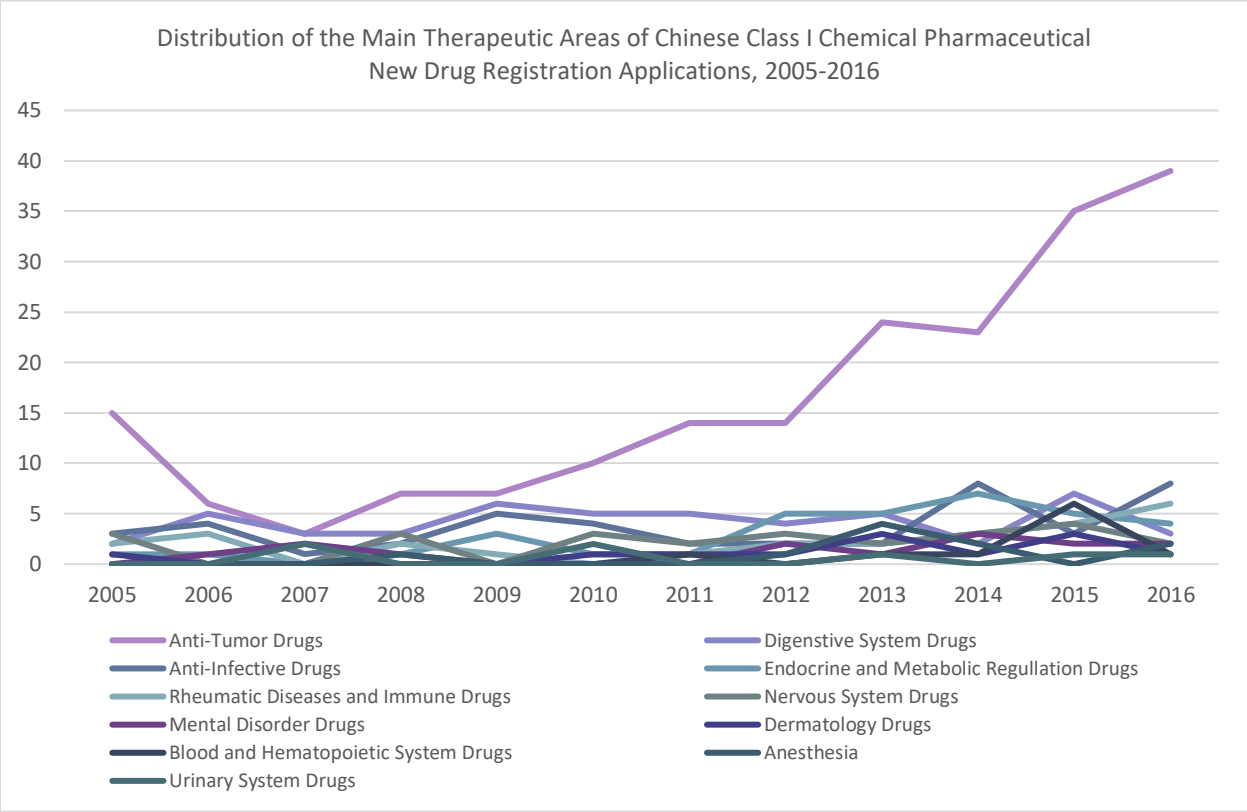


Figure 64 Distribution of the Main Therapeutic Areas of Chinese Class I Chemical Pharmaceutical New Drug Registration Applications, 2005-2016; data from YuLu Fan

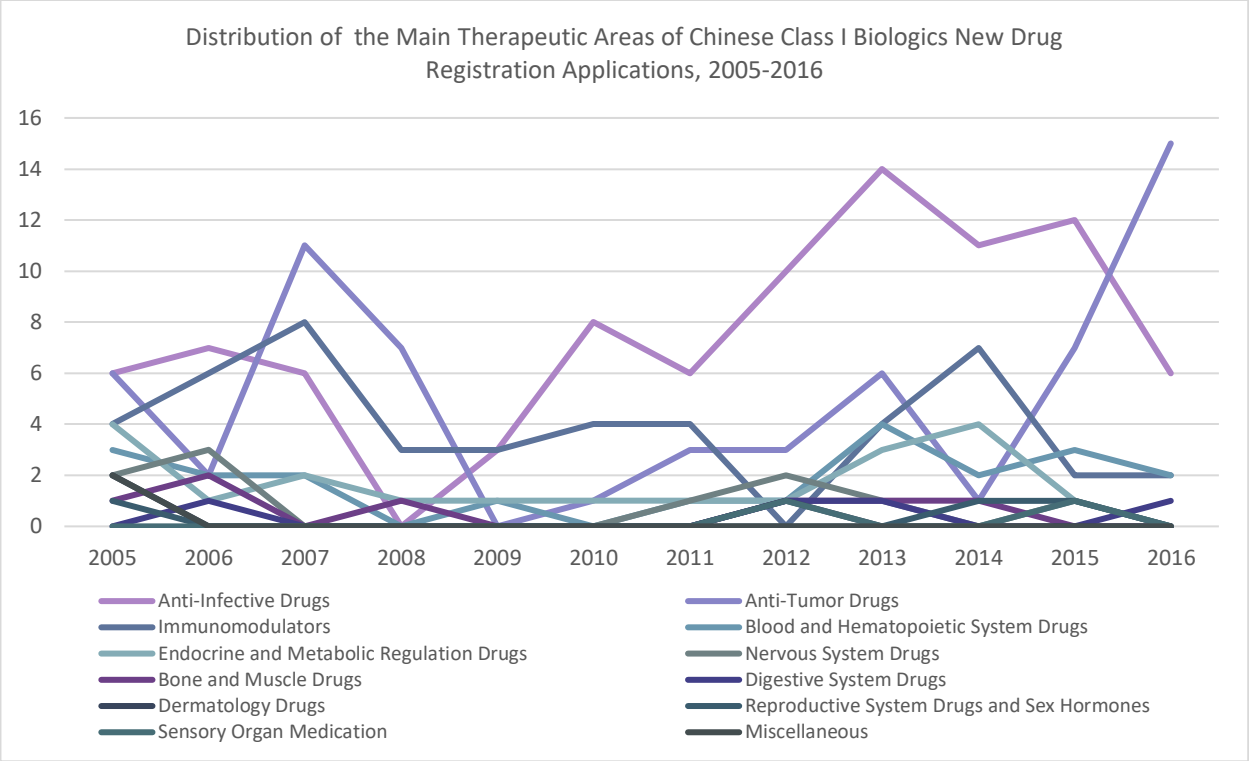


Figure 65 Distribution of the Main Therapeutic Areas of Chinese Class I Biologics New Drug Registration Applications, 2005-2016; data from Yulu Fan

