

Unrealised Potential: Japan's Post-war Pharmaceutical Industry, 1945-2005

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Declaration

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Abstract

Japan's existing pharmaceutical industry was devastated in the Second World War. But the industry recovered quickly, and in 1963, Japan had become the second largest producer of pharmaceuticals after the United States. Unlike its automobile or electronics industries, however, Japan's pharmaceutical industry did not become a global leader. Japan remains a net importer of pharmaceuticals and few Japanese drugs are found outside of Japan. The global pharmaceutical industry is led by firms from the United States, the United Kingdom and Switzerland, rather than those from Japan.

This thesis traces the development of the Japanese pharmaceutical industry after 1945, and offers several explanations for why it did not become a world-leading industry. It uses two classes of medicines, antibiotics and anti-cancer drugs, as case studies for exploring the overall history of the Japanese pharmaceutical industry. These case studies were selected because of their importance to health outcomes in post-war Japan. In the immediate post-war period, the leading causes of death in Japan were infectious diseases such as tuberculosis, but in later decades, cancer morbidity and mortality rose. Japan was found to be much more successful at developing antibiotics than anticancer drugs.

This thesis shows that, while the Japanese pharmaceutical industry had caught up with its Western counterparts by the mid 1970s, it did not exploit its potential to become a global leader. A few of Japan's leading pharmaceutical firms did develop blockbuster

drugs and expand overseas, but most firms remained domestically oriented. The major reasons why Japan did not develop a strong pharmaceutical industry lay in the lack of R&D incentives, the government's protectionist policies, industrial structure, and Japanese medical culture. Other reasons of secondary importance included the industry's historical origins in import houses, national differences in patterns of disease, Japan-specific drug standards, and barriers to entrepreneurship among university academics.

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Abbreviations

BoJ	Bank of Japan
CANPS	Cancer Patients Support Organization
EBC	European Business Council
FDA	Food and Drug Administration
FTC	Fair Trade Commission
GCP	Good Clinical Practice
GHQ	General Headquarters
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GPMSP	Good Post-Marketing Surveillance Practice
ICH	The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
JARA	Japan Antibiotics Research Association
JMA	Japan Medical Association
JPMA	Japan Pharmaceutical Manufacturers Association
MAFF	Ministry of Agriculture, Forestry and Fisheries
METI	Ministry of Economy, Trade and Industry
MHLW	Ministry of Health, Labour and Welfare
MHW	Ministry of Health and Welfare
MIAC	Ministry of Internal Affairs and Communications

MITI	Ministry of International Trade and Industry
MOF	Ministry of Finance
MOSS	Market-oriented and Sector-selective
NCE	New Chemical Entity
NRDC	National Research and Development Corporation
OTC	over-the-counter
PAL	Pharmaceutical Affairs Law
PhRMA	Pharmaceutical Research and Manufacturers of America
PMA	Pharmaceutical Manufacturers Association
SSM	Specific Substance Maruyama
STA	Science and Technology Agency

Conventions

This thesis uses the modified Hepburn system of romanisation, which follows *Kenkyūsha's New Japanese-English Dictionary* (3rd and later editions). Macrons are used to indicate long vowels, except for terms or phrases commonly anglicised such as Tokyo or shogun. Macrons are not used for Japanese pharmaceutical firms as these are generally anglicised, or for referencing Japanese names if these were not used in the original English language work.

Names are presented in Western order, with given name first, followed by surname.

1 Introduction

In 1945, Japan's pharmaceutical industry lay in ruins, devastated by the Allied bombings and the collapse of the Japanese economy. Most of the facilities for the production of pharmaceuticals were out of operation. In any event, few Japanese citizens had the financial capacity to purchase medicine. Moreover, Japan's pre-war industry had not been very large, at least in comparison with the pharmaceutical industries of the more advanced Western countries. In the late 1940s, however, the Japanese pharmaceutical industry began to re-emerge with the aid of the American Occupation authorities. American scientists provided their Japanese counterparts with the materials and guidance needed to produce the first antibiotic, penicillin. By 1948, Japan was self-sufficient in penicillin.

The penicillin venture during the Occupation period formed the foundations of Japan's post-war pharmaceutical industry. In subsequent years, Japanese pharmaceutical firms diversified into other types of medicines. As Japan evolved into a developed economy, pharmaceutical firms shifted from producing medicines to treat diseases of poverty to those that treated diseases of affluence. The phenomenal growth of the Japanese economy was accompanied by a similar expansion of the pharmaceutical market. Japan has been the second largest pharmaceutical market in the world since 1963.

In the 1950s and 1960s, the Japanese government fostered the growth of the pharmaceutical industry. The government encouraged Japanese firms to acquire foreign technologies, sheltered firms from foreign competition, and subsidised

patients who purchased prescription medicines.¹ As Japan's intellectual property regime until 1975 allowed firms to imitate foreign drugs, Japanese firms developed their industry by borrowing and modestly improving upon foreign technologies.

In the mid 1970s, the Japanese pharmaceutical industry opened up to the entry of foreign pharmaceutical firms and became more research oriented. In 1975, the government lifted restrictions on foreign direct investment in the pharmaceutical industry, invited foreign firms to expand business in Japan, and exposed Japanese firms to greater competition. In the following year, Japan's intellectual property regime was changed to discourage firms from launching copies of existing medicines and began to protect the discoveries of innovative drugs. Japanese firms began to increase their investments in pharmaceutical R&D to develop original drugs. In the 1980s, the Japanese authorities further deregulated the market under pressure from the United States and Europe.

Japan's pharmaceutical industry was transformed in the 1990s, as firms intensified their R&D orientation, expanded overseas, and rationalised and restructured their operations. The harmonisation of Japanese pharmaceutical regulations with those of the United States and Europe changed market dynamics, as Japanese drugs were now recognised abroad and vice versa. This led to an influx of foreign firms in Japan, and to a rise in the number of Japanese firms operating overseas. This move to globalise was not just prompted by a search for larger markets. Japanese firms also hoped to obtain

¹ This thesis refers to the pharmaceutical industry in terms of the prescription drugs industry. Prescription drugs refer to medication that can be purchased with a physician's prescription.

quicker drug approvals that were possible in countries such as the United States. As the costs of R&D began to escalate in step with advances in science and technology, the industry began to experience an unprecedented period of reorganisation.

Despite its remarkable growth since 1945, however, the Japanese pharmaceutical industry has not become a world-leading industry. Japan has continued to be a net importer of pharmaceuticals, and Japanese pharmaceutical firms are much smaller and invest much less in R&D compared to their counterparts in the United States and Europe. Few Japanese firms have launched global blockbuster drugs. Some Western observers in the 1980s predicted that Japanese pharmaceutical firms would penetrate global markets and achieve successes similar to Japanese automobile and consumer electronics firms. While it is true that a handful of Japanese pharmaceutical firms, such as Takeda and Daiichi Sankyo, have become global players, the Japanese pharmaceutical industry has remained relatively weak. Japan's leading pharmaceutical firms have a smaller workforce, invest less in R&D, and record much lower sales compared to the leading global firms.

The experience of the pharmaceutical industry illuminates the paradox of Japan's dual economy. Japan has an internationally competitive tier of export industries, such as carmakers and electronics, which coexist with non-competitive industries such as aluminium and food processing. While the Japanese pharmaceutical industry straddles these two tiers, most firms exist in the second tier. Compared to many of the country's stronger industries, the Japanese pharmaceutical industry has been characterised by a

domestic orientation, heavy reliance on imports, and small to medium sized firms.

These phenomena require historical explanation.

In this thesis, I explain why Japan was unable to develop a globally competitive pharmaceutical industry, despite its success in developing other high technology industries. No single factor explains why the Japanese pharmaceutical industry did not become an export-oriented or world-leading industry. I consider a number of factors, including government policy, industrial structure, and medical culture, that influenced industrial development. I aim to provide a comprehensive, multifactorial explanation for the relative weakness of the Japanese pharmaceutical industry.

My study of the Japanese pharmaceutical industry speaks to several broader themes in Japanese economic history. It addresses the role of the state in late economic development and the paradox of Japan's dual economy. I also examine whether the features of Japanese capitalism are conducive to the growth of a high technology industry such as pharmaceuticals. The thesis also shows how Japanese firms have responded to changes in intellectual property regimes and to the recent pressures of deregulation and globalisation.

The pharmaceutical industry is an important field of study in its own right. Most developed economies spend a substantial amount on health care and on medicines. In 2005, for example, OECD countries spent an average 8.9% of GDP on health care, of

which 13.8% was spent on prescription drugs.² In Japan, health care spending accounted for 8.2% of GDP, of which 17.0% was spent on prescription drugs.³ Moreover, therapeutic discoveries launched by pharmaceutical firms have revolutionised health standards and contributed significantly to economic development and social welfare.

Historical works on the Japanese pharmaceutical industry

The Japanese pharmaceutical industry is an important topic, but very little has been written on its history in either English or Japanese. The existing literature is largely confined to company histories written by company employees. Takeda, Daiichi Sankyo and Astellas and other leading Japanese pharmaceutical firms have published such histories.⁴ The in-house company histories are academically useful, as they provide chronologies of firms and other factual information. But they do not engage in rigorous analysis. The Japan Society for the History of Pharmacy published a history of the industry in the mid 1990s.⁵ Similar to the company histories, however, this work was more descriptive than analytical. A recent volume by Takashi Nishikawa provided an account of how the foundations of the post-war pharmaceutical industry were

² Average calculated from Organisation for Economic Co-operation and Development, *OECD Health Data 2008: Statistics and Indicators for 30 Countries* (Paris: Organisation for Economic Co-operation and Development, 2008) in SourceOECD, <http://www.sourceoecd.org>. It should be noted that the methods used to calculate figures vary according to country. In addition, figures for prescription drug expenditures as a percentage of total health care expenditures are not available for all OECD countries. The average has therefore been calculated based on available figures.

³ Ibid.

⁴ See for example, Takeda Pharmaceutical Co., *Takeda 200-nen* [200 Years of Takeda] (Osaka: Takeda Pharmaceutical Co., 1984); Daiichi Pharmaceutical Co., *Daiichi Seiyaku 90-nenshi* [Daiichi Pharmaceutical, a 90 Year History] (Tokyo: Daiichi Pharmaceutical Co., 2007); Sankyo Co., *Sankyo 100-nenshi* [Sankyo, a 100 year History] (Tokyo: Sankyo Co., 1999); Fujisawa Pharmaceutical Co., *Fujisawa Yakuhin 100-nenshi* [Fujisawa Pharmaceutical, a 100 Year History] (Osaka: Fujisawa Pharmaceutical Co., 1995); Yamanouchi Pharmaceutical Co., *Yamanouchi Seiyaku 50-nenshi* [Yamanouchi Pharmaceutical, a 100 Year History] (Tokyo: Yamanouchi Pharmaceutical Co., 1975). Daiichi Sankyo and Astellas were both formed in 2005 as a merger between Daiichi and Sankyo, and Fujisawa and Yamanouchi, respectively.

⁵ Nihon Yakushi Gakkai, *Nihon Iyakuhin Sangyōshi* [The History of the Japanese Pharmaceutical Industry] (Tokyo: Yakuji Nippōsha, 1995).

created during the Occupation period.⁶ But such works are few in number.

In contrast, the histories of the pharmaceutical industries of other industrialised countries have been the subject of extensive research. These include both in-house and scholarly company histories. There are also histories of pharmaceutical industries written of single countries and cross-country comparative histories of the pharmaceutical industry.

Most of the leading global pharmaceutical firms have published company histories. Commissioned works include those by R. P. T. Davenport-Hines, Judy Slinn, and Edgar Jones and John Savage on Glaxo, as well as Edmund Pratt and Jeffrey Rodengen on Pfizer.⁷ There are also scholarly studies of individual pharmaceutical firms. Louis Galambos's recent work on the history of Merck, for example, demonstrated the importance of networks in technological innovation. Galambos's study is widely respected in business history.⁸

In addition to company histories, there are histories of pharmaceutical industries in a single country. These include works such as *The British Pharmaceutical Industry since 1851* by T.A.B. Corley.⁹ In *The Rise of Drug Manufacture in America*, Glenn

⁶ Takashi Nishikawa, *Kusuri Kara Mita Nihon; Shōwa 20-nendai no Genfūkei to Konnichichi* [Looking at Japan from "Medicine": Scenes from the 1940s to the Present] (Tokyo: Yakuji Nippōsha, 2004).

⁷ R. P. T. Davenport-Hines and Judy Slinn, *Glaxo: A History to 1962* (Cambridge: Cambridge University Press, 1992); Edgar Jones and John Savage, *The Business of Medicine: The Extraordinary History of Glaxo, a Baby Food Producer, which Became One of the World's Most Successful Pharmaceutical Companies* (London: Profile, 2001). See also, Edmund T. Pratt, *Pfizer: Bringing Science to Life* (New York: Newcomen Society of the United States, 1985); Jeffrey L. Rodengen, *The Legend of Pfizer* (Fort Lauderdale: Write Stuff Syndicate, Inc., 1999).

⁸ Louis Galambos and Jane Eliot Sewell, *Networks of Innovation: Vaccine Development at Merck, Sharp & Dohme, and Mulford, 1895-1995* (Cambridge: Cambridge University Press, 1996).

⁹ T. A. B. Corley, "The British Pharmaceutical Industry since 1851," University of Reading Department of Economics, Working Paper No. 404, 1999.

Sonnedecker showed how the American industry was transformed from the small handicraft enterprises that existed in the late 18th century to the large, bureaucratized, and mechanized businesses in the early 20th century.¹⁰ Tom Mahoney also wrote on the rise of the early American pharmaceutical industry through the developments of new therapies at major firms such as Eli Lilly, Squibb, and Wyeth.¹¹

These histories of national pharmaceutical industries have been complemented by cross-country comparative histories. For example, Jonathan Liebenau showed how differences in medical science and practice impacted the development of pharmaceutical industries in Germany, the United Kingdom and the United States.¹² Lacy Glenn Thomas illustrated how British policies strengthened the competitiveness of the British industry over the French.¹³

A recent work by Alfred Chandler examined the development of the American and European pharmaceutical and chemical industries.¹⁴ Chandler discussed the Japanese pharmaceutical industry in several paragraphs, but his treatment of the topic was cursory and focused on the partnerships between Japanese and American firms such

¹⁰ Glenn Sonnedecker, *The Rise of Drug Manufacture in America* (Atlanta: Emory University, 1965). Sonnedecker illustrated how, for example, industrialization and scientific advances in organic chemistry, bacteriology, and pharmacology shaped drug manufacture in the United States.

¹¹ Tom Mahoney, *The Merchants of Life: An Account of the American Pharmaceutical Industry* (New York: Harper & Brothers, 1959).

¹² Jonathan Liebenau, "Industrial R&D in Pharmaceutical Firms in the Early Twentieth Century," *Business History* 26, no. 3 (November 1984): 329-346. Liebenau has also written other cross-country histories of the pharmaceutical industry. See for example, Jonathan Liebenau, "Ethical Business: The Formation of the Pharmaceutical Industry in Britain, Germany, and the United States before 1914," *Business History* 30, no. 1 (January 1988): 116-129.

¹³ Lacy Glenn Thomas, "Implicit Industrial Policy: The Triumph of Britain and the Failure of France in Global Pharmaceuticals," *Industrial and Corporate Change* 3, no. 2 (1994): 451-489. Other works by Thomas also emphasize the role of industrial policy in shaping the pharmaceutical industry. See for example, Lacy Glenn Thomas, "Spare the Rod and Spoil the Industry: Vigorous Competition and Vigorous Regulation Promote Global Competitive Advantage," *First Boston Working Paper Series* 90-03, 1990.

¹⁴ Alfred D. Chandler, *Shaping the Industrial Century: The Remarkable Story of the Modern Chemical and Pharmaceutical Industries* (Cambridge: Harvard University Press, 2005), 200, 237. Passing references to Japan are made on pages 189-190, 200, 237, 270-271, and 273-274.

as Takeda and Abbott, or Kirin Brewery and Amgen. Chandler noted that the Japanese pharmaceutical industry did not become a global player like its consumer electronics industry because of “barriers to entry.” Observing the difference between the strengths of Japan’s consumer electronics industry and the weakness of its pharmaceutical and chemical industry, Chandler argued that it was the timing of Japan’s entry into these markets that dictated the different outcomes.

Chandler observed that the chemical and pharmaceutical industry emerged in the late 19th century, whereas the consumer electronics industry emerged much later, in the mid 20th century. He explained that when Japanese consumer electronic firms began to export in the post-war period, it was relatively easy for new entrants to penetrate global markets because the consumer electronics industry itself was young. In contrast, Japanese pharmaceutical firms were unable to enter the markets dominated by the long-established European and American companies since the 1970s and 1980s.¹⁵

The question of timing identified by Chandler helps to explain why the Japanese pharmaceutical industry did not become a global leader, but it is not the only reason. Chandler argues that Japan’s success in consumer electronics and relative weakness in chemicals and pharmaceuticals “cannot be explained in terms of national culture, national political processes and institutions, or national educational institutions.”¹⁶ In this thesis, I argue that some of these factors did play a significant role in shaping Japan’s pharmaceutical industry. Chandler’s work tends to overlook important issues

¹⁵ Ibid., 3-6.

¹⁶ Ibid., 5.

such as the role of state-industry relations in the pharmaceutical industry, the role of smaller-sized firms in pharmaceutical innovation, and the role of culture in shaping industrial development.

The historical literature on the pharmaceutical industry has focussed on a number of themes, such as science and innovation, drug regulation, and the links between academic and industrial research. For example, Alfonso Gambardella wrote on the impact of technological advances on industrial structure, while Peter Temin wrote on the motivations and implications of American drug regulation.¹⁷ Others such as John Patrick Swann, Jeffrey L. Furman and Megan J. MacGarvie examined the American history of cooperative research between universities and the pharmaceutical industry.¹⁸ This thesis engages with these themes and attempts to link the Japanese experience with the growing body of literature on the history of the pharmaceutical industry in other countries.

Non-historical works on the Japanese pharmaceutical industry

While the historical literature on the Japanese pharmaceutical industry remains sparse, a number of non-historians have examined the Japanese pharmaceutical industry. The volume of non-historical literature on the Japanese pharmaceutical industry has

¹⁷ Alfonso Gambardella, *Science and Innovation: The US Pharmaceutical Industry During the 1980s* (Cambridge: Cambridge University Press, 1995); Peter Temin, *Taking Your Medicine: Drug Regulation in the United States* (Cambridge: Harvard University Press, 1980). See also, Peter Temin, "Technology, Regulation, and Market Structure in the Modern Pharmaceutical Industry," *The Bell Journal of Economics* 10, no. 2 (1979): 429-446.

¹⁸ John Patrick Swann, "Universities, Industry, and the Rise of Biomedical Collaboration in America," in *Pill Peddlers: Essays on the History of the Pharmaceutical Industry*, eds. Jonathan Liebenau, Gregory J. Higby, Elaine C. Stroud (Madison: American Institute of the History of Pharmacy, 1990), 73-90; Jeffrey L. Furman and Megan J. MacGarvie, "Early Academic Science and the Birth of Industrial Research Laboratories in the U.S. Pharmaceutical Industry," *Journal of Economic Behavior & Organization* 63 (2007): 756-776.

burgeoned in step with the industry's dramatic transformation since the 1990s.¹⁹ Much of this recent literature has been written from the perspective of political economy, and has emphasised issues such as industrial policy, R&D incentives, and international competitiveness.

Scholars of the Japanese pharmaceutical industry differ in their assessments of Japan's performance in the pharmaceutical industry. Some emphasize the weakness of the industry relative to its foreign counterparts, while others stress its phenomenal growth over the post war period. Another group of scholars occupies a middle ground. It should be noted that these assessments are situated along a continuum. As well, some scholars may differ in their assessments, but share similar views on specific issues.

A particularly negative view of the industry has been put forth by Lacy Glenn Thomas. Thomas argued that the Japanese pharmaceutical industry was dysfunctional, and explored its "pathologies," such as short product life, imitative drug development, uncompetitive firms, and foreign exclusion. Thomas argued that the weak performance of the Japanese pharmaceutical industry was the outcome of flawed industrial policy.²⁰ While Thomas does situate his analysis in a larger social context, his explanation for the weakness of the industry is overly simplistic. Thomas's account

¹⁹ Past scholarship on the Japanese pharmaceutical industry revolved around topical issues of the time. Over the years, these have evolved from writings on capital liberalisation and product patents to R&D, deregulation and industry reorganisation. Recent works include, for example, Shin'ichi Ishii, "Kigyō no Gaiburenkei ni taisuru Ninshiki to Gaiburenkei no Jisshi: Sangakurenkei to Iyakuin Kigyō o Chūshin to Shita Hikakubunseki [The Perception and Reality of External Collaborations: A Comparative Analysis of University-Industry Collaborations in the Pharmaceutical Industry]," *Keiei Kenkyū* 53, no. 3 (2002): 205-217; Takuji Hara, *Innovation in the Pharmaceutical Industry: The Process of Drug Discovery and Development* (Cheltenham: Edward Elgar, 2003); Ryūhei Wakasugi and Harue Wakasugi, "Iyakuin no Kenkyū Kaihatsu to Hōseido [Pharmaceutical R&D and the Legal System]," *Mitagakkai Zasshi* 99, no. 1 (April 2006): 57-74.

²⁰ Lacy Glenn Thomas, *The Japanese Pharmaceutical Industry: The New Drug Lag and the Failure of Industrial Policy* (Northampton: Edward Elgar, 2001).

tends to be overly politicised, and he does not fully consider the impact, for example, of national differences in patterns of disease, culturally distinct approaches to medical therapy, or the lack of entrepreneurship among Japanese firms.

While softer in tone, Jeremy Howells and Ian Neary also adopted a pessimistic view, and stated that the Japanese pharmaceutical industry suffered from “distant, controlled, and reactive” government administration.²¹ Howells and Neary studied how government industry relations shaped the UK and Japanese pharmaceutical industries. They offered valuable insight into how government industry relations were influenced by a complex combination of factors, including industrial structure, the international orientation of industry, the domestic policy-making process, and external pressures from foreign governments or industrial associations. In his study of the biotechnology sector, Stephen Collins also argued that the Japanese bureaucracy was far less coherent and effective in its planning, with much less presence than that of the United States.²²

Other academics have provided a more positive assessment of the industry. Hiroyuki Odagiri’s optimistic depiction of the Japanese pharmaceutical industry was much the opposite of the account given by Thomas. While Odagiri acknowledged that the Japanese pharmaceutical industry lagged behind its US and European counterparts, his emphasis was on the industry’s accomplishments. He argued that the industry’s growth was achieved through the entrepreneurial initiative of firms that adopted Western

²¹ Jeremy Howells and Ian Neary, *Intervention and Technological Innovation: Government and the Pharmaceutical Industry in the UK and Japan* (Basingstoke: Macmillan, 1995).

²² Steven W. Collins, *The Race to Commercialize Biotechnology: Molecules, Markets, and the State in the United States and Japan* (London: RoutledgeCurzon, 2004).

technologies, pursued their own innovations, and transformed their business in response to evolving market conditions.²³ But Odagiri's work is slightly one-sided. He does not elaborate upon why, for example, Japan's pharmaceutical industry did not become an export-oriented industry.

A middle ground has been established by authors such as Tomofumi Anegawa and Michael Reich. These scholars do, however, lean toward a negative assessment of the Japanese pharmaceutical industry. Anegawa argued that the Japanese pharmaceutical industry succeeded in achieving phenomenal growth and contributing to the country's vast improvements in public health. But as the government failed to implement timely policies and as firms failed to seek market opportunities abroad, the industry remained dependent on the domestic market – comprised of firms that were smaller, less profitable, and less R&D intensive compared to its foreign rivals. Reich argued that the Japanese pharmaceutical industry was shaped by a combination of public policies, often through indirect and unintentional means. While acknowledging that the industry was domestically oriented, Reich argued that the industry's globalisation had been led by the entrepreneurship among Japanese firms.

Both Anegawa and Reich argued that while earlier government policies were effective in nurturing the pharmaceutical sector, the government persisted with these policies when they were no longer appropriate.²⁴ In their view, the Japanese pharmaceutical

²³ Hiroyuki Odagiri and Akira Goto, *Technology and Industrial Development in Japan: Building Capabilities by Learning, Innovation, and Public Policy* (Oxford: Oxford University Press, 1996).

²⁴ Michael Reich, "Why the Japanese Don't Export More Pharmaceuticals: Health Policy as Industrial Policy," *California Management Review* 32, no. 2 (1990): 124-150; Tomofumi Anegawa, "Sangyō Seisaku to shite no Seikō to Kisei Seisaku to shite

industry developed a strong capacity for innovation.²⁵ But the government failed to shift and update its policies to encourage the transition to a more mature pharmaceutical industry based on scientific innovation rather than the volume production of imitative products. Scholars such as Anegawa and Reich argued that the delayed shift in policymaking weakened the industry's ability to respond to changes in the market and compete with leading global pharmaceutical firms.

While Reich elaborates upon the combined effects of health and industrial policy, his overemphasis on policy downplays the significance of other factors in the shaping of Japan's pharmaceutical industry. He does not, for example, sufficiently address the impact of industrial structure, Japan's medical infrastructure, or the lack of initiative among Japanese firms to expand into overseas markets. Anegawa provides an excellent account on how government policy, as well as lack of entrepreneurship, has affected Japan's pharmaceutical industry. But he neglects to address the impact of medical culture or the R&D environment in contributing to the relative weakness of the Japanese industry. This thesis attempts to address these issues.

The conclusions of this thesis largely support the views outlined by Anegawa and Reich. It also provides different explanations for the performance of the Japanese pharmaceutical industry. While the government's health and industrial policies did

no Shippai [The Success of Industrial Policy and Failure of Regulatory Policy],” *Doraggu Magajin* 43 (July 2000): 78-88; Tomofumi Anegawa, “Nihon no Iyakuhin Sangyō: Sono Seikō to Shippai [The Japanese Pharmaceutical Industry: Its Success and Failure],” *Iryō to Shakai* 12, no. 2 (2002): 49-78. See also, Robert Neimeth, “Japan's Pharmaceutical Industry Postwar Evolution,” in *The Changing Economics of Medical Technology*, eds. Annetine Gelijns and Ethan A. Halm, Committee on Technological Innovation in Medicine, Institute of Medicine (Washington, D.C., National Academies Press, 1991), 155-168.

²⁵ This view was echoed in other works, such as Elma S. Hawkins and Michael R. Reich, “Japanese-originated Pharmaceutical Products in the United States from 1960 to 1989: An Assessment of Innovation,” *Clinical Pharmacology and Therapeutics* 51 (January 1992): 1-11.

undermine its potentials for growth, the underperformance of Japan's pharmaceutical industry was also due to multiple other factors.

On Japanese industrial policy

This thesis engages with the debate on the role of Japanese industrial policy in explaining post-war economic growth. One viewpoint, often associated with Chalmers Johnson, has argued that a strong and interventionist state was responsible for Japan's success. Johnson argued that a state-directed capitalism orchestrated primarily by the Ministry of International Trade and Industry (MITI) played a central role in guiding Japan's post-war economic development.²⁶ But Johnson's argument was problematic for oversimplifying and exaggerating the role of the MITI. He tended to overlook MITI's failures in industries such as aluminium and petrochemicals, and understated the importance of various other factors ranging from Japanese management styles to collectivist culture.

Scholars such as Daniel Okimoto have expanded upon Johnson's view, and have argued that the relative effectiveness of Japanese industrial policy was supported by other factors, such as the long-standing dominance of the Liberal Democratic Party in the Japanese Diet, the relative weakness of labour based political parties, low military expenditures, and a sizeable homogeneous population.²⁷ But Okimoto did not address

²⁶ Chalmers A. Johnson, *MITI and the Japanese Miracle: The Growth of Industrial Policy, 1925-1975* (Stanford: Stanford University Press, 1982). The Ministry of International Trade and Industry, established in 1949, became the Ministry of Economy, Trade and Industry (METI) in 2001. This thesis refers to the ministry of industry as the Ministry of International Trade and Industry (MITI) as the entity that governed Japanese industries for most of the post-war period.

²⁷ Daniel I. Okimoto, *Between MITI and the Market: Japanese Industrial Policy for High Technology* (Stanford: Stanford University Press, 1989). For other similar views, see for example, T. J. Pempel, *Policy and Politics in Japan: Creative Conservatism, Policy and Politics in Industrial States* (Philadelphia: Temple University Press, 1982); John Zysman, *Governments,*

the role of government policy on the pharmaceutical industry.

The view that industrial policy played a central role in Japanese economic development has been challenged by scholars such as Hugh Patrick and Phillip Trezise, who argued that the drive and momentum of growth lay outside the realm of the state.²⁸ Proponents of this market-regulation thesis have asserted that Japan's economic development occurred through the growth of factor inputs, the dynamism of the private sector, improved education, and amicable labour-management relations. Other scholars provided alternative reasons for Japan's so-called economic miracle. David Friedman, for example, argued that Japanese economic development occurred via small-scale firms that developed flexible manufacturing strategies, which featured extensive and continuous product changes.²⁹

In debating the role of industrial policy on Japan's post-war economic development, both Johnson's proponents and his critics referred mostly to the industries that were regulated by the MITI. The Japanese pharmaceutical industry is an exception in that it came under the jurisdiction of the Ministry of Health and Welfare (MHW), a bureaucracy with different priorities in policy.³⁰ This thesis examines an industry that

Markets and Growth: Financial Systems and the Politics of Industrial Change (Ithaca: Cornell University Press, 1989).

²⁸ Hugh Patrick and Henry Rosovsky, *Asia's New Giant: How the Japanese Economy Works* (Washington, D.C.: Brookings Institution, 1976). See also, Phillip H. Trezise, "Industrial Policy is not the Major Reason for Japan's Success," *Brookings Review* 1, no. 3 (1983): 13-18.

²⁹ David Friedman, *The Misunderstood Miracle: Industrial Development and Political Change in Japan* (Ithaca: Cornell University Press, 1988).

³⁰ One scholar, Gary Saxonhouse did touch upon the role of industrial policy on the pharmaceutical industry in the 1980s. Saxonhouse argued that industrial policy did little in its development of this industry, noting that the government extended few direct subsidies, R&D grants, or tax benefits toward industrial development. See Gary R. Saxonhouse, "Industrial Policy and Factor Markets: Biotechnology in Japan and the United States," in *Japan's High Technology Industries: Lessons and Limitations of Industrial Policy*, ed. Hugh Patrick (Seattle: University of Washington Press, 1986), 97-133. The Ministry of Health and Welfare, established in 1938, became the Ministry of Health, Labour and Welfare (MHLW) in 2001. This thesis refers to the ministry of health as the Ministry of Health and Welfare (MHW) as the entity that governed the pharmaceutical industry for most of the post-war period.

lay outside the jurisdiction of the MITI and expands the discussion on the role of Japanese government policy in industrial development. This thesis also challenges the notion that state intervention led to the development of strong industries, as MHW policies did not always result in industrial growth.

On late economic development

This thesis also builds upon the scholarship on late economic development. In the 1960s, Alexander Gerschenkron introduced the concept of “relative backwardness,” and elaborated upon how late developing economies substituted for the missing prerequisites of economic modernisation through banks or state intervention. He also argued that different economies experienced different trajectories of growth according to their level of development.³¹

Since then, the success of the East Asian economies and the struggles experienced by the Latin America and African economies have prompted further scholarship on late development. Many works have focussed on the role of the state in fostering the growth of the late developing economies. A recent work by Mauro Guillén suggested that countries experience both different paths and ends in development, and questioned the idea of convergence.³² Scholars writing on the experience of the East Asian economies, such as Alice Amsden, Ha Joon Chang, and Takashi Hikino, have discussed the role of a highly interventionist state in economic development. Works on

³¹ Alexander Gerschenkron, *Economic Backwardness in Historical Perspective: A Book of Essays* (Cambridge: Harvard University Press, 1962).

³² Mauro F. Guillén, *The Limits of Convergence: Globalization and Organizational Change in Argentina, South Korea, and Spain* (Princeton: Princeton University Press, 2003).

the East Asian experience have also tended to emphasise how industrialisation often occurred through the borrowing of technologies from advanced nations, and how the pursuit of incremental innovations led to different forms of corporate organisation. Scholars of Latin America and Africa, such as Peter Evans or Robert H. Bates, have often considered the multiple reasons for policy failure and underdevelopment.³³

This thesis relates these concepts on late development to the development of Japan's pharmaceutical industry. Compared to earlier developers, Japan experienced a different trajectory in creating a modern pharmaceutical industry. Over the decades, Japan developed its industry via a strong developmental state, the borrowing of technologies, and different forms of corporate organisation.

In studying the history of Japan's pharmaceutical industry, this thesis also examines the challenges of late developing economies in developing a high technology sector. While scholars such as Amsden and Hikino have tended to refer to the state as a monolithic entity, this thesis attempts to show how different roles of the state – such as to promote industrial growth or improve public health – came into conflict under different ministerial guidance. Moreover, few scholars have examined the evolution of pharmaceutical industries from the perspective of late development. This thesis engages in discussions over the speed of “catch-up” growth, the organisational

³³ Alice H. Amsden and Takashi Hikino, “Staying Behind, Stumbling Back, Sneaking Up, Soaring Ahead: Late Industrialization in Historical Perspective,” in *Convergence of Productivity: Cross-national Studies and Historical Evidence*, eds. William J. Baumol, Richard R. Nelson, and Edward N. Wolff (Oxford: Oxford University Press, 1994), 285-315; Ha-Joon Chang, *Kicking Away the Ladder: Development Strategy in Historical Perspective* (London: Anthem Press, 2002); Peter Evans, *Embedded Autonomy: States and Industrial Transformation* (Princeton: Princeton University Press, 1995); Robert H. Bates, *Markets and States in Tropical Africa: The Political Basis of Agricultural Policies* (Berkeley: University of California Press, 2005). See also, Alice H. Amsden, *The Rise of “The Rest”: Challenges to the West From Late-industrialization Economies* (Oxford: Oxford University Press, 2001).

structure of industry, and the role of the state in guiding industrial development. It also elaborates upon alternative paths to development; particularly on how a late developing economy might catch up or surpass other economies in the newer, knowledge intensive industries, which are based on non-indigenous technologies.

On New Institutional Economics

This thesis also draws upon the insights of New Institutional Economics to examine how institutions shaped the history of Japan's pharmaceutical industry. Douglass North defined institutions as the "rules of the game," referring to the formal laws, informal conventions, and codes of behaviour that shape human interaction.³⁴

Proponents of New Institutional Economics such as Oliver Williamson and Avner Greif have attempted to move beyond the limitations of neoclassical economics to examine the role of legal, political, economic, and social institutions in economic performance.³⁵

The literature on New Institutional Economics is particularly helpful in examining how Japan's intellectual property regime impacted upon industrial development. The delayed adoption of product patents, for example, long discouraged firms from making high R&D investments to pursue breakthrough discoveries. The thesis also indicates how, at times, the lack of credible institutions – such as in drug standards or drug

³⁴ Douglass Cecil North, *Institutions, Institutional Change and Economic Performance* (Cambridge: Cambridge University Press, 1990), 3.