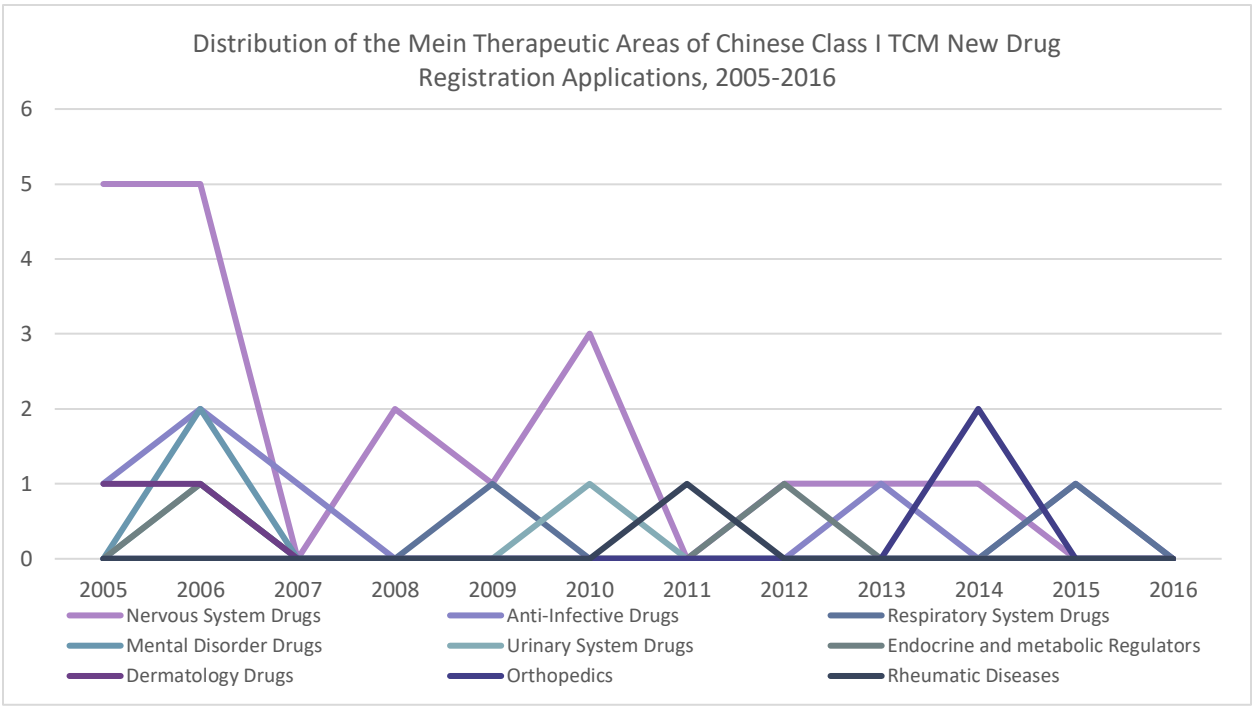


Figure 66 Distribution of the Main Therapeutic Areas of Chinese Class I TCM New Drug Registration Applications, 2005-2016; data from Yulu Fan

In this research, CFDA (MNPA) is used to gain an understanding of the R&D orientation of the Chinese pharmaceutical industry, thereby providing insight in potential developing competency-based differentiation. However, it should be noted that CFDA registration applications fail to capture the whole picture of Chinese pharmaceutical R&D because it contains certain biases. One such bias is the high attrition rate of pharmaceutical R&D. Only 10% of identified small molecule drugs successfully make the transition to candidate (Hughes, Rees, Kalindjian, & Philpott, 2011) (i.e., before entering clinical trials). This introduces bias to the use of this specific data set in its role as an indicator of R&D orientation because the uneven distribution of the molecule's success is based on drug modality and disease target (Takebe, Imai, & Ono, 2018). This means that using this data may understate the actual early investment capital direction, and instead display where success in R&D is found – two distinct measures. In addition, due to the long period between initial research and marketization, this data may act more retroactively – not displaying *current* R&D direction but the R&D direction 5-10 years prior (as current R&D has yet to progress to the regulatory approval stage).

After understanding what the research is, the logical next question is by whom the research is conducted. McKinsey & Co's data indicates that local firms have a growing influence in China's innovation output. Under the background of a 32% clinical-trial application growth from 2016 to 2020, Chinese biotech firms have grown to make up over 56% of total clinical trial applications, with Chinese chemical pharmaceutical companies increasing their applications by 34 applications (though only 3% more than MNCs) (Han, Le Deu, Zhang, & Zhou, 2021).

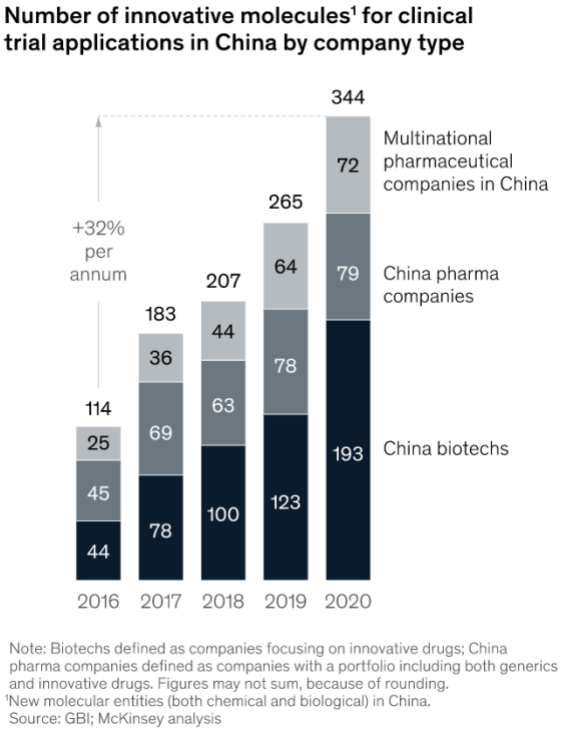


Figure 67 Chinese Innovation Pipeline; McKinsey & Co.

Jiang and Luan investigated the impact and distribution of Chinese pharmaceutical patents by analyzing which patents were getting the most references, and to which category these patents belonged to. Rather than refining the understanding of the *direction* of Chinese R&D,

these data serve to identify the impact of their research in the broader academic and scientific communities – in effect showing what China's competencies are in the eyes of others. They identified that there were 15,422 patents citing Chinese pharmaceutical patents registered in the State Intellectual Property Office, the U.S. Patent Trademark Office, or both for the period 2014-2015, with the 28,075 patents citing U.S.-based patents found for the same period (Jiang & Luan, 2018). Though there is still a significant gap between these two measures of innovation, it should be noted that 20 years prior in the period 1994-1995 only 66 Chinese-referencing patents were identified, while the U.S. had 18,328 U.S.-referencing patents in the same period. China's 15,356-count increase from 1995 to 2015 displays a growth rate of visibility and influence of patents in the global sphere which is outpacing U.S. growth. Jiang and Luan also used this data to conduct innovation convergence measures, i.e., how concentrated the use of patents is in the top 10 assignees. The top 10 assignees referencing Chinese patents (Zhejiang University, 0.73%; Jiangnan University 0.53%, Shanghai Jiao Tong University, 0.37%; Shanghai Institute of Pharmaceutical Industry, 0.34%; China Pharmaceutical University, 0.33%; Shandong New Hope LIUHE Group Co. Ltd, 0.32%; Jinan University, 0.32%; Nanjing Guangkangxie BioPharma Co. Ltd, 0.32%; Qingdao Municipal Hospital, 0.31%; and Shandong University, 0.27%) (two pharmaceutical firms, six universities) made up 3.84% of the retrieved patents, showing that there was a relatively low degree of convergence. This indicates that the concentration of innovation is more spread throughout the industry. Meanwhile, the U.S.'s top ten patent assignees referencing U.S. patents (F. Hoffmann-La Roche Ltd., 1.75%; University of California, 1.03%; Merck Sharp and Dohme Corp., 0.88%; Inserm, 0.53%; Novartis AG, 0.50%; Sanofi-Aventis Deutschland GmbH, 0.49%; Harvard College, 0.47%; University of Texas System, 0.47%; Roche Diagnostics GmbH, 0.46%; John Hopkins University, 0.45%) accounted for 7.03% of patent filings citing U.S. pharmaceutical patents, double the convergence of the Chinese patents.