³⁵ See for example, Oliver E. Williamson, *Markets and Hierarchies: Analysis and Antitrust Implications* (New York: Free Press, 1975); Avner Greif, *Institutions and the Path to the Modern Economy: Lessons from Medieval Trade, Political Economy of Institutions and Decisions* (Cambridge: Cambridge University Press, 2006). See also, Ronald Coase, "The New Institutional Economics," *AEA Papers and Proceedings* 8, no. 2 (May 1998): 72-74.

approval criteria – undermined the development of Japan’s pharmaceutical industry.

On the varieties of capitalism

Scholars writing on the varieties of capitalism have often distinguished the liberal market economies, such as Britain and the United States, from the more coordinated market economies, such as Germany and Japan.³⁶ These works on the typologies of capitalism have given rise to discussions on convergence. Some scholars, such as Susan Strange and Philip Cerny, have suggested that the pressures of globalisation and deregulation would lead to the erosion of the differences between countries.³⁷ On the other hand, scholars, such as Vivien Schmidt, Peter A. Hall and David Soskice have argued that the differences in political and economic institutions lead firms to generate divergent responses and outcomes – and would limit convergence.³⁸

Japanese capitalism has been characterised by the long-term relationships of firms with their employees, other firms, and government. These manifested during the high growth rate period as distinct features of the Japanese economic system, such as lifetime employment, *keiretsu* relationships, and strong state-industry relations.³⁹

Scholars of Japan have debated whether the distinctive features of Japanese capitalism

³⁶ Ronald Philip Dore, *Stock Market Capitalism: Welfare Capitalism: Japan and Germany Versus the Anglo-Saxons* (Oxford: Oxford University Press, 2000).

³⁷ Susan Strange, *The Retreat of the State: The Diffusion of Power in the World Economy* (Cambridge: Cambridge University Press, 1998); Philip G. Cerny, “The Dynamics of Financial Globalization: Technology, Market Structure, and Policy Response,” *Policy Sciences* 27, no. 4 (1994): 319-342.

³⁸ Vivien Ann Schmidt, *The Futures of European Capitalism* (Oxford: Oxford University Press, 2002); David W. Soskice and Peter A. Hall, eds., *Varieties of Capitalism: The Institutional Foundations of Comparative Advantage* (Oxford: Oxford University Press, 2001). Many scholars have written on this theme. See also, Colin Crouch and Wolfgang Streeck, *Political Economy of Modern Capitalism: Mapping Convergence and Diversity* (London: Sage, 1997).

³⁹ Keiretsu refers to a form of Japanese corporate organisation that featured prominently up to the 1990s, where associated member firms were generally centered around a main bank and held interlocking shares. Strong state-industry relations refer, for example, in the government’s promotion of post-war industrial growth through industrial policies implemented via administrative guidance.

have been responsible for the country's economic stagnation since the 1990s. A related issue that has been discussed is whether – or to what extent – Japanese capitalism might converge with the Anglo-Saxon style of capitalism.

Some scholars have argued that the distinctive features of Japanese capitalism are an asset for Japan. For instance, Kozo Yamamura has argued that Japanese capitalism would enable the country to develop a strong high-technology sector as the pace of technological change slowed. Marie Anghodoguy, however, argued that the distinct features of Japanese capitalism became a disadvantage in the information technology age. She argued that Japan's economic system could not respond quickly and flexibly to rapid, discontinuous, and unpredictable advances in science and technology or the increasing pressures of globalisation.⁴⁰ Many viewed this as one of the main causes for Japan's weak performance after the 1990s. Scholars such as Steven Vogel agreed that the Japanese model needed to change, but stressed the limits of convergence with American or British styles of capitalism.⁴¹ The experience of Japan's pharmaceutical industry largely supports this view, and illustrates that while Japanese capitalism was suitable for earlier phases of development, it was less suitable in more advanced phases of development.

This thesis studies how the specific features of Japanese capitalism, such as *keiretsu* structures and government policies, shaped Japan's pharmaceutical industry. Japanese

⁴⁰ Marie Anghodoguy, *Reprogramming Japan: The High Tech Crisis Under Communitarian Capitalism* (Ithaca: Cornell University Press, 2005).

⁴¹ Kozo Yamamura and Wolfgang Streeck, *The End of Diversity?: Prospects for German and Japanese Capitalism* (Ithaca: Cornell University Press, 2003); Steven Kent Vogel, *Japan Remodeled: How Government and Industry are Reforming Japanese Capitalism* (Ithaca: Cornell University Press, 2006).

pharmaceutical manufacturers, for example, long maintained *keiretsu* relationships with pharmaceutical wholesalers rather than vertically integrating. Japanese firms also responded closely to changes in government policy. But in recent years, these features of Japanese capitalism have become less important for leading Japanese pharmaceutical firms that respond increasingly to American or European policies to expand into overseas markets. This thesis considers the extent to which Japan's pharmaceutical industry might converge with leading Western pharmaceutical firms as Japanese firms globalise.

Thesis objectives

This thesis aims to examine the historical causes for the relative weakness of Japan's pharmaceutical industry. Studying the weakness of this industry is important in developing a deeper understanding of the Japanese economy. This thesis advances several reasons, including government policy, industrial structure, and Japanese medical culture, to help explain the why Japan was not able to develop a globally competitive pharmaceutical industry.

It should be recognised that, in all developed countries, government policy plays a central role in the shaping of any pharmaceutical industry. Not only do national governments establish the legal definitions of pharmaceuticals, they grant approvals for each product launch. In addition, national governments monitor all operations beginning from pharmaceutical R&D, manufacturing, marketing, to pricing and distribution. In addition, a country's intellectual property regime and its degree of

protectionism impacts industrial development. Industrial organisation and medical culture also shape the development of a pharmaceutical industry. This is because firm size often dictates the type and size of R&D activity possible and medical culture can dictate the type of medicines in demand. Through the experience of the Japanese pharmaceutical industry, this thesis seeks to provide a more comprehensive understanding of the Japanese economy.

Thesis methodology

My research uses two classes of medicines, antibiotics and anti-cancer drugs, as case studies for exploring the post 1945 history of the Japanese pharmaceutical industry. As will be discussed below, my decision to adopt a medicines-based, rather than company-based approach stems, in part, from the availability of sources. But a medicines-based approach is also useful, because it sheds light on the extent to which the development of the industry was shaped by health needs at a given time, the therapeutic attributes of certain medicines, and variations in approaches to medical treatment.

Demographic statistics indicate high mortality and morbidity rates from infectious disease during the early post-war period, and for diseases of affluence in the more recent period – leading to high demand for drugs to treat these conditions. Infectious disease, particularly tuberculosis, were the leading cause of death in the years after World War II, while cancer has become the leading cause of death in Japan since

1981.⁴² Given that antibiotics were important in the early post-war period and anticancer drugs became more important in subsequent decades, the two case studies encompass the entire post-war period. This thesis examines how Japanese industry responded to high demand conditions during earlier and later phases of the post-war era.

A case study of the antibiotics sector sheds light on the initial course of development in Japan's pharmaceutical industry – alongside economic trends, demographic change and scientific/technological advances. In turn, a case study of the anti cancer drug sector illustrates how the industry evolved in later years, in step with revisions toward stricter regulatory guidelines for drug development, advances in drug discovery methods, and globalisation. This approach also reveals how differences in therapeutic attributes, as well as differences between older and newer drugs, influence market dynamics.⁴³

There are other reasons why a case study of the antibiotics sector and anticancer drug sector will be helpful in examining the historical dynamics of Japan's pharmaceutical industry. Both sectors are large: Japan's antibiotics and anticancer drug markets remain the second largest in the world.⁴⁴ As the most produced and exported pharmaceuticals in Japan for much of the post-war era, the antibiotics sector provides an ideal forum to examine the acquisition of production as well as export capacities in

⁴² Ministry of Health, Labour and Welfare, "Deaths by Leading Cause of Death" Population and Households," <http://www.stat.go.jp/english/data/chouki/02.htm>, (accessed 1 December 2007).

⁴³ For example, market dynamics differ markedly between chronic and acute ailments.

⁴⁴ Datamonitor, "Japan – Antibacterial Drugs," *Industry Profile* (London: Datamonitor, 2002); Datamonitor, "Japan – Cancer drugs," *Industry Profile* (London: Datamonitor, 2002).

the pharmaceutical industry. As Japanese pharmaceutical firms have launched globally successful drugs in both sectors, a case study of antibiotics and anticancer drugs in Japan will also shed valuable insight into evolution of pharmaceutical innovation in Japan.

This thesis has selected different therapeutic sectors, rather than firms, to study the history of the pharmaceutical industry. As mentioned earlier, adopting an industry-level perspective and examining different therapeutic sectors was partly due to the availability of sources. The adoption of an industry-level approach stems from the lack of firm-level data available over the entire 1945 period. Opting for a firm-based approach would also have required access to company archives. But access to company archives has been notoriously difficult in the pharmaceutical industry. While a more in-depth case study of individual pharmaceutical firms through company archives might have provided a more insight into the motivations behind firm behaviour, I have tried to supplement this by examining the experiences of several firms through publicly available documents. These include scientific journals, newspaper and magazine articles, trade journals and company security filings – as well as company histories.

While the types of information available in these sources were adequate enough to follow the drug development at individual firms, in many ways they do not provide a comprehensive view of any given firm. However, it is debatable whether access to corporate archives will prove easier in the future. Still, examining the industry through

therapeutic sectors allows for qualitative data to supplement substantial gaps in both industry-wide and firm-level data.

To a certain extent, the selection of specific firms for case studies in the antibiotics and anticancer drug sector was also dictated by availability of sources. The firms selected were those that developed the leading drugs during a given period. It is recognised that they are not representative of the entire pharmaceutical industry; for the most part, they showed the Japanese pharmaceutical industry at its best. But by selecting the strongest of Japanese firms across time, the case studies should also provide a more convincing explanation as to why – even with its best pharmaceutical firms – Japan was not able to develop a world leading pharmaceutical industry.

Sources

This thesis consulted a range of both archival and published sources from across government, industry, and academia. Several interviews were also conducted. The thesis follows the evolution of the Japanese pharmaceutical industry with consideration to the strengths, weaknesses, and biases of source material.

Archival sources were primarily used to investigate efforts to build a modern pharmaceutical industry at the end of the war and during the Allied Occupation of Japan between 1945 and 1952. This was done by looking at how Japanese firms acquired antibiotic production capacities – with the help of the Japanese military, American Occupation forces, and the Japanese government.

Japanese military documents pertaining to penicillin production efforts up to 1945 were viewed at the Naito Museum of Pharmaceutical Science and Industry in Gifu Prefecture, Japan. Sources consulted include memoranda by Katsuhiko Inagaki, who led initial penicillin production efforts in Japan, minutes of the Penicillin Committee, and writings by domestic scientists involved in production efforts.⁴⁵ These sources provided a detailed chronology of penicillin development in Japan.

The American Occupation forces played a fundamental role in establishing the foundations of Japan's post-war pharmaceutical industry. Memoranda, correspondence, and official publications by the Public Health and Welfare Section of the Occupation regime were consulted at the National Diet Library in Tokyo.⁴⁶ The Prange Collection at the University of Maryland provided a wealth of material contained in popular press and trade journals from the Occupation period.⁴⁷ The Rutgers University Special Collections and University Archives held correspondence between Japanese government and American scientists regarding technology transfers to Japan at the end of the Occupation era.⁴⁸

It is recognised that the official documents of the Public Health and Welfare Section are biased in favour of the Occupation regime, and that this needs to be taken into

⁴⁵ Penicillin Papers, Naito Museum of Pharmaceutical Science and Industry, Kagamihara, Japan.

⁴⁶ Papers on the Allied Occupation of Japan, National Diet Library, Tokyo, Japan.

⁴⁷ Occupation-period Newspapers and Magazines, Gordon W. Prange Collection, University of Maryland Library, College Park, Maryland, United States.

⁴⁸ Selman A. Waksman Papers, Special Collections and University Archives, Rutgers University Library, New Brunswick, New Jersey, United States.

account when considering, for example, the discrepancies of statistical data between Japanese sources. At the same time, however, much of the memoranda and correspondence consulted were not public documents at the time, and contained detailed information on the motivations and actions of the American Occupation authorities in building a modern pharmaceutical industry in Japan.

This thesis consulted a range of published sources. These included official government publications, company documents, academic and trade journals, as well as the popular press. Published government sources provided information on state administration as well as statistical data on industry performance. While statistical information has been compiled by various ministries, changes in government policy and industry trends are summarised in *Yakumu Kōhō* [Bulletin of Pharmaceutical and Supply Bureau], a MHW bulletin that records actions by the Ministry of Health and Welfare toward pharmaceutical administration.⁴⁹ The publication also provides data on approvals granted for new drugs (New Chemical Entities) or manufacturing licenses granted. Other MHW publications such as the *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry], *Iyakuhin Sangyō Jittai Chōsa Hōkoku* [Report on the Status of the Pharmaceutical Industry] provide annual statistics on industry.⁵⁰ The former provide figures on production and trade according to

⁴⁹ Ministry of Health and Welfare, *Yakumu Kōhō* [Bulletin of Pharmaceutical and Supply Bureau] (Tokyo: Yakumu Kōhōsha, 1949-2006).

⁵⁰ Ministry of Health and Welfare, *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Yakugyō Keizai Kenkyūjo, 1953-1967); Ministry of Health and Welfare, *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Yakugyō Keizai Kenkyūjo, 1968-2000); Ministry of Health, Labour and Welfare, *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Jihō, 2001-2006); Ministry of Health and Welfare, *Iyakuhin Sangyō Jittai Chōsa Hōkoku* [Report on the Status of the Pharmaceutical Industry] (Tokyo: Ministry of Health and Welfare, 1988-2000); Ministry of Health, Labour and Welfare, *Iyakuhin Sangyō Jittai Chōsa Hōkoku* [Report on the Status of the Pharmaceutical Industry] (Tokyo: Ministry of Health, Labour and Welfare, 2001-2006).

therapeutic sector as well as production sites, while the latter provide detailed information ranging from firm size, workforce, and market concentration.

There are several limitations with the figures contained in the *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei* and *Iyakuhin Sangyō Jittai Chōsa Hōkoku*. The first involves production values contained in the *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei*. These production values have been used as proxy measures for market size. It is recognised that production values do not accurately measure market size, as they do not reflect additional expenses such as handling, shipment, and warehousing, which are included in sales values. However, production values are widely used as proxy measures in Japan because historical sales figures do not exist for the pharmaceutical industry.

Other limitations with the production values also need be addressed. Production figures contained in the *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei* are based on questionnaires sent via prefectural agencies to individual firms. This method of data collection is subject to firm bias, as firms are likely to submit overly favourable values, and as the stronger firms will be more likely to respond. Moreover, while production values are lower than statistics for shipment values, it is not entirely clear how these figures have been calculated – and there is likely to be considerable variation at individual firms. Despite their weaknesses, however, these production values remain the best indicators of industry-wide performance over time.

Similar limitations exist in statistics compiled in the *Iyakuhin Sangyō Jittai Chōsa*

Hōkoku, such as for firm size, workforce, and market concentration. These data are collected from individual firms using questionnaires sent from prefectural agencies. As a result, not only are firms likely to submit favourable figures, but the data gathered will also be more representative of firms willing and capable of submitting strong results. Data gathered are likely to present the Japanese pharmaceutical industry in a slightly more positive light than its actual status.

As the *Iyakuhin Sangyō Jittai Chōsa Hōkoku* is not available prior to 1988, market concentration data for the years between 1975 and 1994 were obtained from the Fair Trade Commission (FTC).⁵¹ The statistics made available by the FTC are based on responses to questionnaires sent to individual firms. These figures are also prone to firm biases, as stronger firms may under-report figures and weaker firms may over-report figures. The data are also based on submitted responses of production values, which differ from actual sales figures and are subject to the idiosyncrasies of calculation methods used at individual firms. However, they remain the best historical estimates of market concentration available.

Official prices for prescription drugs in Japan are available in three publications: the *Hokenyaku Jiten* [Insured Drugs Almanac], *Shakai Hoken Yakka Kijun* [Insured Drug List] and *Yakka Kijun* [Drug List].⁵² The first two are published by a pharmaceutical publisher while the latter is published by a legal publisher, but there should be no

⁵¹ Japan Fair Trade Commission, *Shuyō Sangyō ni okeru Ruiseki Seisan Shūchūdo* [Concentration Ratio of Main Industries] (Tokyo: Japan Fair Trade Commission, 1975-1994) <http://www.jftc.go.jp/katudo/ruiseki/ruisekidate.html> (accessed 1 June 2008).

⁵² Yakugyō Kenkyū-kai, *Hokenyaku Jiten* [Insured Drugs Almanac] (Tokyo: Jihō, 1969-2006); Nihon Yakuzai-shi-kai, *Shakaihoken Yakka Kijun* [Insured Drug List] (Tokyo: Yakuji Nippōsha, 1977-2006). Shin Nihon Hōki Shuppan, *Yakka Kijun* (Tokyo: Shin Nihon Hōki Shuppan, 1965, 1968, 1972, 1975, 1977-2006).

discrepancy in the figures, save for differences stemming from the month of publication. Prices refer to the brand name drug by the original developer. While official figures may differ from market prices, they are still relevant in indicating price reduction trends or incentives to minimise investment risk by developing new drugs with minimal innovative value and short product life.

Figures on pharmaceutical trade are based on trade statistics in the *Tsūshō Hakusho* [White Paper on International Trade] by the MITI, which differ slightly from figures compiled by MHW in the *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei*.⁵³ While the former are based on customs declarations upon export or import, the latter are based on questionnaires sent via prefectural agencies which ask firms applying for import or export approval to provide expected import or export values. Although both figures may reflect incentives to underreport, trade figures from the *Tsūshō Hakusho* are used from the view that custom declarations are likely more accurate than responses for expected import/export values.⁵⁴

It should be noted that trade figures include both finished and bulk products. Japan has historically relied on the imports of bulk products to produce finished products. Any analysis based on imported values therefore obscures the degree of reliance on bulk products, which are much lower in price compared to finished products.

⁵³ In Japan, white papers refer to reports published by government ministries that provide information on the current status of relevant policy areas and address future agendas.

⁵⁴ See Ministry of International Trade and Industry, *Tsūshō Hakusho* [White Paper on Trade] (Tokyo: Ōkurashō Insatsukyoku, 1958-1973); Ministry of International Trade and Industry, *Tsūshō Hakusho* [White Paper on Trade] (Tokyo: Gyōsei, 1974-2000). From 2001, this data has been available at Ministry of Economy Trade and Industry, *Bōeki Dōkō Dētabēsu* [Database on Trends in Trade], http://www.meti.go.jp/policy/trade_policy/trade_db/html/01.htm (accessed 12 May 2008).

Figures for the pharmaceutical technology trade were collected from the *Kagaku Gijutsu Kenkyū Chōsa Hōkoku* [Report on the Survey of Research and Development] conducted by the Ministry of Internal Affairs and Communications (MIAC).⁵⁵ Values for technology trade refer to fees stemming from the use of patents, trademarks and know-how. It should be noted that, the figures indicated are likely to be slightly lower than actual figures, as the survey does not capture companies capitalised at less than 100 million yen, and because figures do not reflect the use of patents filed by Japanese firms in overseas jurisdictions. The latter is particularly relevant for figures since the 1990s, as greater numbers of Japanese firms established overseas operations during this time.

These figures need to be considered carefully. Due to different methodological approaches, technology trade figures compiled by MIAC may overestimate technology exports and underestimate technology imports compared to figures compiled the Bank of Japan's (BoJ) releases of *Kokusai Shūshi Tōkei Geppō* (Balance of Payments Monthly).⁵⁶ This is because the BoJ only includes foreign currency payments made for the explicit purpose of technological assistance whereas the MIAC includes payments for the use of patents, know-how, technological guidance and provision, and other technological assistance. Moreover, MIAC only collects data

⁵⁵ Bureau of Statistics, Office of the Prime Minister, *Kagaku Gijutsu Kenkyū Chōsa Hōkoku* [Report on the Survey of Research and Development] (Tokyo: Office of the Prime Minister, 1961-1984); Statistics Bureau & Statistics Centre of the Management and Coordination Agency, *Kagaku Gijutsu Kenkyū Chōsa Hōkoku* [Report on the Survey of Research and Development] (Tokyo: Management and Coordination Agency, 1985-2000); Statistics Bureau, Ministry of Internal Affairs and Communications, ed., *Kagaku Gijutsu Kenkyū Chōsa Hōkoku* [Report on the Survey of Research and Development] (Tokyo: Ministry of Internal Affairs and Communications, 2001-2006).

⁵⁶ See Bank of Japan, *Kokusai Shūshi Tōkei Geppō* [Balance of Payments Monthly] (Tokyo: Bank of Japan, 1966-2007).

from firms engaged in R&D activities, while BoJ data includes additional figures from quasi-governmental research institutes as well as service and retail establishments. BoJ figures thus tend to be lower than MIAC figures in technology exports, particularly as the BoJ does not account for exports from “plants,” while BoJ figures tend to be higher than MIAC figures for technology imports, because MIAC figures do not include technology imports by quasi-governmental research institutes.⁵⁷

In general, combined figures for both prescription and over-the-counter drugs have been used as proxy measures of the prescription drugs industry. This is partly because the legal distinction between prescription drugs and over-the-counter drugs was not made until the “Basic Policies for Drug Manufacturing Approval” were introduced in 1967. But it is also because official statistics have not distinguished between prescription and over-the-counter drugs in the post 1968 period, except for production figures available in the *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei*. Production figures after 1968 in this thesis therefore reflect the prescription drug sector, while trade and R&D figures reflect the combined sectors. The use of combined figures, however, should remain representative of general trends observed in the prescription drugs sector, as prescription drugs account for the majority of the drugs in the pharmaceutical industry.⁵⁸

⁵⁷ For an explanation of differences between MIAC and BoJ figures, see Section 2, Chapter 3-1-1 “Wagakuni no Gijutsu Bōeki no Dōkō [Trends in Technology Trade in Our Country],” in *Kagaku Gijutsu Hakusho* [White Paper on Science and Technology], by Ministry of Education, Science and Culture (Tokyo: Ministry of Education, Science and Culture, 1984), http://www.mext.go.jp/b_menu/hakusho/hakusho.htm (accessed 30 May 2008).

⁵⁸ In value. See Ministry of Health and Welfare, *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Yakugyō Keizai Kenkyūjo, 1953-1967); Ministry of Health and Welfare, *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Yakugyō Keizai Kenkyūjo, 1968-2000); Ministry of Health, Labour and Welfare, *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Jihō, 2001-2006).

The published corporate sources consulted in this thesis include company security filings and business reports, which were used to obtain firm-level data.⁵⁹ While the information contained in these sources are biased to portray firms in a positive light, they were used to obtain company data on sales, profits, workforce, and R&D data – as well as outlines of individual company histories. Company histories have also been consulted. While generally heavily biased to portray firms favourably, these publications have helped identify the nature and impact of government on individual firms. Similarly, histories of industry and professional organisations such as the Japan Pharmaceutical Manufacturers Association (JPMA), the Japan Medical Association (JMA) and various regional medical associations reveal the evolving concerns of the respective organisations.⁶⁰

I also consulted various academic journals dating from the late 1940s to 2000s. Journals such as *Iyaku Jānaru* [Journal of Pharmaceuticals] and *Gekkan Yakuji* [The Pharmaceuticals Monthly] helped to identify the concerns facing the pharmaceutical industry over the years, while others, such as the *Journal of Antibiotics* and *Gann* [Cancer] helped to show the advances in drug development methods and techniques.⁶¹

⁵⁹ Company securities filings refer to the *Yūka Shōken Hōkokusho* [Annual Securities Report] published by Ōkurashō Insatsukyoku.

⁶⁰ See for example, Japan Pharmaceutical Manufacturers Association, *10-nen no Ayumi* [A 10 year History] (Tokyo: Japan Pharmaceutical Manufacturers Association, 1978); Japan Pharmaceutical Manufacturers Association, “*Seiyakukyō 20-nen no Ayumi* [A 20 year History of the Japan Pharmaceutical Manufacturers Association] (Tokyo: Japan Pharmaceutical Manufacturers Association, 1988). Japan Medical Association, *Nihon Ishikai Sōritsu Kinenshi: Sengo 50-nen no Ayumi* [Japan Medical Association Anniversary Publication: A 50-year Post-war History] (Tokyo: Japan Medical Association, 1997).

⁶¹ See for example, *Iyaku Jānaru*-sha, *Iyaku Jānaru* [Journal of Pharmaceuticals] (Osaka: *Iyaku Jānaru*-sha, 1965-2006); Yakuji Kenkyūkai, *Gekkan Yakuji* [The Pharmaceuticals Monthly] (Tokyo: Yakugyō Jihōsha, 1959-2006). The *Journal of Antibiotics* has changed names over the years. It began as Japan Penicillin Research Association, *Penishirin Sonota no Kōseibusshitsu* [Penicillin and Other Antibiotics] (Tokyo: Japan Penicillin Research Association, 1948-1950); Japan Penicillin Research Association, *Journal of Antibiotics* (Tokyo: Japan Penicillin Research Association, 1951-1952). Thereafter, Japan Antibiotics Research Association, *Japanese Journal of Antibiotics Series A* (Tokyo: Japan Antibiotics Research Association, 1953-1967); and Japan Antibiotics Research Association, *Japanese Journal of Antibiotics Series B* (Tokyo: Japan Antibiotics Research Association,

The latter publication was also used to identify the collaborative entities involved in the development of specific therapies.

References to the Japanese pharmaceutical industry were also made in the popular press. General newspapers and journals such as the *Asahi Shimbun*, *Yomiuri Shimbun*, *Aera*, and *Bungei Shunjū* were consulted for this thesis.⁶² While popular publications do have ideological biases, they helped ascertain key developments, public perceptions, and the significance of industry to the broader economy. Diet proceedings were examined to identify key debates on the pharmaceutical industry.⁶³ While subject to personal biases, articles and memoirs by entrepreneurs were consulted to better understand the opportunities and risks felt by business leaders that lay behind corporate responses to government policies.⁶⁴

Several trade publications were consulted as well. The two major annual trade publications on the Japanese pharmaceutical industry are the *Yakuji Handobukku* [Pharmaceutical Affairs Handbook] and *Saikin no Shinyaku* [New Drugs in Japan] released by the industry research firms Jihō and Yakuji Nippōsha, respectively.⁶⁵ The former summarises key trends in government policy and industry performance while

1953-1967); Japan Antibiotics Research Association, *Japanese Journal of Antibiotics* (Tokyo: Japan Antibiotics Research Association, 1968-2006). See also, Japanese Cancer Association, *Gann: The Japanese Journal of Cancer Research* (Tokyo: Japanese Cancer Association, 1907-1984); Japanese Cancer Association, *Japanese Journal of Cancer Research* (Tokyo: Japanese Cancer Association, 1985-2002).

⁶² *Asahi Shimbun* and *Yomiuri Shimbun* are daily newspapers with nation-wide circulation. *Aera* and *Bungei Shunjū* are magazines that discuss current affairs.

⁶³ See Kokkai Gijiroku Kensaku Shisutemu [Full-text Database System for the Minutes of the Diet] <http://kokkai.ndl.go.jp/> (accessed 1 July 2008).

⁶⁴ For example, Chōbei Takeda, "Iyakuhin Yushutsu no Genjō to Mondaiten [The Status of Pharmaceutical Exports and its Problems]," *Keizaidantai Rengōkai* 6, no. 8 (October 1958): 18-19; Benzaburō Katō, "Ōbei Kigyō no Kenkyū Katsudō o Shisatsu shite," *Keidanren Geppō* 11, no. 1 (January 1963): 44-47. Chōbei Takeda and Benzaburō Katō were the presidents of Takeda and Kyowa Hakko, respectively.

⁶⁵ Yakugyō Jihōsha was renamed Jihō in 2000. Yakugyō Jihōsha, *Yakuji Handobukku* [Pharmaceutical Affairs Handbook] (Tokyo: Yakugyō Jihōsha, 1968-1999); Jihō, *Yakuji Handobukku* [Pharmaceutical Affairs Handbook] (Tokyo: Jihō, 2000-2007); Yakuji Nippōsha, *Saikin no Shinyaku* [New Drugs in Japan] (Tokyo: Yakuji Nippōsha, 1950-2006).

the latter introduces the key therapeutic attributes of recent drugs launched in Japan and includes a summary development history. Both publications are descriptive: the former is mainly sourced from government and private agencies, while the latter is mainly sourced from scientific journals. The *Yakuji Nenkan* [Pharmaceutical Affairs Annual] and *Yakugyō Keizai Nenkan* [Annual on the Economics of the Pharmaceutical Industry] are no longer in circulation, but they are similar in content to the *Yakuji Handobukku*. These publications by Yakuji Nippōsha were also consulted for data between the 1950s and 1980s.⁶⁶ In addition to statistical data, these sources were particularly helpful in identifying prevailing concerns in the industry over the years, such as safety and efficacy during the 1960s or capital liberalisation and product patent protection in the 1970s. For comparative data, non-Japanese trade publications such as *Scrip* and *Datamonitor*, among others, were consulted.⁶⁷

Unless otherwise stated, figures cited in this paper are given in real terms to better evaluate long-run trends, for example, in production, R&D expenditure, and trade. Nominal values have been converted into 2005 values using the consumer price index (CPI). Figures in US dollars were converted into 2005 US dollars using CPI data available from the U.S. Department of Labor, Bureau of Labor Statistics.⁶⁸ Figures in Japanese yen were converted into 2005 yen with CPI data available from Statistical Survey Department, Statistics Bureau, Ministry of Internal Affairs and

⁶⁶ Yakugyō Keizai Kenkyūjo, *Yakuji Nenkan* [Pharmaceutical Annual] (Osaka: Nihon Yakugyō Shimbunsha, 1951, 1957, 1961, 1964); Yakugyō Keizai Kenkyūjo, *Yakugyō Keizai Nenkan* [Economics of the Pharmaceutical Industry Annual] (Tokyo: Yakuji Nippōsha, 1967, 1971, 1979, 1984, 1987).

⁶⁷ For example, Robert Tulloch, *Pharmaceutical Markets in the Pacific Rim, Scrip Reports* (Richmond: PJB, 1995); *Datamonitor*, "Japan – Pharmaceuticals," *Industry Profile* (London: Datamonitor, 2002).

⁶⁸ U.S. Department of Labor, Bureau of Labor Statistics, "Consumer Price Index History Table," U.S. Department of Labor, <http://www.bls.gov/cpi/home.htm> (accessed 1 July 2008).

Communications.⁶⁹ CPI figures have been used for conversion as a widely used measure that reasonably reflects the changes in prices over time. Nominal values are given in the footnotes and the appendix.

Interviews and correspondence were also conducted with company executives. While this thesis is not based primarily on oral histories, interviews and correspondence helped illuminate published archival sources and strengthen analyses from my research findings. More specifically, they helped ascertain major shifts in the research orientation and the international competitiveness of the Japanese pharmaceutical industry as firms responded to changes in government policy as well as scientific/technological advances and globalisation.

Key individuals interviewed included Kenjirō Nagasaka, chairman of Banyu Pharmaceutical, who oversaw the firm's transformation from a small, family run firm into Merck Japan. Nagasaka also played a central role in the distribution reforms in the pharmaceutical industry in the 1990s, and provided a detailed account of the challenges of deregulation and internationalisation facing Japanese firms. Sapan Shah, president and CEO of Shionogi America and David Drutz, former vice president of Daiichi Pharmaceutical in the United States, shed light on recent developments in industry from the viewpoint of non-Japanese nationals employed at Japanese pharmaceutical firms.

⁶⁹ Statistical Survey Department, Statistics Bureau, Ministry of Internal Affairs and Communications, "General Index Excluding Imputed Rent for Japan," Ministry of Internal Affairs and Communications, <http://www.e-stat.go.jp/SG1/estat/List.do?bid=000000730006&cycode=0> (accessed 1 July 2008)

Robert Neimeth and P. Reed Maurer provided the perspectives of foreign firms conducting business in Japan. Both individuals were previously representatives of the Pharmaceutical Research and Manufacturers of America (PhRMA, the American industry association) in Japan.⁷⁰ Neimeth and Maurer elaborated upon the changing dynamics of the Japanese pharmaceutical industry and the challenges of operating in Japan as executives at leading foreign pharmaceutical firms.

Other individuals consulted included Valdis Jākobsons, chairman of Grindeks, and Naoko Wakao, representative of Japan's Cancer Patients Support Organization (CANPS), who provided written responses to letters of enquiry.⁷¹ Through the experience of a Soviet firm, Jākobson described how technology transfers to Japan were arranged in the late 1960s, while Wakao explained how patient organisations worked to obtain Japanese approval of new therapies already recognised overseas.

Chapter outline

The thesis is organised into five chapters. This introductory chapter has offered a brief introduction to the thesis. It began by highlighting the aims and significance of this research, then provided an overview of the existing literature. This was followed by a discussion of the thesis methodology and limitations with the sources. It concludes by

⁷⁰ Robert Neimeth was executive vice president of Pfizer and was involved with Pfizer's operations in Japan for over 20 years. He served as chairman of the Japan Committee of the Pharmaceutical Manufacturers of America (PMA, now PhRMA) from 1991 to 1993. P. Reed Maurer was vice president of Eli Lilly Japan and Merck Japan, and has worked in the Japanese pharmaceutical industry since 1970. He was the first representative in Japan for PhRMA.

⁷¹ Grindeks is a pharmaceutical manufacturer that was once a part of the Institute of Organic Synthesis in Latvia. In the late 1960s, this organisation provided Japanese firms with the technology to produce an anticancer drug.

providing an outline of the thesis chapters.

The following chapter provides a historical analysis of the Japanese pharmaceutical industry. It examines why this industry remained relatively weak, both in comparison with global leaders and with other Japanese industries. It follows the evolution of Japan's pharmaceutical industry across several phases of development, from its origins in the late 19th century to a modern industry in 2005. The chapter closes by suggesting several reasons for the underperformance of Japan's pharmaceutical industry.

Chapter 3 and Chapter 4 present the studies on the evolution of Japan's antibiotics sector and anticancer drug sector, respectively. Each chapter follows the evolution of the therapeutic sector across several stages of development. Case studies of drug development at individual firms are used to gain a more intricate understanding of firm behaviour in response to government policy and changing market conditions. While Chapter 3 provides several explanations for the strong performance of Japan's antibiotics sector, Chapter 4 offers several reasons for the weak performance of Japan's anticancer drug sector.

Chapter 5 is the conclusion of the thesis. The chapter opens with a summary of the reasons for the relative weakness of Japan's pharmaceutical industry, based on the studies of the antibiotics and anticancer drugs sectors. This is followed by a discussion on the contributions of this research to existing scholarship. The chapter closes by considering possible options for future research in this area.

2 Overview chapter

From the ashes of World War II, Japan's pharmaceutical industry has experienced phenomenal growth. Japanese firms were able to catch up with leading global firms, in terms of their ability to discover drugs. But while Japanese pharmaceutical firms were able to develop a highly profitable domestic industry, relatively few firms succeeded in international markets.⁷² In the early twenty-first century, the Japanese pharmaceutical industry remained much smaller and more domestically-oriented compared to its counterparts in the United States, Britain or Switzerland.⁷³ The failure of the Japanese pharmaceutical industry to become a global leader is striking, given the strong performance of Japanese automobile or electronics firms in the global market.