By taking this same data, Jiang and Luan were able to identify the focus of patents citing previous Chinese- and U.S.-referencing patents. The purpose of this was to find "possible cutting-edge frontiers towards which the industry is advancing," by identifying which patent subjects were gaining the most traction. See Figure 68, which identifies the convergence of Chinese pharmaceutical innovation.

The network map identifies four major convergence points in those citing Chinese pharmaceutical patents. The largest convergence point, TCM, comes as no surprise as TCM-based novel drug discovery is an increasing method for the identification of novel compounds (Wu, et al., 2014) as a means of natural medicine discovery and development (Ni, et al., 2017). This is strengthened by Chinese public entities attempting to capitalize on the pharmacologic and commercial potential of TCM (Jiang & Luan, 2018), and most likely benefits from the rich history of TCM development in China.

Figure 69, then, displays the convergence innovations on the frontiers of the global pharmaceutical industry that cite *both* Chinese and U.S. patents. The highest convergence points were pharmaceutical composition, cancer treatment, and chronic diseases and mental illnesses. This shows shared areas in pharmaceutical patents that are mutually and frequently cited.

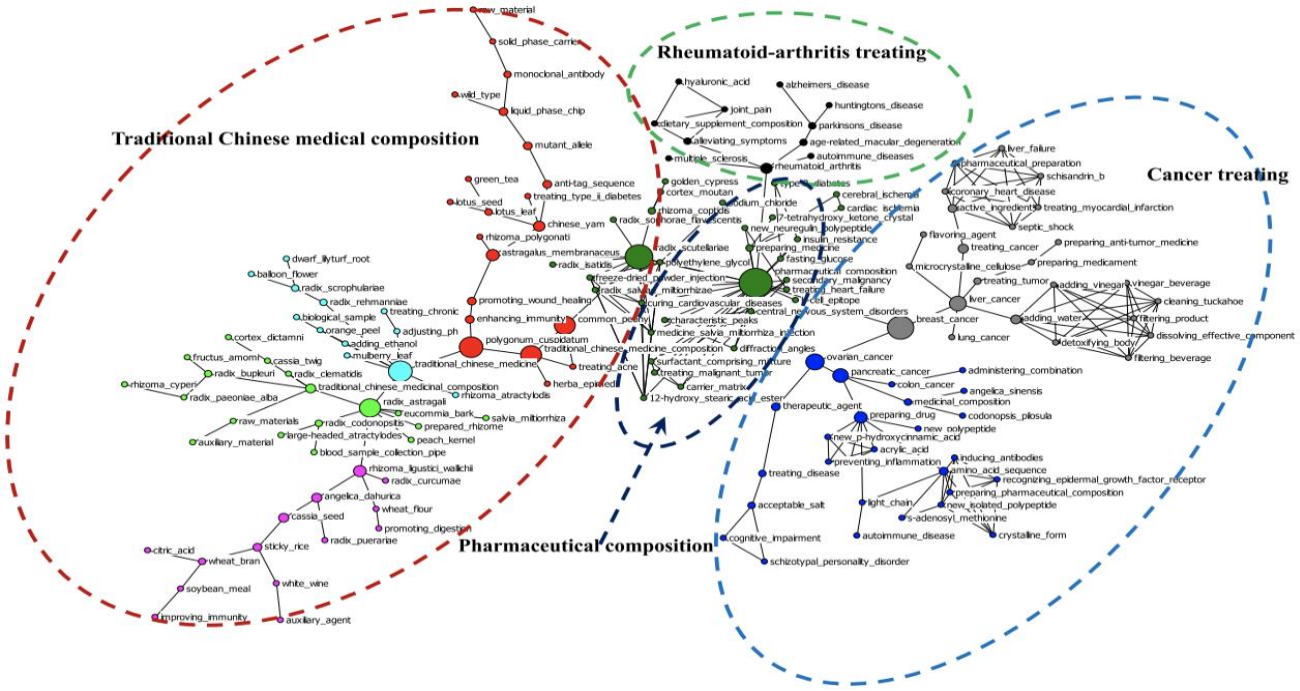


Figure 69 Convergence of Chinese Pharmaceutical Innovations in the Global Pharmaceutical Industry; from Jiang & Luan

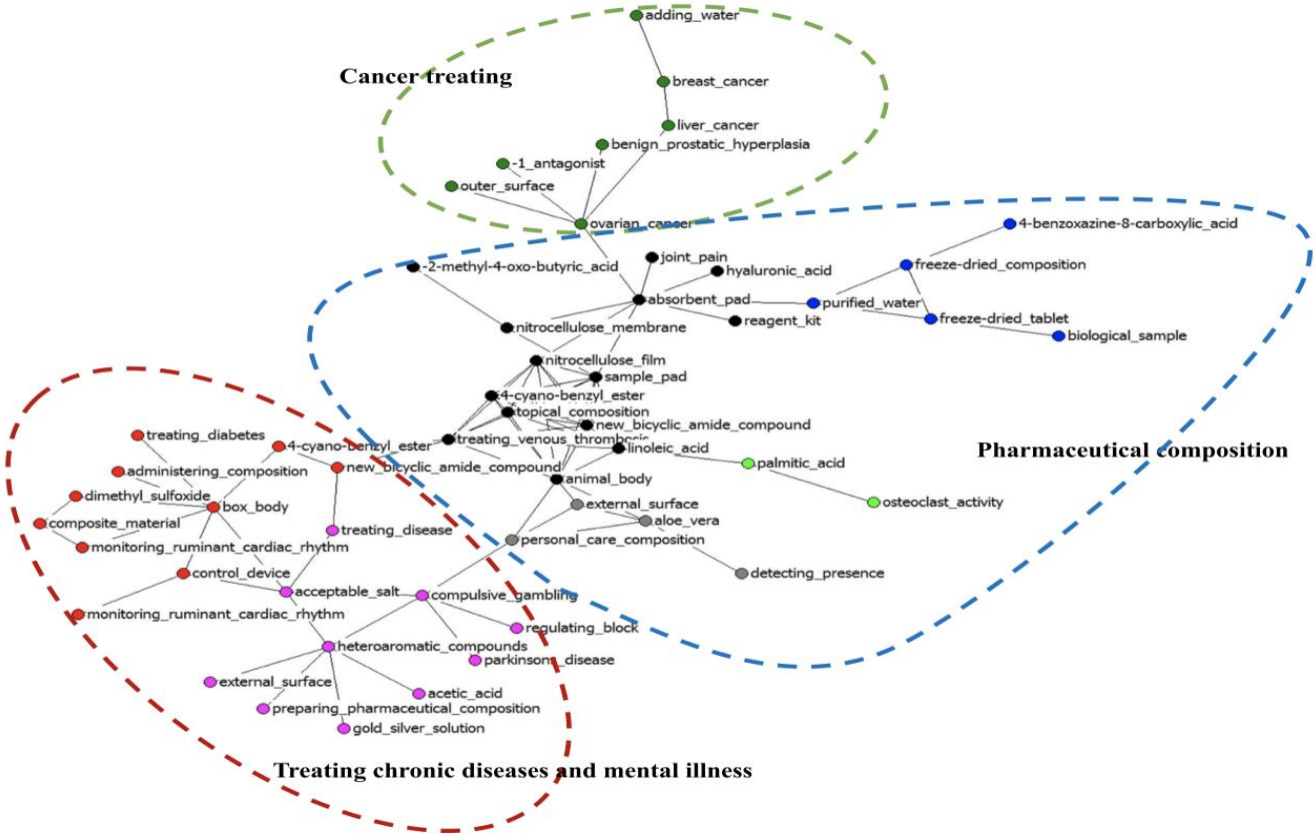


Figure 68 Convergence of Both Chinese and U.S. Pharmaceutical Innovations in the Global Pharmaceutical Industry; from Jiang & Luan