This chapter surveys the history of Japan's pharmaceutical industry and examines why it failed to realise its potential of becoming a global leader. Several factors help explain the relative weakness of Japan's pharmaceutical industry. But one of the key reasons lay in the lack of an industrial policy designed to develop a research-intensive, globally competitive pharmaceutical industry. Governed by the Ministry of Health and Welfare (MHW) – rather than the Ministry of International Trade and Industry (MITI) – the government long prioritised public health agendas to produce drugs at low cost

⁷² In pharmaceuticals, R&D has two major components: discovery and development. Drug discovery refers to the identification of a potential therapeutic substance. Drug development refers to the process of transforming this substance into a commercially viable therapy. Drug development, for example, requires the capacity to conduct clinical trials and meet the criteria set by the regulators for drug approval. Japanese firms have demonstrated a strong research capacity to discover potential cures, but they have been much weaker at developing drugs into commercially successful medicines.

⁷³ Japan Pharmaceutical Manufacturers Association, *JPMA Databook* (Tokyo: Japan Pharmaceutical Manufacturers Association, 2007), 13-15, 56-58, 60-63.

for its large population.⁷⁴ The government also long protected Japanese firms from foreign competition and allowed firms to prosper without substantial investments in R&D. Most Japanese pharmaceutical firms began to pursue R&D much later than their Western counterparts. With their belated adoption of R&D, the Japanese pharmaceutical industry had compromised their ability to compete against Western leaders in a globalising industry.

The history of Japan's pharmaceutical industry will be examined across seven phases. The first phase was the transition from Chinese to Western medicine from the Meiji period (1868 and 1912) up to the First World War. During this time, the Japanese government adopted Western medicine in favour of traditional Chinese medicine, and Japanese firms began to import Western, mostly German, drugs. In the second phase, which began during the First World War, Japanese firms shifted from the import to the manufacture of Western style drugs. This transition was prompted by the sudden end of trade with Germany during the war. Between 1915 and 1945, Japan developed a small pharmaceutical industry and expanded into mainland Asia.

The third phase began with Japan's defeat in the Second World War. Between 1945 and 1952, Japan was occupied by the Allied powers that implemented reforms that transformed Japan – including its pharmaceutical industry. Indeed, the Occupation authorities created the foundations of Japan's post-war pharmaceutical industry by

⁷⁴ The Ministry of Health and Welfare, established in 1938, became the Ministry of Health, Labour and Welfare (MHLW) in 2001. The Ministry of International Trade and Industry, established in 1949, became the Ministry of Economy, Trade and Industry (METI) in 2001.

enabling Japanese firms to produce drugs and establishing modern pharmaceutical regulations to support subsequent development. The fourth phase began when Japan regained its sovereignty in 1952. Between 1952 and 1961, Japan's pharmaceutical industry began to grow as it produced foreign-discovered drugs under license in a highly protected environment. The leading drugs produced during this period were vitamins and antibiotics, which supplemented lacking nutrients and treated infectious diseases, respectively.

The fifth phase refers to the period between 1961 and 1975, when Japan's pharmaceutical industry grew through the volume production of imitative drugs. After 1961, Japanese firms embarked upon an extraordinary pace of expansion, as the government nurtured firms through import-substitution policies and by underwriting demand through a universal health care system. Japan's intellectual property regime, based on process patents, also protected Japanese firms from foreign firms who would have had to disclose the research results of new drug discoveries without much reward. As the country prospered, Japan's pharmaceutical firms also began to produce drugs that would treat diseases of affluence. The next phase began in 1975, when Japanese pharmaceutical firms shifted from manufacturing-based growth to research-based growth. Between 1975 and 1990, Japanese pharmaceutical firms became increasingly research oriented in order to compete against new entrants from other sectors of its domestic economy and from abroad. This research orientation intensified as the government liberalised capital controls and introduced product patents.

In the most recent phase, between 1990 and 2005, Japan's pharmaceutical industry began to globalise. Globalisation was driven by several reforms to the regulatory landscape. For example, Japan harmonised its pharmaceutical regulations with those of the United States and the European Union, which made it easier for drugs approved in Japan to be approved the United States and Europe – and vice versa. As a result, there was increasing foreign competition in the Japanese market. These competitive pressures prompted an unprecedented wave of corporate reorganisation and mergers. Combined with the escalating costs of drug R&D, leading Japanese firms such as Takeda and Daiichi Sankyo began to transfer a large part of their operations abroad.⁷⁵

2.1 The Meiji Restoration and the Meiji pharmaceutical industry, 1868-1914

Following the Meiji Restoration in 1868, the Japanese government adopted Western medicine in place of traditional Chinese medicine.⁷⁶ As part of its attempts to modernise the country, the Meiji government established institutions and organisations to promote the use of Western medicine in Japan. These efforts by government laid the foundations of Japan's pharmaceutical industry.⁷⁷

The Japanese pharmaceutical industry was concentrated in the Doshōmachi district of Osaka, which had long been a centre for distributors of Chinese herbal medicines.

⁷⁵ Developments on Japan's post-war pharmaceutical industry are well documented in the white papers released annually by the Ministry of Health. See, Ministry of Health and Welfare, *Kōsei Hakusho* [White Paper on Health and Welfare] (Tokyo: Ōkurashō Insatsukyoku, 1955-2000); and Ministry of Health, Labour and Welfare, *Kōsei Rōdō Hakusho* [White Paper on Health, Labour and Welfare] (Tokyo: Ōkurashō Insatsukyoku, 2001-2007).

⁷⁶ This transition had occurred rather smoothly, as even through centuries of seclusion from foreign countries during the Edo period (1603-1868), Japan had kept abreast of Western science and technology, including Western medicine, through Dutch learning. For developments of Japan's pharmaceutical industry in the Meiji period, between 1868 and 1912, see Yakugyō Keizai Kenkyūjo, *Yakuji Nenkan* [Pharmaceutical Annual] (Osaka: Nihon Yakugyō Shimbunsha, 1951), 229-241.

⁷⁷ A discussion of Meiji era developments has been written by Whitney Willis Norton, "Notes on the History of Medical Progress in Japan," *Transaction of the Asiatic Society of Japan* 12 (1885): 244-399.

Since the 17th century, wholesalers had gathered to examine imported medicines and bargain over prices. From Osaka, the goods were distributed nation-wide. Major firms, such as Takeda, Tanabe, Shionogi, Fujisawa and Ono, originated as importers and distributors of Chinese medicines. After the Meiji Restoration, they shifted into importing Western medicine.

It should be remembered that the major aim of the Meiji government was to resist colonisation by the Western powers by adopting Western learning, reforming Japan's institutions, and encouraging industrialisation. Adopting Western pharmaceuticals was part of this larger project. Pharmaceutical regulation in the Meiji era was designed to curb the circulation of fraudulent, if not toxic, medicines, and myriad regulations were introduced to control the sale of imported drugs in Japan.⁷⁸ This focus on safety regulation might be expected, given the widespread concerns over fraudulent drugs in circulation at the time.

In 1874, the government launched its first Pharmaceutical Affairs Law (PAL), which also specified the roles and qualifications required of physicians and pharmacists.⁷⁹

Indeed, the introduction of a formal education system in Western medicine supported

⁷⁸ These included *Baiyaku Toroshimari Kisoku* [Rules to Control Pharmaceutical Sales] in 1870, *Baiyaku Kisoku* [Rules for Pharmaceutical Sales] in 1877, and *Yakuin Eigyō Narabi ni Yakuin Torishimari Kisoku* [Regulations on Pharmaceutical Operations and Products] in 1889. The Japanese Pharmacopoeia was also introduced in 1886. See, Ministry of Health and Welfare, *Chikuji Kaisetsu Yakujihō* [Explanatory Notes on the Pharmaceutical Affairs Law] (Tokyo: Gyōsei, 1973), 1-13. See also, Nihon Kōgakukai [Japan Federation of Engineering Societies], *Meiji Kōgyōshi* [History of Industry in the Meiji Period] (Tokyo: Nihon Kōgakukai, 1925), 992-1015; Hajime Sōda, "Ishinki no Seiyaku [Manufacturing Pharmacy during the times of the Meiji Restoration]," *Iyaku Jānaru* 11 (August 1972): 38-42. Also Hajime Sōda, "Ishinki no Seiyaku [Manufacturing Pharmacy During the Times of the Meiji Restoration]" *Iyaku Jānaru* 11 (September 1972): 57-60.

⁷⁹ Ministry of Health and Welfare, *Chikuji Kaisetsu Yakujihō* [Explanatory Notes on the Pharmaceutical Affairs Law] (Tokyo: Gyōsei, 1973): 1-13. See also, Noriko Fukushima and Kayoko Matsumoto, "A Historical Study of the Administration of Pharmaceutical Affairs in Japan: In Relation to a Relaxation of Regulations," *Yakushigaku Zasshi* 35, no. 2 (2000): 240-246. Under traditional practices stemming from Chinese medicine, Japanese physicians both prescribed and dispensed medicines. While this practice continued well into the late 20th century, discussions on the legal separation of this role was introduced in the Meiji period.

the emergence of a pharmaceutical industry based on Western drugs in Japan.⁸⁰ Japan learned of Western medicine by hiring foreign teachers, sending students overseas, and establishing numerous schools of pharmacy. In the 1870s, departments of pharmacy were established at universities alongside technical schools that taught students to inspect, evaluate and produce Western medicines.⁸¹ This education system produced eminent scientists of international renown such as Nagayoshi Nagai, Kiyoshi Shiga, and Hideyo Noguchi, who studied overseas and became researchers at foreign research institutes. These scholars strengthened the foundations of Western medical science at the turn of the 20th century, and helped guide Japan's early pharmaceutical industry.⁸²

The Western pharmaceutical industry in Japan began with the Meiji Restoration. From the late 19th century to the early 20th century, wholesalers of Western medicine, who showed little interest in manufacture or discovery, dominated the industry. During this same period, Germany and the United States were developing a research-based pharmaceutical industry in their respective countries – the former originated from

⁸⁰ See Kōji Yamakawa, "Yakugaku Kyōiku [Pharmaceutical Education]," *Yakushigaku Zasshi* 31, no. 2 (1996): 143-146; Kōji Yamakawa, "Yakugaku Kyōiku [Pharmaceutical Education]," *Yakushigaku Zasshi* 39, no. 1 (2004): 128-134. The transfer of knowledge was essential for a country where Western pharmaceutical science did not exist. German scholars such as Erwin von Baelz and Julius Scriba, for example, relayed foreign knowledge to Japanese students at the Tokyo University School of Medicine. Overseas students, sent by the Meiji government to study German medicine, were particularly valuable in building the foundations of industry – acting as conduits of knowledge, later leaders of academe, and entrepreneurs. The pharmacologist Nagai Nagayoshi, for example, advised on the building of the first semi-state-owned pharmaceutical firm, held a professorship at Tokyo University, was a director of government laboratory, and chaired various academic bodies. Other scholars followed. Jōichi Takamine, for example, was an overseas student in United States and Britain who discovered drugs such as Takadiastase and Adorenarin, who became the president of Sankyo, a leading pharmaceutical firm, and founder of Riken, a national research institute.

⁸¹ Hajime Sōda, "Ishinki no Seiyaku [Manufacturing Pharmacy during the times of the Meiji Restoration]" *Iyaku Jānaru* 11 (October 1972): 54-58. Since the turn of the century, two types of education were offered: professional education at private institutions that catered to pharmacists, and academic education at public institutions who nurtured scientists. The former, with its commercial orientation, emphasized methods of pharmaceutical evaluation, inspection and production to the offspring of pharmaceutical wholesalers, while the latter encouraged the discovery of new therapeutic substances to prospective scientists. To a certain extent, these differences in educational orientation, combined with a sense of contempt in academic circles – that academic research should not be influenced by commercial motivations – prevented the transfer of academic knowledge into industry.

⁸² See for example, Yoshio Izumi and Kazuo Isozumi, "Modern Japanese Medical History and the European Influence," *Keio Journal of Medicine* 50 (June 2001): 91-99.

academic science while the latter originated from pharmacy practice.⁸³ While the Meiji government played an important role in establishing the framework of Japan's early pharmaceutical industry, government measures mostly aimed to secure the safety of imported drugs that were in circulation.

2.2 The First World War and the birth of manufacturing pharmacy

Before World War I, there had been a few tentative attempts to manufacture Western-style drugs in Japan. In 1883, the government established Dainippon Pharmaceuticals, a joint venture with Osaka based entrepreneurs, to manufacture Western-style drugs. Pharmaceutical wholesalers such as Tanabe and Shionogi also made some attempts at production.⁸⁴ But while a handful of firms produced medicines such as santonin, quinine, and chloroform, most Japanese firms at the turn of the 20th century were concerned with the inspection and sale of imported drugs.⁸⁵ This began to change after 1914.

The outbreak of World War I gave rise to the manufacture of pharmaceuticals in Japan. When German imports came to a halt during World War I, Japan was faced with a dearth of medicines – and a domestic industry that lacked the capacity to produce them.⁸⁶ The Japanese government's response to this crisis was similar to that of the

⁸³ Jonathan Liebenau, "Industrial R&D in Pharmaceutical Firms in the Early Twentieth Century," *Business History* 26 (November 1984): 329-346.

⁸⁴ For details on the pre-war pharmaceutical industry, see Yakuseki Nippōsha, *Yakugyō Nenkan* [Pharmaceutical Industry Annual] (Tokyo: Yakuseki Nippōsha, 1935, 1938).

⁸⁵ Dainihon Pharmaceutical Co., *Dainihon Seiyaku 100-nenshi* [A One Hundred Year History of Dainihon Pharmaceutical] (Tokyo: Dainihon Pharmaceutical Co.: 1993): 1-17. Dainihon Pharmaceutical was established in 1897 as a semi-state owned enterprise with 21 Osaka based entrepreneurs dealing in pharmaceuticals. See also Hajime Sōda, "Ishinki no Seiyaku [Manufacturing Pharmacy during the times of the Meiji Restoration]" *Iyaku Jānaru* 11 (November 1972): 58-63.

⁸⁶ Germany was an enemy power of Japan during World War I.

British and American governments. It adopted an import-substitution policy that introduced subsidies for pharmaceutical production, nullified Germany's patent rights, and disclosed detailed production methods from government laboratories.⁸⁷

During the First World War, the government's policies gave birth to a new wave of Japanese pharmaceutical firms, such as Daiichi, Yamanouchi, and Banyu, which were dedicated to the production of Western medicines. This new breed of firms competed against each other to produce and sell similar drugs that could no longer be imported from Germany. One of the medicines replicated during this period was salvarsan, an antisyphilitic drug that had been developed in Germany in the early 1910s.⁸⁸ Daiichi, Banyu, Sankyo, and Nippon Shinyaku, competed to sell their salvarsan drugs, which were branded as Arsemin, Eramisol, Arsaminol, and Sabiol, respectively. In the interwar period, Japanese pharmaceutical firms diversified into the manufacture of vitamins, hormonal preparations, anthelmintics and sulfa drugs.⁸⁹

The First World War proved crucial in enabling Japanese firms to overcome limitations in domestic capital, technology and expertise, and produce modern therapies. But the policy emphasis was on the acquisition of manufacturing

⁸⁷ For developments in Japan's pharmaceutical industry from the World War I up to World War II, see Yakugyō Keizai Kenkyūjo, *Yakuji Nenkan* [Pharmaceutical Annual] (Osaka: Nihon Yakugyō Shimbunsha, 1951), 241-246. See "Iyakuhin [Pharmaceuticals]," *Meiji Hyakunen Kigyō no Rekishi* [Company Histories 100 Years after Meiji] (Tokyo: Keizai Shunjusha, 1968), 239-240. In addition to publicising data on research conducted at the government's research laboratories (*Naimushō Eisei Kenkyūjo*) on specific production methods, the government provided subsidies to industry via the Law to Promote Chemical and Pharmaceutical Production (*Senryō Iyakuhin Seizō Shōrei hō*). This prompted production at a range of firms, including Tanabe, Dainihon, Shionogi, Sankyo and Takeda. The Wartime Act on Intellectual Property Rights (*Kōgyō Shoyūken Senjihō*) also voided the patent rights of enemy countries, legally enabling the production of patented pharmaceuticals for profit.

⁸⁸ Jurgen Drews, "Paul Ehrlich: Magister Mundi," *Nature Reviews Drug Discovery* 9 (3 September 2004): 797-801.

⁸⁹ Anthelmintics refer to medicines that rid the body of worms. Sulfa drugs were discovered by Gerhard Domagala in the early 1930s as one of the first chemotherapeutic substances that could cure bacterial infections.

capacities. After all, Japan's pharmaceutical industry was still rather small. In 1937, it produced \$1.5 billion worth of drugs at a time when the pharmaceutical industry in the United States produced \$4.7 billion worth of drugs.⁹⁰ Manufacturing pharmacy in Japan emerged out of an incentive to reduce uncertainty and risks inherent in import operations. It developed more as an economic response to minimise cost and risk, rather than a scientific response to discover novel and innovative therapies for society. Intent on acquiring some manufacturing capacities from the West, the development of industrial research did not enter into government policies or corporate strategy until well after World War II.

Japanese firms also ventured into overseas markets in the interwar years. This expansion was fuelled by two major factors. As German imports began to re-enter Japan after World War I, Japanese firms were squeezed out of the home market. As a result, Japanese firms sought to exploit commercial opportunities in East Asia. Takeda, for example, established sales and manufacturing operations in Taiwan, Korea and China in the 1930s, in medicines ranging from vitamins to quinine. Other firms such as Sankyo established branches in Manchuria, Korea, and China, to produce and sell vitamins and galenic preparations.⁹¹ Firms such as Banyu expanded operations in Korea and China to offer sulfa drugs and a variety of other drugs.⁹²

⁹⁰ In nominal terms, Japan produced 215.9 million yen worth of drugs when the United States produced \$345.9 million worth of drugs. Historical exchange rates are available in Japan Statistical Association, ed. *Historical Statistics of Japan* Vol. 3 (Tokyo: Japan Statistical Association, 1988). Yakugyō Keizai Kenkyūjo, *Yakuji Nenkan* [Pharmaceutical Annual] (Osaka: Nihon Yakugyō Shimbunsha, 1957), 289; U.S. Department of Commerce, Bureau of the Census, *Statistical Abstract of the United States 1940* (Washington D.C.: United States Government Printing Office, 1941), 820.

⁹¹ Sankyo Co., *Sankyō 100-nenshi* [Sankyo, a 100 year History] (Tokyo: Sankyo Co., 1999), 94-100; Takeda Pharmaceutical Co., *Takeda 200-nen* [200 Years of Takeda] (Osaka: Takeda Pharmaceutical Co., 1984), 101-106. Galenic preparations refer to widely-used herbal remedies that were introduced by the ancient Greek physician, Galen.

⁹² Japan Business History Association, *Banyū Seiyaku 85-nenshi* [Banyu Pharmaceutical: 85 Year History] (Tokyo: Banyu Pharmaceutical Co., 2002), 47-59.

Japan's military ventures into East Asia also supported the expansion of the Japanese pharmaceutical industry. Between 1936 and 1942, production levels grew twenty percent from 138 billion yen to 167 billion yen.⁹³ Most of this growth came from sales in East Asia; exports to this region accounted for 20% of Japanese production in 1936. Indeed, exports still accounted for 17.5% of production in 1943.⁹⁴

From the late 1930s into the early 1940s, Japan's pharmaceutical industry evolved amidst a war economy. Medicines were considered an essential good, and the pharmaceutical industry benefited from the military's support during the war years. The military supplied firms with raw materials, monitored production, purchased the drugs for rationing, and monitored their distribution.⁹⁵ With heavy demand for medicines and bolstered by the military's support, Japan's pharmaceutical industry grew during the first few years of the Second World War. But as Japan began to sustain heavy damages and scarce resources were diverted into other war industries, drug production peaked in 1942, and fell swiftly until the end of the War.⁹⁶

⁹³ Yakugyō Keizai Kenkyūjo, *Yakuji Nenkan* [Pharmaceutical Annual] (Osaka: Nihon Yakugyō Shimbunsha, 1957), 289. As consumer price indices are not available for dates prior to 1947, these values were converted using the domestic corporate goods index produced by the Bank of Japan. This data is reprinted in Ministry of Internal Affairs and Communication, *Historical Statistics of Japan*, vol. 4 (Tokyo: Japan Statistical Association, 2006), 492-495.

⁹⁴ *Ibid.*

⁹⁵ In 1938, the military began to control imports of medicine and the allocation of raw materials for drug production, which were soon followed by controls over the production and prices of drugs. As rations were introduced in 1941, the government procured and distributed drugs to rationing posts. Developments during World War II are often documented in company histories. See for example, Takeda Pharmaceutical Co., *Takeda 200-nen* [200 Years of Takeda] (Osaka: Takeda Pharmaceutical Co., 1984), 79-81.

⁹⁶ Yakugyō Keizai Kenkyūjo, *Yakuji Nenkan* [Pharmaceutical Annual] (Osaka: Nihon Yakugyō Shimbunsha, 1957), 289.

2.3 The Occupation era and the rebirth of Japan's pharmaceutical industry, 1945-1952

As in other industries, World War II left the pharmaceutical industry devastated. In 1946, production levels were approximately 15% of 1941 levels.⁹⁷ A survey by the General Headquarters (GHQ) taken in January 1946 found that only 592 manufacturing establishments remained in business.⁹⁸ But Japan's pharmaceutical industry suffered much less damage than, for example, the steel and coal industries, which had been targeted by Allied forces during the war. The factories of leading pharmaceutical firms such as Takeda, Shionogi, Fujisawa and Daiichi remained largely unscathed.⁹⁹ In fact, Japan's pharmaceutical industry had suffered much more from the loss of East Asian markets than the actual physical damages incurred to its domestic facilities.¹⁰⁰ Despite the severe lack of raw materials and low purchasing power in the country, however, Japan was able to build upon the rudimentary production capacities, distribution networks, and human capital it had developed before the war.

The Allied Occupation of Japan was led by the Americans, who established their headquarters in Tokyo. The GHQ employed many civilian and military experts from the United States to work with Japanese government officials in implementing their

⁹⁷ Ibid.

⁹⁸ General Headquarters, 28 January, Memorandum on Pharmaceutical Production, AG440 PH, reprinted in Takashi Nishikawa, *Kusuri Kara Mita Nihon; Shōwa 20-nendai no Genfūkei to Konnichi* [Looking at Japan from "Medicine": Scenes from the 1940s to the Present] (Tokyo: Yakuji Nippōsha, 2004), 22.

⁹⁹ "Trade and Industry: Pharmaceuticals," February 22, 1947. This is also documented in numerous company histories and corporate security filings of the 1940s. See also, Katsuhiro Matsumura, "Seiyaku Kigyō no Saihen Seibi to Gōrika Katei, Shōwa 20-nen kara 25-nen zenhan made [The Reorganisation and Rationalisation of the Pharmaceutical Industry, from 1945 to early 1950]" *Iyaku Jānarū* 12 (March 1973): 42-48.

¹⁰⁰ This is documented in the security filings of various firms in the late 1940s.

policies. There were several reasons why the GHQ became interested in rebuilding Japan's pharmaceutical industry. The American occupation forces believed that improving public health conditions for Japanese civilians would help to prevent social unrest, a resurgence of militarism, or a turn for Communism. In addition, the production of insecticides such as DDT and BHC was considered crucial in containing the spread of epidemics. The GHQ also needed to supply medicines such as penicillin to American military personnel stationed in Japan.¹⁰¹ The Occupation authorities believed that domestic production would enable low-cost provision of essential medicines for both civilian and military purposes while adjusting flexibly to fluctuations in demand, without the costs and risks of relying on imports.¹⁰²

To enable Japanese firms to produce essential medicines, the Occupation authorities substituted for missing supply and demand. The government prioritised the allocation of raw materials for pharmaceutical production, and purchased the medicines produced.¹⁰³ It also established formal transfer mechanisms through rations and distribution controls.¹⁰⁴ The GHQ also provided government, firms, and academia with new technologies through foreign advisors. The GHQ's introduction of penicillin

¹⁰¹ A steady supply of penicillin was particularly important because many American soldiers in Japan had acquired the venereal disease, syphilis, which could be cured with this drug.

¹⁰² General Headquarters, Supreme Commander for the Allied Powers, Public Health and Welfare Section, *Public Health and Welfare in Japan. Annual Summary: 1949* (Tokyo: Supreme Commander for the Allied Powers, Public Health and Welfare Section, 1949): 121. See also, Takashi Nishikawa, *Kusuri Kara Mita Nihon: Shōwa 20-nendai no Genfūkei to Konnichi* [Looking at Japan from "Medicine": Scenes from the 1940s to the Present] (Tokyo: Yakuji Nippōsha, 2004). A brief overview of developments in the Occupation period has been written by Tōru Yamazaki, "Sengo Yakugyōshi [A Postwar History of the Pharmaceutical Industry] (1)," *Yakkyoku* 16, no. 8 (August 1965): 3-8.

See also Kinoichi Tsunematsu, "Senryōka ni Okeru Yakuji Eisei Taisaku [Public Health and Welfare Policy Under the Occupation]," *Iyaku Jānarū* 9 (July 1970): 56-58.

¹⁰³ General Headquarters, Supreme Commander for the Allied Powers, Public Health and Welfare Section, *Public Health and Welfare in Japan. Annual Summary: 1949* (Tokyo: General Headquarters, Supreme Commander for the Allied Powers, Public Health and Welfare Section, 1949), 173-175. See also, Takeda Pharmaceutical Co., *Takeda 200-nen* [200 Years of Takeda] (Osaka: Takeda Pharmaceutical Co., 1984): 126-129.

¹⁰⁴ Kunihiko Futaba, "Sengo no Iyakuhin Ryūtsūshi: Haisen ni yoru Shijō Ryūtsū no Konran to Saiken [The History of Distribution in the Pharmaceutical Industry: Chaos and the Rebuilding of a War-devastated Market and Distribution System]," *Iyaku Jānarū* 11 (May 1972): 42-58.

in Japan played a particularly important role in helping firms to catch up with the West and building the foundations of Japan's post-war pharmaceutical industry.¹⁰⁵

The GHQ conducted infrastructural reforms and created modern institutions and organisations during the Occupation period. These reforms not only improved public health conditions in Japan, but also supported the growth of the pharmaceutical industry.¹⁰⁶ The authoritarian nature of the Occupation regime ensured the swift and effective execution of these reforms.¹⁰⁷

Among the most prominent of these reforms was the revision of the existing Pharmaceutical Affairs Law (PAL) in 1948, whereby the government improved quality standards and delegated the monitoring of pharmaceutical firms to prefectural authorities.¹⁰⁸ Foreign advisors, again, played an important role in reform. In July 1949, a mission of the American Pharmaceutical Association conducted a comprehensive survey of pharmacy in Japan and provided several recommendations for modernisation. These reforms spanned the “the education and organization of pharmacists, the manufacture, control and distribution of pharmaceuticals, and the practice of pharmacy, in general, in Japan.”¹⁰⁹

¹⁰⁵ Nihon Penishirin Kyōkai [Japan Penicillin Association], *Penihshirin no Ayumi: 1946-1961* [The History of Penicillin: 1946-1961] (Tokyo: Nihon Penishirin Kyōkai, 1961).

¹⁰⁶ Yakugyō Keizai Kenkyūjo, *Yakujī Nenkan* [Pharmaceutical Annual] (Osaka: Nihon Yakugyō Shimbunsha, 1957), 227.

¹⁰⁷ The American efforts at improving public health conditions in Japan is well documented in an interview of Crawford Sams, who was the head of the GHQ's Public Health and Welfare Section. See Crawford F. Sams, interview by Darryl Podoll, 3 May 1979, interview OH037, transcript, Washington University School of Medicine Oral History Project, Bernard Becker Medical Library, St Louis, Missouri, <http://beckerexhibits.wustl.edu/oral/interviews/sams.html>.

¹⁰⁸ *Yakujī hō*, 29 July 1948, Law no. 197. See also Public Health and Welfare Section, Memorandum, 7 October 1948, Declassified EO 12065 Section 3-402/NNNDG no. 775024. (NDL). A brief overview of developments leading up to the revision of the Pharmaceutical Affairs Act in 1948 is documented in Ministry of Health and Welfare, “Iyakuin [Pharmaceuticals]” in *Isei Hyakunenshi* [A 100 Year History of Administration in Medicine] (Tokyo: Gyosei, 1976): 447-451.

¹⁰⁹ Crawford Sams, Public Health and Welfare Section, GHQ, SCAP, “Memorandum to Ministry of Welfare, Japanese Government: Report of Mission of the American Pharmaceutical Association,” 30 July 1949, Declassified EO 12065 Section 3-402/NNNDG no. 775024, 5 (NDL).

The GHQ developed a particular interest in reforming Japan's pharmaceutical education system to improve the country's standards of pharmacy. A new medical system was set forth under the Medical Practitioners Law (*Ishi-hō*) and the Medical Care Law (*Iryō-hō*) in 1948, and educational standards for physicians and pharmacists were raised.¹¹⁰ Modelled on the American system, the Occupation authorities introduced a new curriculum, extended the duration of study, and introduced a license to practice pharmacy in Japan. A national board of pharmacy was also established to examine and license new pharmacists, and continuing education was established for professional pharmacists.¹¹¹ The Occupation forces were also instrumental in the formation of professional organisations such as the Japan Pharmaceutical Association, which aimed to improve standards of pharmacy.¹¹²

The Occupation authorities also conducted structural reforms within Japanese

¹¹⁰ General Headquarters, Supreme Commander for the Allied Powers, Public Health and Welfare Section, (1949). *Public Health and Welfare in Japan* (Tokyo: Supreme Commander for the Allied Powers, Public Health and Welfare Section, 1949), 211-212. See also, B.N. Riordan, Public Health and Welfare Section, "Meeting of Pharmaceutical Education Council" (meeting held by the Pharmaceutical Education Council in Tokyo, Japan, 19 July 1946, 17 January, 14 March 1947, 12 January, 6 July 1951, Declassified EO 12065 Section 3-402/NNDG no. 775024 (NDL). *Ishi hō*, 30 July 1948, Law no. 201; *Iryō hō*, 30 July 1948, Law no. 205.

¹¹¹ Charles Band, General Headquarters Supreme Commander for the Allied Forces, Chief, Supply Division, Public Health and Welfare Section, Memorandum for Record, Fifth Refresher Course for Public Health Pharmaceutical Officers," 12 January 1949, Declassified EO 12065 Section 3-402/NNDG no. 775024 (NDL); Charles Band, General Headquarters Supreme Commander for the Allied Forces, Chief, Supply Division, Public Health and Welfare Section, Memorandum for Record, "Meeting of Pharmaceutical Education Committee," 20 July 1950, Declassified EO 12065 Section 3-402/NNDG no. 775024 (NDL); J.M. Bransky, General Headquarters Supreme Commander for the Allied Forces, Public Health and Welfare Section, Narcotic Investigator, Memorandum for Record, "Conference Relative to Raising Standards of Pharmaceutical Education," 11 June 1946 Declassified EO 12065 Section 3-402/NNDG no. 775024 (NDL); B.N. Riordan, General Headquarters Supreme Commander for the Allied Forces, Public Health and Welfare Section, Chief, Supply Division, Memorandum for Record, "Meeting of Pharmaceutical Education Council," 19 July 1946, 17 January, 14 March 1947, 12 January, 6 July 1951 Declassified EO 12065 Section 3-402/NNDG no. 775024 (NDL).

¹¹² B.N. Riordan, General Headquarters Supreme Commander for the Allied Forces, Chief, Supply Division, Public Health and Welfare Section, Memorandum for Record, "Reorganization of the Japan Pharmacists Association," 16 September 1947, Declassified EO 12065 Section 3-402/NNDG no. 775024 (NDL); Charles Band, General Headquarters Supreme Commander for the Allied Forces, Chief, Supply Division, Public Health and Welfare Section, Memorandum for Record, "Meeting of House of Delegates, Japan Pharmaceutical Association," 20 October 1948, Declassified EO 12065 Section 3-402/NNDG no. 775024 (NDL); Charles Band, General Headquarters Supreme Commander for the Allied Forces, Chief, Supply Division, Public Health and Welfare Section, Memorandum for Record, "First Convention, Japan Pharmaceutical Association, Kyoto 22-25 October 1948," 29 October 1948, Declassified EO 12065 Section 3-402/NNDG no. 775024 (NDL); W. Speer, General Headquarters Supreme Commander for the Allied Forces, Narcotic Control Division Memorandum for Record, "Reorganization of Japan Pharmacist Association," 20 February 1948, Declassified EO 12065 Section 3-402/NNDG no. 775024, 3 (NDL).

ministries. In 1949, for example, the Pharmaceutical and Supply Bureau at the Ministry of Welfare was reorganised to place greater emphasis on commercial pharmaceutical production for domestic and export markets.¹¹³ These reforms implemented by the Occupation forces supported the continued growth of Japan's antibiotics sector into the following decade.

The Japanese Pharmacopoeia was also revised in 1951.¹¹⁴ In 1952, the government introduced a new pricing system whereby it set prices on official drugs.¹¹⁵ The pricing system was aimed to ensure universal health care access to Japanese citizens in a poor, developing economy where acute and infectious diseases were serious concerns.¹¹⁶ This pricing policy – which effectively capped prices – would prove both highly contentious and heavily influential in shaping the direction of the post-war pharmaceutical industry, as it dented the innovative incentives of Japanese firms relative to their Western counterparts.

Following these reforms, Japanese firms began to build new plants in the late 1940s. Given the limitations to knowledge, funds and technologies, however, Japanese factories were mostly engaged in producing antibiotics and insecticides – and

¹¹³ Charles Band, General Headquarters Supreme Commander for the Allied Forces. Chief, Supply Division. Public Health and Welfare Section, Memorandum for Record, "Reorganization of the Pharmaceutical and Supply Bureau: Ministry of Welfare," 26 March 29 March, 1 October 1949. Declassified EO 12065 Section 3-402/NNDG no. 775024 (NDL).

¹¹⁴ Ministry of Health and Welfare, *Yakkyokuhō, Dairokujū Kaisei* [Japanese Pharmacopoeia, 6th revision] (Tokyo: Ministry of Health and Welfare, 1951). A discussion of the revision to the pharmacopoeia has been written by Gen'ichirō Fukuchi, "Nihon Yakkyokuhō no Kaisei," *Kagaku Asahi*, 1 May 1948, 34-35.