Financial Environment

Though important to all industries, financing and capital sourcing has a particular importance to the pharmaceutical industry due to the long and risky research and development process required to develop, optimize, market, and sell novel drugs. Investors must invest large amounts of money to fund high risk activity with low probability of pay off. Due to both the high investment volume necessary in this highly innovative industry as well as the high risk undertaken by both the firm and its investors, the financial environment must not be overlooked.

In this section, financial trends in the PRC affecting the pharmaceuticals industry are examined to give a greater understanding on how volume of capital inflow, source of capital inflow, and use of capital over time.

Private Investment

Foreign direct investment (FDI) is a broad category of financial interactions between a foreign entity and a domestic entity in which ownership, funding, or debt is pursued. It includes activities like private equity investment (PE), venture capital investment (VC) (if from a foreign entity), establishment of facilities, M&A activity, etc. The development of modern China has been significantly impacted by FDI. FDI volume tripled from 46.9 billion USD to 126.2 billion USD in the years 2001-2013. The FDI investment in the pharmaceutical industry has likewise experienced both a volume increase and an increase in the percentage of manufacturing FDI received. In 2006 the Chinese pharmaceutical industry had a total FDI value of 0.5 billion USD, which grew to 2.1 billion USD by 2016. The ratio of the pharmaceutical industry's FDI to the manufacturing industry's increased from 1.29 to 5.93% in the same period (Li, Angelino, Yin, & Spigarelli, 2017).

When it comes to R&D funding specifically, the cornerstone for pharmaceutical innovation and growth, private funding is at an insufficient level. Ping Deng et al. finds that, considering increasing demand for pharmaceuticals, government support to R&D is needed to fill in for the shortcomings of private funding (Deng, Lu, Hong, Chen, & Yang, 2019). They cite the relatively low R&D intensity of Chinese high-tech industries as compared to developed countries. Lan Qiu et. al. agrees, arguing that, despite a rapid increase in pharmaceutical R&D investment in the past decade, China must still increase investment size to have an investment intensity analogous to other global high-tech industries, and to achieve a status as a competent pharmaceutical innovation system (Qiu, Chen, Lu, Hu, & Wang, 2014).

Venture capital (VC) is a type of financing based on private equity with the goal of providing startup companies the financial capital necessary to start. The investor generally aims to find companies and industries that they believe have positive long-term growth opportunities. By the nature of investing in startups, VC is often highly risky and cost intensive. In order to create profit, VC institutions will divest from the startup when it is able to enter the public market via. IPO, equity buyback from the startup itself, equity sale to employees, etc. It is clear that VC is a particularly important factor for encouraging and growing innovation in an economy (Lerner & Nanda, 2020).

Venture capital in China remains in its infancy when compared to that of developed economies. The VC market began in the 1980s and has since grown with the Chinese economy

(Ahlstrom, Bruton, & Yeh, 2007). A significant portion of VC investment comes from foreign VC firms, which constitute approximately 30% of total VC deals (Daxue Consulting, 2021) (Figure 70). In 2012, 34.03% of Chinese VC funding came from unlisted companies and 18.87% came from individual sources (Figure 72). However, the VC market is young when compared to developed countries. In the 1980-2009 period, China's VC investment into biopharmaceuticals only reached 10.51%, which was significantly smaller than the 18% of U.S. VC investment during the same period (Fu & Ng, 2021). Lower activity of VCs may contribute to this lower proportion of investment. S&P Capital IQ found that 711 VC and private equity firms had life science investments in the U.S., while there were only 89 similar funds in the PRC, with only 19 of these funds making more than one investment, with many of these VCs focusing on short term profit rather than more innovative projects as a way to reduce VC-borne risk (Ni, et al., 2017). In addition to this, Chinese venture capital declined from 2018 through 2019, according to DaXue Consulting, which will increase financial barriers for startup operations (Figure 71).

Yawei Fu and Sin Huei Ng state that it is imperative to take steps to expand venture capital fundraising sources and their exit channels to increase the viable innovative ability in innovative industries and to continue to drive the growth of entrepreneurial startups (Fu & Ng, 2021).

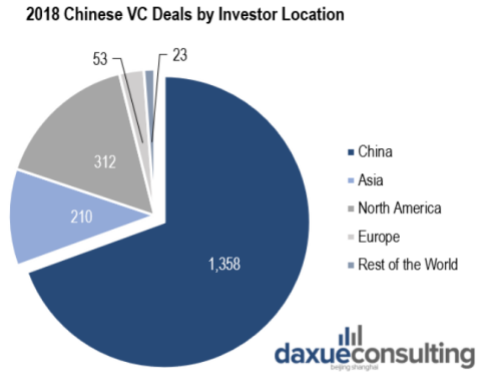


Figure 70 2018 Chinese VC Deals by Investor Location, from Daxue Consulting, data from Pitchbook

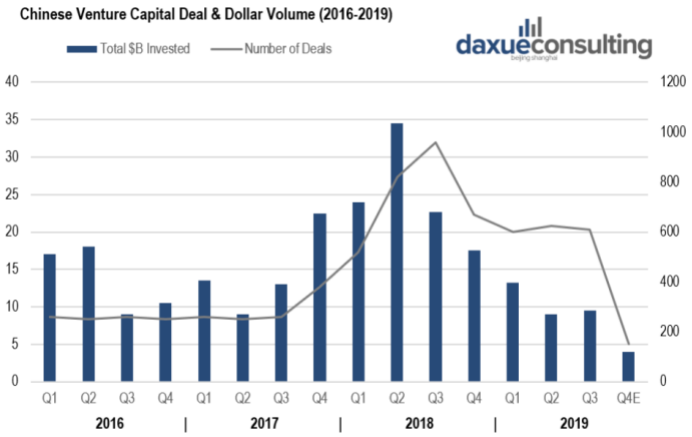


Figure 71 Chinese Venture Capital Deal & Dollar Value (2016-2019), from Daxue Consulting, data from Crunchbase

Public Funding

Public funding is an important source of pharmaceutical capital, with the National Bureau of Statistics of the PRC reporting that public funding for R&D institutes in the pharmaceutical sector constituted a key funding source with more than 81% of R&D expenditure accounted for by public funding, while private investment only accounted for 5.41% in 2021 (though only 4.7% of R&D investment was used to improve basic research, an important factor for new drug discovery) (Ni, et al., 2017).

Public institutions also have a significant presence in VC investment, with VC used as a common way for State-backed VC institutions to invest in startups - often state-owned enterprises. These state-backed funds offer more targeted encouragement to specific industries

(Daxue Consulting, 2021). In 2012, the government and state-owned enterprises accounted for 30.59% of VC investment (Qiu, Chen, Lu, Hu, & Wang, 2014).

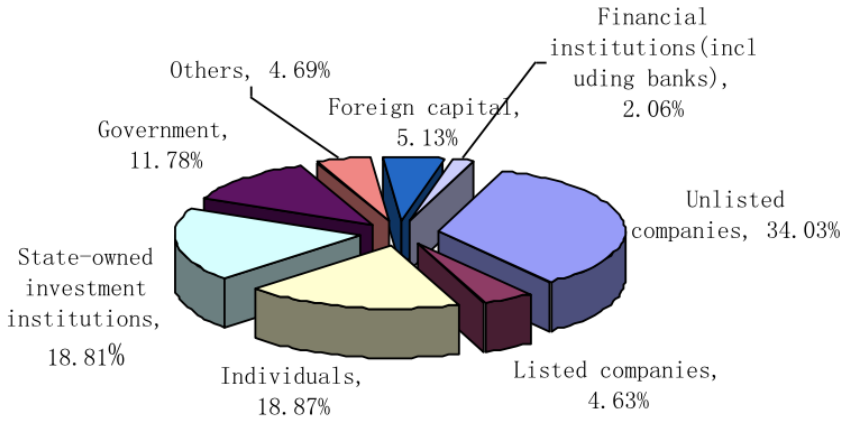


Figure 72 Capital Sources of China's Venture Capital, from Lan Qiu et. al.

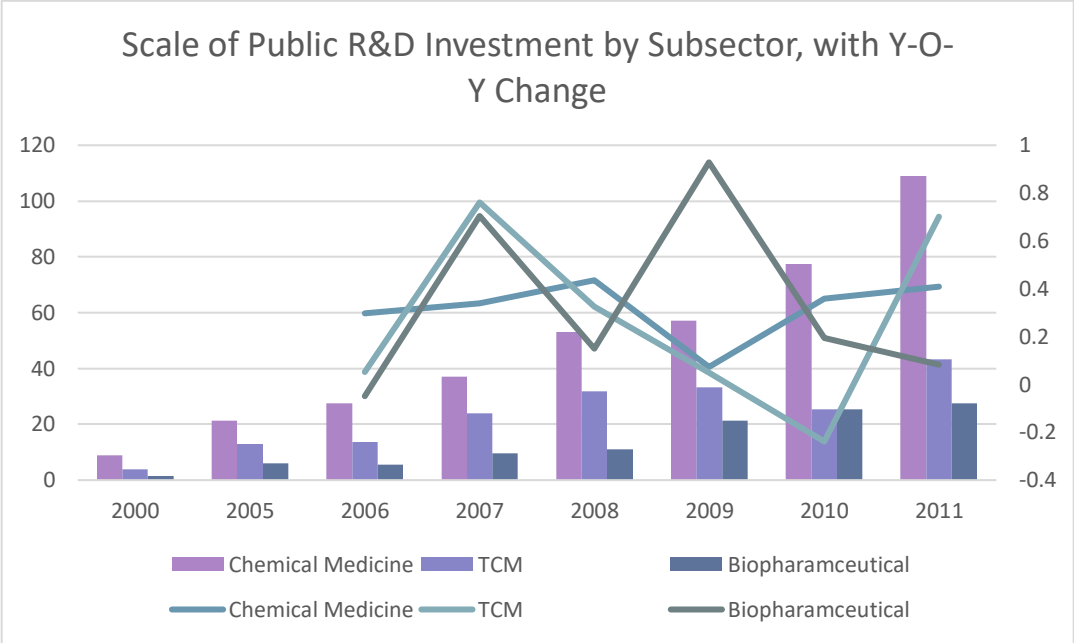


Figure 73 Scale and Y-o-Y Change of Public R&D Investment by Subsector, data from Lan Qiu et. al.

Knowledge Environment

Though we have already discussed R&D activity as a tool to create and maintain a competitive advantage, it is important to understand the interaction between pharmaceutical firms and external players. As both a knowledge and capital-intensive industry, the

pharmaceutical industry relies on knowledge innovation to maintain a competitive advantage, differentiation, and even market viability.

To maintain competitive ability, pharmaceutical firms often participate in multiple types of innovation: incremental innovation focusing on improving or finding novel applications for existing drugs, and radical innovation focusing on creating new breakthrough innovation. Innovation itself is the result of recombining new knowledge inputs; however, when relying on internal knowledge sources for recombination, a lack of knowledge diversity is created which hampers the ability to create breakthrough innovation (Dong & McCarthy, 2019). As a latecomer industry, Chinese pharmaceuticals must catch up to more integrated firms in the global sphere by closing the technology and knowledge gap via. increasing collaborating with domestic and international technology leaders (Ren & Su, 2015).

Firm collaboration is frequently described by scholars according to two fundamental families of managerial theory: the resource-based view and the institution-based view. The resource-based view of innovative external collaboration asserts that firms and organizations have unique resources that are valuable, hard-to-imitate, and immobile (tacit). These resources are the source for an organization's success and differentiation and are fundamental to an organization's competitive advantage. In this sort of collaboration, RBV theory states that value is created not just from complementary information sharing, but through the collaboration *process* through which tacit knowledge is gained. The RBV perspective is the most widely acknowledged reason for collaboration in Western pharmaceuticals. An alternative managerial theory, the institution-based view, was developed after gaps between RBV theory and practice were identified. The IBV states that conditions within an industry determine firm performance – that is, firms must consider the formal and informal rules of business to succeed. The IBV perspective is proposed to be of even greater significance in emerging economies like China, where the institutional environment is variable (Li, Zheng, & Wang, 2015). Through the impact of IBV perspective in emerging economies is under researched (Li, Zheng, & Wang, 2015), Kafouros points out that, in contrast to developed markets whose pharmaceutical firms have invested in internal R&D for decades and have built innovation models around homogeneous institutions and established systems, pharmaceutical firms from emerging markets are less able to be self-sufficient and exhibited a greater dependence on the local environment (Kafouros, Wang, Piperopoulos, & Zhang, 2015). For example, nonhomogeneity in China's local institutions and environment were analyzed by Kafouros et al., ultimately finding that variation in IPR enforcement, international openness, and quality of academic institutions (URLs) had significant and variable impact on the success of firm innovation even within China (Figure 74) (Kafouros, Wang, Piperopoulos, & Zhang, 2015).

In addition to the impact of RBV and IBV preservatives on innovation, the type of collaborative relationship formed between two entities is also of great significance to the orientation and outcome of successful collaboration. As a result of the necessity to recombine knowledge to achieve innovation, greater collaboration is used to encourage inter-organizational learning (Li, Zheng, & Wang, 2015), among these interorganizational learning forms, collaborative techniques are frequently divided into inter-firm collaboration and academic collaboration. Both of these knowledge sourcing-, collaboration-techniques are used in various ways within the industry to achieve specific goals, as both industry-partners and academic organizations have distinct goals that will characterize the nature of the collaborative relationship. Figure 75 exemplifies the difference the market- or academic- nature of the partner has on innovation, based on the knowledge network theory which suggests the number of

connections a firm has compared to the maximum possible number of connections is positively correlated with the benefits gained from the network (Dong & McCarthy, 2019).