¹¹⁵ Tōru Watanabe, "The Changes of Pharmaceutical Administration in Japan after World War II (1)," *Yakushigaku Zasshi* 26 (1991): 1-6

¹¹⁶ The pricing system introduced in 1952 proved extremely beneficial in improving health care conditions in Japan. But in later years, in the context of a more developed economy, the capping of the drug price at the official list price, determining the profitability of a drug without reference to the market dynamics significantly dented innovative incentives among Japanese pharmaceutical firms compared to those abroad. By comparison, in the United States, for example, firms could be rewarded for launching innovative medicines with high prices that would remain constant for the patent protection period.

repackaging bulk imports. Very few companies were involved in any R&D. Firms could manufacture pharmaceuticals with little cost or risk: demand for medicines was strong, supplies were provided with government aid, technology transfers were readily available, and the medicines produced were purchased under government procurement. With low barriers to entry, the pharmaceutical industry attracted new entrants from various non-traditional sectors, ranging from food, beverages, confectionery and breweries to textiles. As there was weak demand for their non-essential goods after the war, many firms in these sectors sought new opportunities in the pharmaceutical industry by producing drugs at idle manufacturing facilities. Rather than the traditional pharmaceutical firms who, as import-distributors, had limited production capacities, it was these new entrants who pioneered the re-emergence of Japan's pharmaceutical industry.

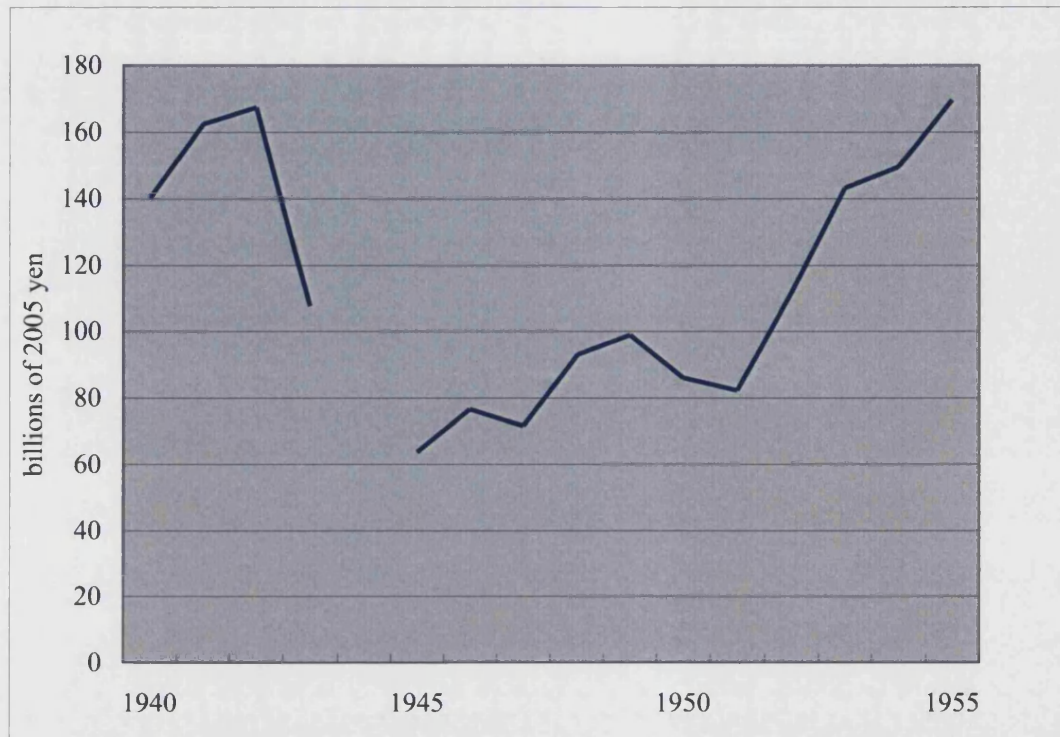


Figure 1. Recovery of Pharmaceutical Production, 1940-1955¹¹⁷

Indeed, numerous small firms competed intensely to produce highly profitable drugs such as antibiotics and sulfa drugs. Production levels grew rapidly from 76.4 billion yen in 1946 to 111.6 billion yen in 1952.¹¹⁸ But despite this increase, Japanese firms were unable to keep up with demand. In 1949, for example, the pharmaceutical industry only satisfied demand for 32 of the 339 varieties of medicines it produced.¹¹⁹ It was only in the mid 1950s that the production of pharmaceuticals in Japan would recover to pre-war levels.

The Allied Occupation was essential to the rebuilding of Japan's pharmaceutical

¹¹⁷ Yakugyō Keizai Kenkyūjo, *Yakuji Nenkan* [Pharmaceutical Annual] (Osaka: Nihon Yakugyō Shimbunsha, 1957), 289. As consumer price indices are not available for dates prior to 1947, these values were converted using the domestic corporate goods index produced by the Bank of Japan. This data is reprinted in Ministry of Internal Affairs and Communication, *Historical Statistics of Japan*, vol. 4 (Tokyo: Japan Statistical Association, 2006), 492-495.

¹¹⁸ In nominal terms, production grew from 1.8 billion yen to 58.6 billion yen. Ibid.

¹¹⁹ "Trade and Industry: Pharmaceuticals," *The Oriental Economist*, 13 November 1948, 969.

industry. Not only did the GHQ provide the demand, supply, and transfer mechanisms for Japanese industry, it also provided government, firms, and academia with new technologies, regulation, and education standards tailored to Japan's level of development that would help sustain and foster growth over the following decades. The momentum for production launched in this period and the modern institutions and organisations created during this period gave life to Japan's post-war pharmaceutical industry. As the Allied Occupation drew to a close, Japanese firms also became more autonomous, and began to arrange their own licensing agreements independently with foreign firms, rather than rely upon the Occupation authorities or the Japanese government. But the policy emphasis on acquiring manufacturing capacities through imported technologies also created the foundations of an imitation industry that relied on technology transfers and neglected the development of industrial R&D in Japan.

2.4 Import substitution policies in the 1950s

The Korean War between 1950 and 1953 injected further life into Japan's pharmaceutical industry. By 1950, many Japanese firms had begun to suffer from falling prices, lack of credit, and excess capacity.¹²⁰ But special procurements by the United States for civilian and military use bolstered demand and provided solvency to struggling firms. For the Americans, shipments from Japan offered a flexible and low-cost means of providing medicines to American troops in Korea. As in other sectors of the Japanese economy, this strong external demand from the US military

¹²⁰ See Katsuhiro Matsumura, "Seiyaku Kigyō no Keiei Kiban Kyōka Katei, Shōwa 25-nen Zenhan kara 30-nen Goro made [Pharmaceutical Firms Strengthen the Foundations of their Business, from the Early 1950s to around 1955]," *Iyaku Jānaru* 12 (May 1973): 46-52. Many corporate histories also document this. See for example, Sankyo Co., *Sankyō 100-nenshi* [Sankyo, a 100 year History] (Tokyo: Sankyo Co., 1999), 107; Daiichi Pharmaceutical Co., *Daiichi Seiyaku 80-nenshi* [Daiichi Pharmaceutical, a 80 Year History] (Tokyo: Daiichi Pharmaceutical Co., 1996), 99-100.

resuscitated many domestic firms.¹²¹

In 1950, the Japanese government embarked upon an import substitution policy that restricted capital inflows, imported foreign technology, and recognised process patents. Process patents encouraged the dissemination of technology by legally authorising Japanese firms to reverse engineer drugs discovered abroad, find another method to manufacture the drug, and launch this drug as a “new” product in Japan. Under the Foreign Exchange Control Law and the Foreign Investment Law of 1949 and 1950, respectively, capital controls were eased, but Japanese firms remained sheltered from foreign competition.¹²² For example, imports were subject to strict quotas, firms required licenses to produce pharmaceuticals, and ceilings were capped on royalty rates. Moreover, foreign firms who wished to enter into Japan were restricted to manufacturing ventures, required to form joint ventures of up to a 49% stake with local firms, and begin local manufacturing operations within two years.

By imposing restrictive and unfavourable conditions, the Occupation era policy protected Japan’s emerging pharmaceutical industry from foreign competition into the 1970s.¹²³ By recognising process patents and insisting upon technological diffusion across government, industry and academia, Japanese firms were able to enhance their

¹²¹ Tōru Yamazaki, “Sengo Yakugyōshi [A Postwar History of the Pharmaceutical Industry] (2),” *Yakkyoku* 16, no. 9 (September 1965): 7-12.

¹²² For a brief overview of the history of foreign direct investment in Japan, see Ralph Paprzycki and Kyoji Fukao, “The Extent and History of Foreign Direct Investment in Japan,” *Hi-Stat Discussion Paper Series* 84 (April 2005): 13-14. For an in-depth discussion, see Mark Mason, “The Screen Door. 1950-1870” in *American Multinationals in Japan: The Political Economy of Japanese Capital Controls* (Cambridge: Harvard University Press, 1992), 150-198.

¹²³ Even before the yen could freely be exchanged with foreign currencies in 1963, a few foreign firms such as Roche, Schering, and Pfizer had established manufacturing operations in Japan. Between 1957 and 1963, foreign firms were allowed to invest over 50% in yen-based firms. But after foreign direct investments became subject to government approval in 1963, new pharmaceutical ventures were virtually excluded from the market.

production capacities within a sheltered environment.¹²⁴

In the 1950s, Japanese firms developed production capacities based on technology imports ranging from antibiotics, hormonal preparations, sulfa drugs, antihistamines and anti-tubercular preparations. Indeed, Japanese firms became increasingly reliant on technology imports, which increased from \$11.9 million in 1955 to \$18.4 million in 1960.¹²⁵ While most pharmaceutical technology originated from American firms such as Merck, Parke Davis and Eli Lilly, technology imports also originated from other countries, such as Ciba and Geigy in Switzerland or Behring and Grunenthal in Germany.¹²⁶ Japanese firms acquired technological capacities by importing technology, reverse engineering, inviting overseas advisors, or sending scholars abroad to learn and adopt new technologies into the Japanese pharmaceutical industry.¹²⁷

Production levels rose as Japanese firms acquired more manufacturing capacities in a protected environment. Production levels corresponded roughly with the pace of economic growth. Between 1952 and 1961, production levels grew 3.3 fold from 370.7 million yen to 1.24 billion yen at a time when GDP grew 2.1 fold from \$196.5 billion to \$408.7 billion.¹²⁸ The rise in production levels, however, was well in excess

¹²⁴ The Japanese had recognised process patents for medicines in 1921, but the country only recognised product patents for medicines in 1976.

¹²⁵ In nominal terms, technology imports increased from \$1.6 million to \$2.8 million. Yakugyō Keizai Kenkyūjo, *Yakuji Nenkan* [Pharmaceutical Annual] (Osaka: Nihon Yakugyō Shimbunsha, 1961), 123.

¹²⁶ Yakugyō Keizai Kenkyūjo, *Yakuji Nenkan* [Pharmaceutical Annual] (Osaka: Nihon Yakugyō Shimbunsha, 1961), 120-124.

¹²⁷ See "Shihon, Gijutsu no Dōnyū oyobi Yushutsu [The Import and Export of Capital and Technology]," *Yakuji Nenkan* [Pharmaceutical Annual] (Osaka: Nihon Yakugyō Shimbunsha, 1961), 178-181.

¹²⁸ In nominal terms, production levels grew from 58.6 million yen to 420.2 billion yen. Yakugyō Keizai Kenkyūjo, *Yakuji Nenkan* [Pharmaceutical Annual] (Osaka: Nihon Yakugyō Shimbunsha, 1961), 1; Ministry of Health and Welfare, *Yakuji Kogyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Yakugyō Keizai Kenkyūjo, 1953-1967); Angus Maddison and Organisation for Economic Co-operation and Development Development Centre, *The World*

of demand. With such low barriers to entry into Japan's pharmaceutical industry, the market became over-heated. While the Korean War had stimulated production in the early 1950s, the end of the War resulted in overproduction – particularly in drugs such as penicillin, vitamins, and insecticides.¹²⁹

The excess supply of drugs began to cause strain in the distribution system. In a desperate bid to dispose of their products, advertisements began to make exaggerated claims, and some companies began to sell their products at extremely low prices. To defend against collapsing prices and to secure profits, pharmaceutical wholesalers began to form vertical groupings with manufacturers. Examples included Eisai's *Chokora-kai*, Sankyo's *Sankyo-kai*, and Takeda's *Uroko-kai*. As a profitable venture that did not have to rely on bank loans, Japan's pharmaceutical industry did not form the sort of *keiretsu* structures associated with other industries such as steel or chemicals. *Keiretsu* in these sectors generally referred to a group of firms centred around a main bank that lent funds and held equity stakes in member companies. Groupings within the pharmaceutical industry were in the form of several wholesalers associated with a manufacturer who held shares in these wholesalers who specialised in the distribution of manufacturers' products in defined regions.¹³⁰ These vertical linkages effectively served as a formidable barrier to entry for new entrants, including

Economy, Vol. 2. (Paris: Organisation for Economic Co-operation and Development, 2006), 552.

¹²⁹ See Yakugyō Keizai Kenkyūjo, *Yakuji Nenkan* [Pharmaceutical Annual] (Osaka: Nihon Yakugyō Shimbunsha, 1957), 230-231; Tōru Yamazaki, "Sengo Yakugyōshi [A Postwar History of the Pharmaceutical Industry] (2)," 7-12.

¹³⁰ Kunihiro Futaba, "Sengo no Iyakuin Ryūtsūshi: Dōran ni Yoru Kakkyō to Ranbai Mondai no Hassei [The History of Distribution in the Pharmaceutical Industry: The Korean War Boom and Emerging Problems with Dumping]," *Iyaku Jānaru* 11 (June 1972): 40-54. See also Kunihiro Futaba, "Sengo no Iyakuin Ryūtsūshi: Kajō Seisan ni Taisuru Shijō no Kakudai to Tōsei no Hōsaku [The History of Distribution in the Pharmaceutical Industry: Strategies for Controlling a Market Expanding with Overproduction]" *Iyaku Jānaru* 11 (July 1972): 59-70. See also, "Iyakuin Ryūtsū Būmon [The Distribution of Pharmaceuticals]" *Yakuji Nenkan* [Pharmaceutical Annual] (Osaka: Nihon Yakugyō Shimbunsha, 1961), 49.

foreign pharmaceutical firms.

As well, the pharmaceutical industry reorganised and became more concentrated as larger firms enjoyed greater bargaining power in signing international licensing agreements and economies of scale in production. By the 1960s, 11 firms had more than 1,000 workers. It was true that Japanese pharmaceutical was still comprised of smaller firms than its Western counterparts. After all, more than 75% of Japanese pharmaceutical firms employed less than 50 workers.¹³¹ But the larger, pre-war pharmaceutical firms regained their dominance in Japan's pharmaceutical industry.

In the 1950s, the government helped Japanese firms develop the pharmaceutical industry through a combination of policies under a protected environment. In particular, government's import substitution policy helped Japanese firms catch up and acquire manufacturing capacities through technology imports. The government's recognition of process patents further fostered the dissemination of technology across a many firms. Both government and firms seemed content with the acquisition of technology and disinterested in the development of new technologies. In particular, the lack of industrial policy to encourage R&D at a time when the US or British governments generously rewarded innovation severely undermined the development of a research-intensive pharmaceutical sector in Japan.¹³²

¹³¹ Organisation for Economic Co-operation and Development, *Pharmaceuticals: Gaps in Technology* (Paris: Organisation for Economic Cooperation and Development, 1969), 48.

¹³² Laecy Glenn Thomas, III, "Implicit Industrial Policy: The Triumph of Britain and the Failure of France in Global Pharmaceuticals," 451-489.

2.5 Volume-based growth under universal health care, 1961-1975

Supported by a combination of health and industrial policies, Japanese firms built a highly successful domestic industry between 1961 and 1975. To better regulate the quality and efficacy of drugs, the government revised the PAL in 1961. In the same year, the government also introduced a universal health care system. While there had been some coverage for prescription drugs before 1961, the universal health care system enabled almost all Japanese citizens to purchase medicines with a small co-payment. The introduction of universal health care triggered a period of volume-based growth as the government underwrote demand for prescription pharmaceuticals.¹³³ Japan's pharmaceutical industry expanded rapidly as many firms launched domestic versions of foreign discovered drugs. In the meanwhile, recurrent drug accidents ranging from thalidomide to cold ampoules prompted a series of legislation that improved drug safety and standards in Japan.

2.5.1 Thalidomide

The 1960s began with the shock of the thalidomide scandal, which exposed severe lapses in existing drug standards and revealed the urgent need to improve drug safety and efficacy criteria. Thalidomide was originally developed in Germany by the pharmaceutical firm Grunenthal, and was used by pregnant women to treat morning sickness. The drug was distributed widely between 1957 and 1962 in 46 countries.¹³⁴

¹³³ Ministry of Health and Welfare, "Kokumin Kaihoken Seido no Kakuritsu [The Establishment of a Universal Healthcare System]," in *Showa 36-nendo Kōsei Hakusho* [White Paper on Health, 1961] (Tokyo: Ōkurashō Insatsukyoku, 1962).

¹³⁴ Stefan Timmermans and Valerie Leiter, "The Redemption of Thalidomide: Standardizing the Risk of Birth Defects," *Social Studies of Science* 30, no. 1 (2000): 41-71.

Thalidomide acquired notoriety when it caused tens of thousands of birth defects and deaths among babies born to patients taking the drug.¹³⁵

The thalidomide tragedy underscored the importance of drug regulation. The United States had managed to avert a national tragedy when the Federal Drug Administration (FDA) refused to approve the drug in 1960.¹³⁶ In Germany, the authorities swiftly banned the drug's use in November 1961 after the scientist Widukend Lenz published an article that linked thalidomide to birth defects among babies.¹³⁷ But the Japanese government was much slower to respond. For example, Asia Pharmaceuticals was granted approval for thalidomide in February 1962, and Dainihon Pharmaceuticals – who had been marketing thalidomide since 1958 – only stopped shipments of the drug in May 1962.¹³⁸ The Japanese government's belated response to the thalidomide tragedy revealed serious lapses in prevailing drug standards and official attitudes toward drug safety.