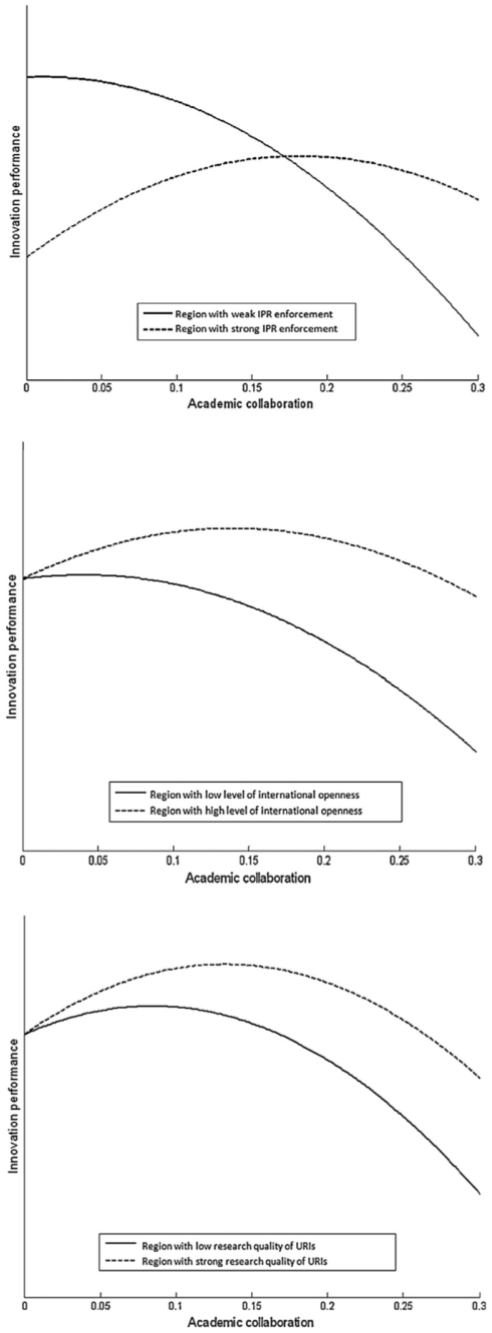


Figure 75 Moderating Effects of Regional Institutions in China, from Kafouros, Mario et al.

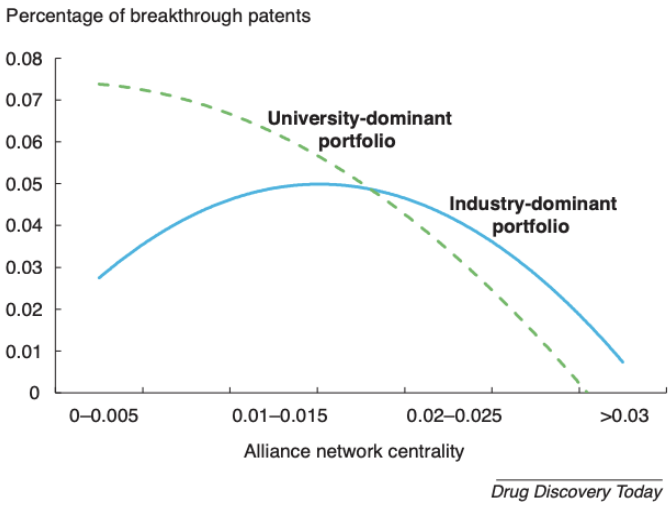


Figure 75 Alliance partner type and breakthrough patents, from Dong, John and McCarthy, Killian

Inter-Industry Collaboration

Inter-industry collaboration, or industry-industry collaboration is a form of partnership or collaboration in which the market-based firms have similar goals: using applied knowledge with clear commercial applications and innovate to meet market needs (i.e., seeking proprietary technology) (Dong & McCarthy, 2019; Perri, Scalera, & Mudambi, 2017).

Despite the RBV perspective's advantages of domestic and international industry-industry collaboration and open innovation methods, Perri et al. identified that many MNEs in emerging countries take a more conservative approach to collaboration due to a higher risk of knowledge expropriation stemming from weak IPR regimes (Perri, Scalera, & Mudambi, 2017). However, this resistance to such MNE-local collaboration seems to have started to subside in recent years with an increase in partnerships (Han, Le Deu, Zhang, & Zhou, 2021; Haden-Smith, 2021). Domestic collaboration parks have continued growing, with the establishment of 22 biomedicine science parks aimed at promoting domestic inter-firm collaboration (Haden-Smith, 2021).

More research should be conducted into the prevalence of various forms of domestic and international industry-industry collaboration in Chinese pharmaceuticals to gain a greater understanding of how knowledge flows between domestic and international operators.

Industry-Academia Interaction

Despite the growing importance of inter-firm collaboration for knowledge sharing as a driver of innovation in the Chinese pharmaceutical industry, literature largely suggests that firm-academic collaboration has potential to play an even greater role in facilitating knowledge-sharing based connections to drive the intake and dissemination of advanced technical knowledge (Perri, Scalera, & Mudambi, 2017; Kafouros, Wang, Piperopoulos, & Zhang, 2015). In fact, while developed countries cite universities as their least frequent source of information, 33-50% of external R&D firms focus on academic collaboration (Kafouros, Wang, Piperopoulos, & Zhang, 2015). Firm-academic collaboration has district motivations from inter-firm collaborations, as university and research institution partners are often science-based knowledge creators that focus on fundamental knowledge development with the purpose of adding to academic depth rather than developing commercial application (Dong & McCarthy, 2019). One reason for the superiority of academic cooperation and collaboration is academic knowledge network organization – that is to say academics develop strong interpersonal ties throughout local and distant institutions, which allows for broader learning, better results in research activity, more widespread recognition, and reduced institutional threats to the innovation process. Furthermore Perri et al. points out that inter-firm collaboration is often focused to a greater extent on short-term objective of commercialization, while academic institutions tend to focus more on long-term innovation. Firm-academic collaborations do not have a direct 1:1 manifestation in profit and effectiveness (as measured in profit), but in fact have an inverse-U distribution, meaning that firm-academic collaborations are beneficial for the firm but only to a certain point, after which an over utilization of external knowledge may reach the firm's knowledge absorption capacity (Kafouros, Wang, Piperopoulos, & Zhang, 2015; 张新鑫, 侯文华, & 申成霖, 2016).

While Chinese pharmaceuticals exhibit a strong use of academic collaboration to advance the innovation level of the industry, there is still a significant gap between academic research output and firm output. On one level, firms must bear a cost for assimilating and using external knowledge – while this cost is minimized in inter-firm interactions due to goal homogeneity, academic institution knowledge sourcing necessitates more resources devoted to integrating nonhomogeneous information into the firm (e.g. taking basal research from academic institutions and developing that for use in a commercial product); furthermore the output quality goal varies between these two types of organizations, as the firm focuses on developing a product to the lowest possible point able to pass regulation in order to minimize cost, while academic organizations wish to develop the invention to optimal quality (Kafouros, Wang, Piperopoulos, & Zhang, 2015). Both provide varying goal-based barriers which add difficulty to firm-academic collaboration. To complement this gap, academics tend to focus on the "hot," or most advanced research areas to maximize the impact of their academic papers, gaining merit for themselves and their institution. For example, Chinese academia has been among the top three leaders in nanotechnology publications for over 20 years and is adept at gene delivery technologies, though Chinese pharmaceutical firms continue to predominantly use conventional technologies such as tablets, capsules, and injections (Zhong & Ouyang, 2019).

The interaction between industry and research organizations continues to lag behind that of the United States. In an analysis of university-industry collaboration, Zhou et al. found that China's university with the highest university-industry collaboration (UIC) productivity, as measured through publication utilization, was Shanghai Jiao Tong University, with a UIC productivity of 651 (the 10th greatest UIC productivity was Xi'an Jiaotong University at 251). In the USA, Harvard University had the greatest UIC productivity measurement at 3,756 (while the 10th highest UIC productivity was Columbia University at 1,646. When looking at the "life sciences" industrial sector in specific (Table 76) we see that a huge gap exists between Chinese and U.S. university collaboration with the industry. However, the distribution of UIC differs from that of the U.S. Figure 77 and Figure 78 display that half or more of leading Chinese universities collaborate with domestic industry, yet most of the industrial partners have a distance greater than 50 kilometers from the university, with a large proportion of collaboration occurring internationally. On the other hand, U.S. universities display a far greater rate of domestic collaboration and a far smaller rate of international collaboration (Zhou, Tijssen, Leydesdorff, & Hernandez Montoya, 2016). Despite the disadvantage of university-industry collaboration volume, it is possible that the greater internationalization of UIC introduces a more diverse set of implicit and tacit knowledge input factors which may lead to the diversity of knowledge necessary to "spark a breakthrough" (Dong & McCarthy, 2019).

Rank	China		P(UIC-USA)/P(UIC-China)	USA	
	University	P(UIC)		P(UIC)	University
1	Fudan Univ	113	7.5	844	Harvard Univ
2	Zhejiang Univ	111	3.9	432	Stanford Univ
3	Shanghai Jiao Tong Univ	110	3.9	431	Univ Calif—San Diego
4	China Agr Univ	104	4.0	419	Johns Hopkins Univ
5	Peking Univ	101	3.9	397	**Univ Calif—San Francisco**
6	Peking Union Med Coll	100	3.7	368	Univ Washington—Seattle
7	**China Pharmaceut Univ**	74	4.9	366	**Duke Univ**
8	**Tsinghua Univ**	70	4.9	341	Cornell Univ
9	Sun Yat-sen Univ	67	5.1	340	Univ Florida
10	Sichuan Univ	57	5.8	331	**Univ Calif—Los Angeles**

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Figure 76 Top 10 Universities in domestic ranking in UIC productivity in "Life Sciences" (2009-2012), from Ping Zhou et al.

Rank	University	P(UIC)	%UIC	%Local	%Domestic	%Foreign
1	Fudan Univ	113	3.4	31	46	58
2	Zhejiang Univ	111	2.5	20	49	55
3	Shanghai Jiao Tong Univ	110	3.1	40	55	48
4	China Agr Univ	104	3.1	37	52	48
5	Peking Univ	101	3.4	33	48	54
6	Peking Union Med Coll	100	3.3	32	57	46
7	China Pharmaceut Univ	74	6.8	34	80	20
8	Tsinghua Univ	70	4.8	34	47	54
9	Sun Yat-sen Univ	67	2.1	21	61	45
10	Sichuan Univ	57	2.7	30	65	37

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Figure 77 Collaboration Distance of Top-10 Chinese Universities in UIC Productivity in "Life Sciences," from Ping Zhou et al.

Rank	University	P(UIC)	%UIC	%Local	%Domestic	%Foreign
1	Harvard Univ	844	6.9	32	81	25
2	Stanford Univ	432	8.9	38	88	18
3	Univ Calif—San Diego	431	7.4	38	85	21
4	Johns Hopkins Univ	419	8.1	6	80	26
5	Univ Calif—San Francisco	397	8.4	31	89	16
6	Univ Washington—Seattle	368	6.6	25	86	19
7	Duke Univ	366	7.7	16	78	26
8	Cornell Univ	341	5.6	10	73	34
9	Univ Florida	340	5.9	13	82	20
10	Univ Calif—Los Angeles	331	7.1	10	82	27

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Figure 78 Collaboration Distance of Top-10 US Universities in UIC Productivity in "Life Sciences," from Ping Zhou et al.

Summary

Pharmaceuticals is a unique industry due to highly complex government intervention, which impacts product price, intellectual property rights, quality, and corruption management. Adding to the complexity is the need for a highly complex innovation system which necessitates a high degree of knowledge synthesis, resulting in abnormally high M&A movement. In this paper, we attempted to examine this industry through the lens of a U.S.-China bilateral industry comparison. In this way, relevant changes in the industry dynamics of these two economic powers can be identified and better understood.

From a historical perspective, the U.S. market has been a lead innovator in this industry since at least WWII. The industry has since grown substantially in the interim decades, reaching a value of 369 bn USD in 2019. The Chinese market had a much slower start, with production during and after the Reform and Opening period focusing on low-quality pure product imitation with the goal of increasing production *volume* to provide ample medicine to the country's large population with little to no innovation activity. The Chinese industry has since progressed to a stage of independent innovation, ultimately yielding an industry value of 149.8 bn USD.

Today, these two pharmaceutical industries are faced with their own unique issues impacting the ability of the industry to continue its innovation-intensive R&D. Both countries are experiencing population aging resulting in increased pharmaceutical demand – a key driver for industry growth. The U.S. has a particular issue with expiring patent terms resulting in the "patent cliff," which in turn reduces industry revenue and reduces the ability to fund future projects. Chinese pharmaceuticals' largest modern issue is market structure, which reduces the power, differentiation ability, and innovation ability of firms.

Pharmaceutical prices in the U.S. receive no government regulation, allowing firms to set prices according to what they believe consumers are willing to pay. This unique policy direction (or lack thereof) is based on the belief that without full free-market pricing, firms would lose the incentive to innovate new medicine, although the relationship between price and innovation is still highly contested. Meanwhile, China has several price-control tools for pharmaceuticals including the recently nationally implemented bulk-purchase scheme, which leverages high volume demand to reduce the cost of prices to the consumer.

Corruption is present in all industries and is enabled by latent opportunities that exist therein. The U.S. has three notable facets: the allowance of direct-to-consumer advertising which shares low-quality information and testimonials to influence end consumer choice; PBMs, which some authors argue would violate the Corrupt Practices Act if outside the U.S. due to adding no value to the product; and significant lobbying efforts carried out by the pharmaceutical industry to influence government decision making. In China, bribery seems to be the predominant form of corruption, with firms bribing government officials for price increases.

One of China's most notable differences with U.S. pharmaceutical governance lies in the central strategy present in government policy. Through policies such as Made in China 2025 and the Belt and Road Initiative, the pharmaceutical industry is placed as a priority industry for development. Firms therein are encouraged to shift to a more innovative position in the supply chain and expand into the international market. In contrast, the U.S. has traditionally had a more hands-off approach to regulating the strategic *direction* of the industry, only altering a few

aspects of the industry to increase generics competition (as an example); yet, in the face of growing international competition, particularly as it applies to China, the U.S. is at an inflection point: should a more directed governance approach be adopted to ensure sustained superiority?

In terms of market structure, the U.S. maintains an extreme degree of industry concentration, falling just short of the oligopoly classification. With ¾ of the market share being commanded by major players, some experts worry such concentration has resulted in reduced competition. The U.S. generics industry is far less centralized, with ¼ of total revenue attributed to four firms. This structure has been shifting since the start of the biopharmaceutical revolution – with an uptick in M&As and firms more willing to stray from the traditional "blockbuster" (a response to the growing cost and risk of developing medicine).

The Chinese market, characterized by many small and unorganized firms, provides a strong contrast to that of the United States. Due to its origins in low-innovation, high-volume generic drug manufacturing, the Chinese market still retains excessive interfirm competition, damaging the ability of firms to collect excess profit to be used for R&D and other forms of differentiation, thereby restricting many Chinese pharmaceutical firms to low value-added operations (i.e., low-end lock-in). The government has particularly taken note of this industry composition and has begun to push for a reorganization via. M&As, hoping to create larger and more resource-rich organizations more suitable for innovation-based international competition.

The U.S. places a heavy emphasis on R&D innovation, attaining a 15-18% R&D capital funding strength measure. Trends in the substance of research point out that oncology, neurology, and infectious diseases are the drug classifications with the highest volume (Figure 42), with pharmaceutical composition patents tending to gain the most industry traction. The Chinese pharmaceutical market still lags behind the U.S. in its emphasis on R&D, with low-value-added activities maintaining a prominent role in the industry, exemplified through an R&D capital funding strength of 1-2%, with most drugs developed focusing on anti-tumor medication, with cancer treatment falling behind TCM as the most cited Chinese patented.

Private funding for Chinese pharmaceuticals is at an insufficient level and public funding falls behind what some scholars view as a suitable level. Venture Capital is one form of insufficient private funding due to the novelty of VC in China, as well as the low activity rate of VC firms. Public funding, contrastingly, makes up more than 81% of R&D expenditure. In the United States, the vast majority of funding for late-stage pharmaceutical development comes from private sources, such as VCs, R&D alliances, etc. On the other hand, public funding through sources like the NIH is concentrated largely on basal research, which focuses on foundational research rather than research necessary to commercialize a product.

In the knowledge environment, the most significant variance between the behavior of U.S.-based pharmaceutical firms and China-based pharmaceutical firms lies in their approaches to Industry-Academica collaboration – a form of collaboration marked by cooperation with academic research entities. In this regard, the U.S. has a very high degree of collaboration, with the university with the highest degree of University-Industry Collaboration reaching 3756. The Chinese university with the highest degree of UIC only reaches a 651, displaying that China lags behind the U.S. in its industry-applied absorptive capacity.

Notes As the author's first venture into the field of research, he acknowledges the limited scope and depth of the research model. He hopes the accumulation, summation, and brief explanation of information on this complex industry can aid others identify resources and form

an understanding of the pharmaceutical industry. The author enthusiastically welcomes any feedback, information, or discussion pertaining to this literary review.

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Additional Resources

Distribution of the Main Therapeutic Areas of Chinese Class I Chemical Pharmaceutical New Drug Registration Applications, 2005-2016														
Therepeutic Field	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**Total**	**Percentage**
Anti-Tumor Drugs	15	6	3	7	7	10	14	14	24	23	35	39	197	45.92%
Digenstive System Drugs	2	5	3	3	6	5	5	4	5	2	7	3	50	11.66%
Anti-Infective Drugs	3	4	1	2	5	4	2	2	2	8	3	8	44	10.26%
Endocrine and Metabolic Regullation Drugs	1	1	0	1	3	1	1	5	5	7	5	4	34	7.93%
Rheumatic Diseases and Immune Drugs	2	3	0	2	1	0	1	2	2	3	4	6	26	6.06%
Nervous System Drugs	3	0	0	3	0	3	2	3	2	3	4	2	25	5.83%
Mental Disorder Drugs	0	1	2	1	0	0	0	2	1	3	2	2	14	3.26%
Dermatology Drugs	1	0		0	0	1	1	1	3	1	3	1	12	2.80%
Blood and Hematopoietic System Drugs	0	0	0	0	0	0	1	0	1	1	6	1	10	2.33%
Anesthesia	0	0	0	1	0	0	0	1	4	2	0	2	10	2.33%
Urinary System Drugs	0	0	2	0	0	2	0	0	1	0	1	1	7	1.63%

Figure 79 Distribution of the Main Therapeutic Areas of Chinese Class I Chemical Pharmaceutical New Drug Registration Applications, 2005-2016, from Research on the Influencing Factors and Incentive Policies of China's New Drug Research and Development by YuLu Fan

Distribution of the Main Therapeutic Areas of Chinese Class I Biologics New Drug Registration Applications, 2005-2016														
Therepeutic Field	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**Total**	**Percentage**
Anti-Infective Drugs	6	7	6	0	3	8	6	10	14	11	12	6	89	32.96%
Anti-Tumor Drugs	6	2	11	7	0	1	3	3	6	1	7	15	62	22.96%
Immunomodulators	4	6	8	3	3	4	4	0	4	7	2	2	47	17.41%
Blood and Hematopoietic System Drugs	3	2	2	0	1	0	1	1	4	2	3	2	21	7.78%
Endocrine and Metabolic Regulation Drugs	4	1	2	1	1	1	1	1	3	4	1	0	20	7.41%
Nervous System Drugs	2	3	0	0	0	0	1	2	1	0	1	0	10	3.70%
Bone and Muscle Drugs	1	2	0	1	0	0	0	1	1	1	0	0	7	2.59%
Digestive System Drugs	0	1	0	0	0	0	0	1	1	0	0	1	4	1.48%
Dermatology Drugs	2	0	0	0	0	0	0	1	0	0	0	0	3	1.11%
Reproductive System Drugs and Sex Hormones	1	0	0	0	0	0	0	0	0	1	1	0	3	1.11%
Sensory Organ Medication	0	0	0	0	0	0	0	1	0	0	1	0	2	0.74%
Miscellaneous	2	0	0	0	0	0	0	0	0	0	0	0	2	0.74%

Figure 80 Distribution of the Main Therapeutic Areas of Chinese Class I Biologics New Drug Registration Applications, 2005-2016 from Research on the Influencing Factors and Incentive Policies of China's New Drug Research and Development by Yulu Fan

Distribution of the Mein Therapeutic Areas of Chinese Class I TCM New Drug Registration Applications, 2005-2016														
Therepeutic Field	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**Total**	**Percentage**
Nervous System Drugs	5	5	0	2	1	3	0	1	1	1	0	0	19	50.00%
Anti-Infective Drugs	1	2	1	0	0	0	0	0	1	0	1	0	6	15.79%
Respiratory System Drugs	0	0	0	0	1	0	0	0	0	0	1	0	2	5.26%
Mental Disorder Drugs	0	2	0	0	0	0	0	0	0	0	0	0	2	5.26%
Urinary System Drugs	0	1	0	0	0	1	0	0	0	0	0	0	2	5.26%
Endocrine and metabolic Regulators	0	1	0	0	0	0	0	1	0	0	0	0	2	5.26%
Dermatology Drugs	1	1	0	0	0	0	0	0	0	0	0	0	2	5.26%
Orthopedics	0	0	0	0	0	0	0	0	0	2	0	0	2	5.26%
Rheumatic Diseases	0	0	0	0	0	0	1	0	0	0	0	0	1	2.63%

Figure 81 Distribution of the Main Therapeutic Areas of Chinese Class I TCM New Drug Registration Applications, 2005-2016, from Research on the Influencing Factors and Incentive Policies of China's New Drug Research and Development by Yulu Fan