The thalidomide tragedy resulted in a public outcry, which heightened awareness to the potential dangers of drugs and propelled regulatory reforms in drug safety and efficacy around the world. The Americans reacted swiftly to the tragedies overseas by passing the Kefauver-Harris Amendments in 1962, which bolstered existing US

¹³⁵ For an overview of the thalidomide disaster, see for example, Sunday Times Insight Team, *Suffer the Children: The Story of Thalidomide* (London: Andre Deutsch, 1979); Harvey Teff, *Thalidomide: The Legal Aftermath* (Farnborough: Saxon House, 1976).

¹³⁶ The American response to the Thalidomide tragedy has been documented in many articles, books. See for example, Philip Hilts, "Thalidomide," in *The FDA, Business, and One Hundred Years of Regulation* (New York: Knopf, 2003), 144-165.

¹³⁷ "Drug is Defended by Germany Maker; Thalidomide's Link to Baby Deformities Held Lacking," *The New York Times*, 4 August 1962, 20.

¹³⁸ Hideo Fujiki and Mitsuhiro Kida, eds., *Yakuhiin Kōgai to Saiban: Saridomaido Jiken no Kiroku kara* [Drug Accidents and Trials: From the Records of the Thalidomide Disaster] (Tokyo: University of Tokyo Press, 1974). Mitsuhiro Kida, *Thalidomide Embryopathy in Japan* (Tokyo: Kodansha, 1987).

regulations over drug development. While Britain, for example, legislated quality, safety, and efficacy guidelines in 1968, equivalent measures in Japan were only implemented when the PAL was revised in 1979.¹³⁹

2.5.2 Health care reform and the creation of a domestic industry

With the introduction of universal health care, the Japanese government began to underwrite demand for prescription drugs. Japanese pharmaceutical firms also benefited from a series of other reforms over the 1960s and 1970s. Of particular importance were the 1973 reforms that lowered co-payment levels and provided free health care – including medicines – for the elderly. These measures increased demand for prescription drugs and led to their over prescription. But for many Japanese pharmaceutical firms, these health care reforms were important in supporting their growth.

In Japan, physicians both prescribed and dispensed prescription drugs. This practice fuelled demand for prescription drugs, because pharmaceutical firms sold drugs at discounted prices to physicians who profited from reselling their drugs at the official rate. The government's fee-for-service system also created strong incentives for physicians to prescribe new, higher priced drugs that tended to have greater pharmaceutical price differentials. This was not only because physicians could profit

¹³⁹ Stuart L. Nightingale, "Drug Regulation and Policy Formulation," *The Milbank Memorial Fund Quarterly. Health and Society* 59, no. 3 (1981): 412-444; John G. Fleming, "Drug Injury Compensation Plans," *The American Journal of Comparative Law* 30, no. 2 (1982): 297-323; PA Andrews, GM Thompson, GM, and C Ward, "A Regulatory View of the Medicines Act in the United Kingdom" *Journal of Clinical Pharmacology* (1984): 6-8; Harvey Teff, "Drug Approval in England and the United States." *The American Journal of Comparative Law* 33, no. 4 (1985): 567-610; Shōsuke Koga, "Yakujihōsei no Hensen [Changes to the Pharmaceutical Affairs Act]," *Gekkan Yakuji* 21 (November 1979): 31-40.

from dispensing drugs, but also because the official fees for medical services rewarded physicians more for prescription services than for medical consultations.¹⁴⁰ It should also be noted that the Japan Medical Association (JMA) traditionally wielded significant power over health care policy in Japan. This was particularly true during the JMA's leadership by Tarō Takemi between 1957 and 1982.¹⁴¹

The rapid rate of Japanese economic growth also propelled growth in the pharmaceutical industry, not just by raising demand among wealthier patients, but also by encouraging companies from other sectors of the economy to enter the pharmaceutical sector. New entrants came from various sectors, ranging from chemicals (such as Sumitomo Kagaku and Mitsubishi Kasei) to textiles (such as Toray and Teijin).¹⁴² Indeed, Japan's growth in pharmaceutical production paralleled its GDP growth, as both pharmaceutical production levels and GDP grew 3.4 fold between 1960 and 1975.¹⁴³

Along with other sectors of the economy in the 1960s, Japanese pharmaceutical firms also built central research laboratories to develop the industry. But apart from a few entrepreneurial firms, most industrial R&D was restricted to process innovations

¹⁴⁰ See Shūzō Nishimura, "Iryō Sangyō [The Health Care Industry]," in *Sengo Nihon Sangyōshi* [A History of Japanese Industries in the Post-war Period], ed. Sangyō Gakkai [The Society for Industrial Studies] (Tokyo: Tōyō Keizai Shinpōsha, 1995), 769-786.

¹⁴¹ See James Kondo, "The Iron Triangle of Japan's Healthcare," *BMJ (British Medical Journal)* 330 (January 2005): 55-56. See also Chūsei Mizumaki, *Nihon Ishikai: Hōraku Suru Seiki* [The Japan Medical Association: Its Crumbling Power] (Tokyo: Chūōkōron, 2003).

¹⁴² These firms also entered pharmaceuticals because they were facing saturation in the domestic market in their respective sectors. See Japan Society for the History of Pharmacy, *Nihon Iyakuin Sangyōshi* [A History of the Japanese Pharmaceutical Industry] (Tokyo: Yakuji Nippōsha, 1995), 121-122. The experience of Kirin Brewery, for example, was recently written by Michael Lynskey, "The Locus of Corporate Entrepreneurship: Kirin Brewery's Diversification into Biopharmaceuticals," *Business History Review* (Winter 2006): 689-723.

¹⁴³ Ministry of Health and Welfare, *Yakuji Kogyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Yakugyō Keizai Kenkyūjo, 1953-1967); Ministry of Health and Welfare, *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Yakugyō Keizai Kenkyūjo, 1968-2000); Angus Maddison and Organisation for Economic Co-operation and Development Development Centre, *The World Economy*, Vol. 2. (Paris: Organisation for Economic Co-operation and Development, 2006), 552.

or minor product innovations. In fact, technology imports rose almost three fold from \$18.5 million to \$64.7 million between 1960 and 1975.¹⁴⁴ The creation of these research laboratories did prompt the shift of some pharmaceutical research from academia to industry. But the lack of facilities, equipment, and human capital left pharmaceutical firms reliant on academia to pursue research in pharmaceutical innovation.¹⁴⁵ Scholars such as Hiroyuki Odagiri have noted that much of pharmaceutical R&D in Japan has occurred as collaborative projects between academia and industry.¹⁴⁶ In Japan, many firms lacked incentives to invest in R&D, not only because of capital limitations, but also due to the lack of facilities and equipment, the high cost of raw materials, and lack of export-oriented policies supported by the MITI in other industrial sectors.

¹⁴⁴ In nominal terms, technology imports rose from \$2.8 million to \$17.8 million. Bureau of Statistics, Office of the Prime Minister, *Kagaku Gijutsu Kenkyū Chōsa Hōkoku* [Report on the Survey of Research and Development] (Tokyo: Office of the Prime Minister, 1961-1984).

¹⁴⁵ This is evident in drug development records. See Yakuji Nippōsha, *Saikin no Shinyaku* [New Drugs in Japan] (Tokyo, Yakuji Nippōsha, 1950-2006).

¹⁴⁶ See Hiroyuki Odagiri, "Transaction Costs and Capabilities as Determinants of the R&D Boundaries of the Firm: A Case Study of the Ten Largest Pharmaceutical Firms in Japan," *Managerial and Decision Economics* 24 (2003): 187-211.

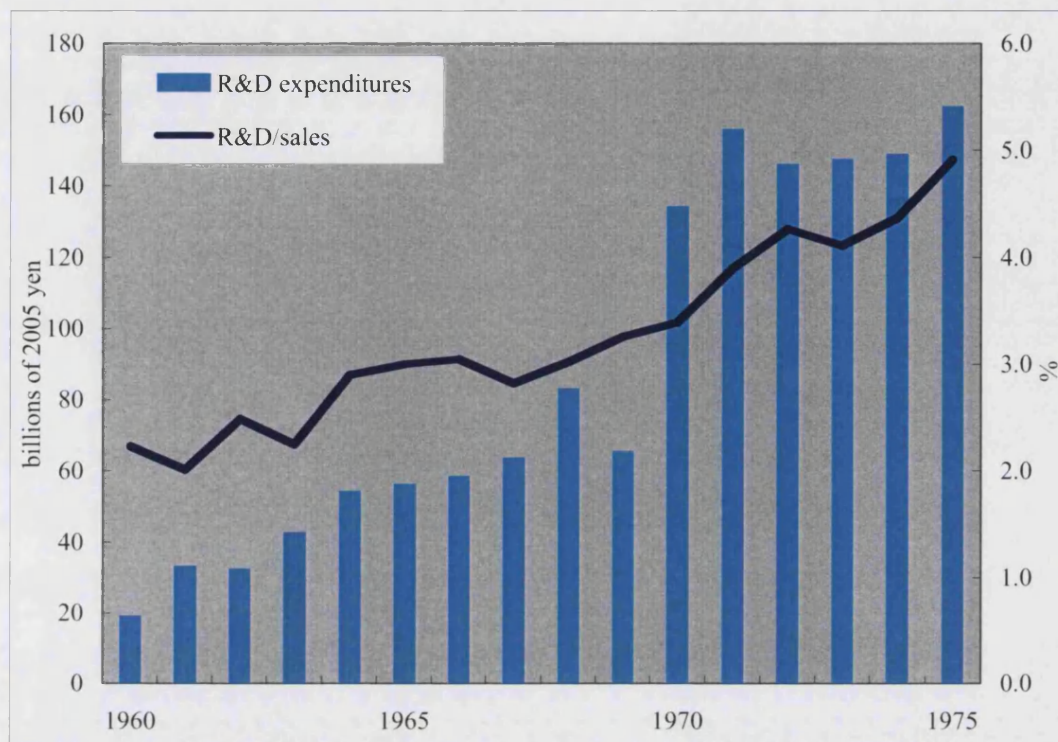


Figure 2. R&D Expenditures, 1960-1975¹⁴⁷

R&D expenditures did increase, particularly as the government gradually opened its doors to foreign competition. But while R&D expenditures increased 8.5 fold from 19.2 billion yen to 162.4 billion yen and while R&D expenditure as a percentage of sales rose 2.2 fold from 2.2% to 4.9% between 1960 and 1975, it was much smaller than leading Western counterparts.¹⁴⁸ In 1972, for example, R&D expenditures as a percentage of total sales in Japan stood at 4.2% compared to 9.2% in the United States and 8.1% in the United Kingdom, respectively.¹⁴⁹ Not surprisingly, few Japanese drugs were competitive in export markets. Japanese trade in pharmaceuticals did grow from 66.5 billion yen in 1960 to 291.8 billion yen in 1975.¹⁵⁰ But imports exceeded

¹⁴⁷ Bureau of Statistics, Office of the Prime Minister, *Kagaku Gijyutsu Kenkyū Chōsa Hōkoku* [Report on the Survey of Research and Development] (Tokyo: Office of the Prime Minister, 1961-1984).

¹⁴⁸ In nominal terms, R&D expenditures between 1960 and 1975 increased from 3.7 billion yen to 95.2 billion yen. *Ibid.*

¹⁴⁹ *Ibid.*, Pharmaceutical Research and Manufacturers of America, *Pharmaceutical Industry Profile 2008* (Washington, DC: PhRMA, March 2008), 53; Great Britain, Business Statistics Office, *Industrial Research and Development Expenditure and Employment: 1975* (London: H.M.S.O., 1979), 27.

¹⁵⁰ Pharmaceutical trade refers to the sum of imports and exports in pharmaceuticals. In nominal terms, Japanese trade in

more than twice the value of exports over the 1960s, and most of Japan's exports were in relatively simple drugs, such as antibiotics and vitamins, that were shipped to the developing world.¹⁵¹ Moreover, few Japanese drugs were recognised overseas. Between 1950 and 1967, less than 2% of drugs introduced in the US, UK, or German markets were discovered in Japan. Conversely, of drugs in Japan, 30.6% was from the United States, 12.9% was from Switzerland, and 11.8% was from Germany. Japanese drugs comprised 24.7% of the home market.¹⁵²

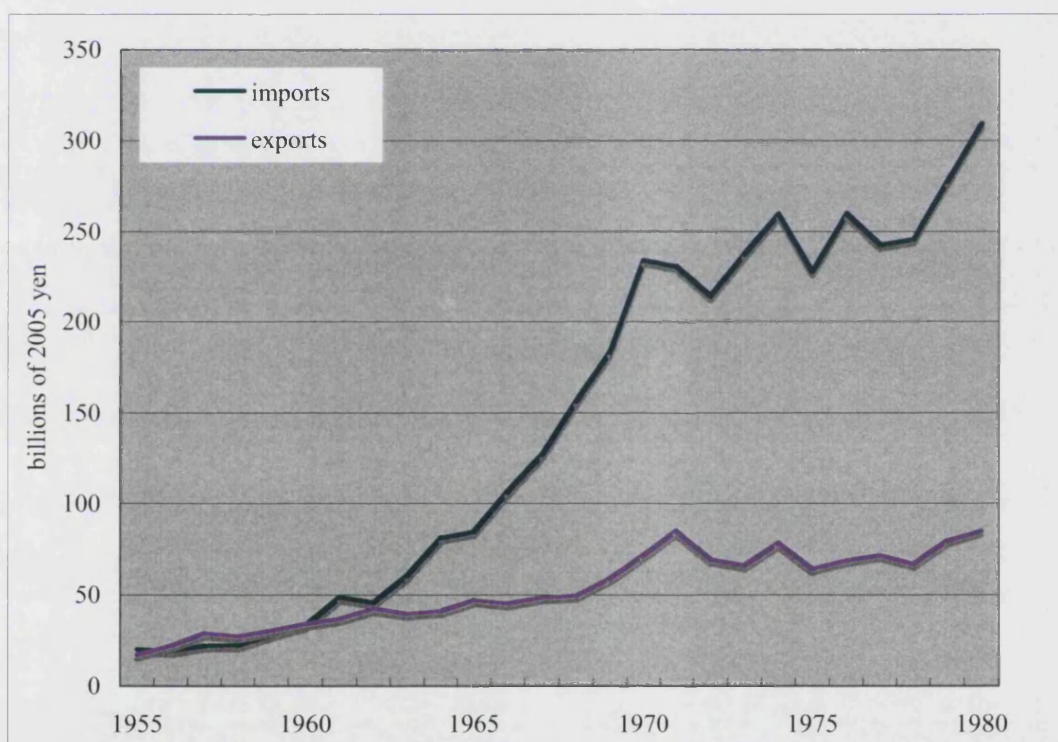


Figure 3. Value of Pharmaceutical Trade, 1955-1980¹⁵³

pharmaceuticals increased from 12.7 billion yen in 1961 to 167.5 billion yen in 1975. See Ministry of International Trade and Industry, *Tsūshō Hakusho* [White Paper on Trade] (Tokyo: Ōkurashō Insatsukyoku, 1958-1973).

¹⁵¹ Mostly Asia. See Yakugyō Keizai Kenkyūjo, *Yakugyō Keizai Nenkan* [Pharmaceutical Economics Annual] (Tokyo: Yakuji Nippōsha, 1967), 132-137.

¹⁵² See Organisation for Economic Co-operation and Development, *Pharmaceuticals: Gaps in Technology*, 127.

¹⁵³ Ministry of International Trade and Industry, *Tsūshō Hakusho* [White Paper on Trade] (Tokyo: Ōkurashō Insatsukyoku, 1958-1973); Ministry of International Trade and Industry, *Tsūshō Hakusho* [White Paper on Trade] (Tokyo: Gyōsei, 1974-2000).

2.5.3 Economic development and Steps toward capital liberalisation

As the economy grew, the international community intensified pressures on Japan to liberalise its capital. The Foreign Exchange Control Law and the Foreign Investment Law had effectively locked out foreign direct investment since 1950. But with its accession to the OECD and IMF in 1964, Japan agreed to phase in capital liberalisation. The imminent introduction of full capital liberalisation and product patents altered industry dynamics, as they incentivised firms to raise their R&D investments, modernise facilities, and adopt improved quality standards.¹⁵⁴

While the pharmaceutical industry was not fully deregulated until 1975, the government gave approval for up to 50% investments in 1967.¹⁵⁵ While Japanese firms were still much smaller than leading foreign pharmaceutical firms in terms of capital, gaps between the West were narrowing – in profitability, R&D capacity, as well as the number and ability of workers.¹⁵⁶ And while the Japanese pharmaceutical industry still grew through the volume based production of drugs discovered overseas, it relied less on technology imports compared to other sectors of the Japanese economy.¹⁵⁷

¹⁵⁴ Yakugyō Keizai Kenkyūjo., *Yakugyō Keizai Nenkan* [Pharmaceutical Economics Annual] Tokyo: Yakuji Nippōsha, 1967), 236-244.

¹⁵⁵ Yakugyō Jihōsha, *Nihon no Iyakuin Sangyō* [The Japanese Pharmaceutical Industry] (Tokyo: Yakugyō Jihōsha, 1973), 160-161. [Editorial Committee for the 50 Year History of the Ministry of Health and Welfare, “Jiyūka to Kokusaika no Shinten [Progress in Capital Liberalisation and Internationalisation],” in *Kōseishō 50-nenshi* [A 50 Year History of the Ministry of Health and Welfare] (Tokyo: Kōsei Mondai Kenkyūkai, 1988), 1624-1626.

¹⁵⁶ See Organisation for Economic Co-operation and Development, *Pharmaceuticals: Gaps in Technology*. However, the profitability among firms was heavily bolstered by the health care system and is not an accurate indicator of the ability of Japanese firms to compete against foreign counterparts.

¹⁵⁷ Yakugyō Keizai Kenkyūjo., *Yakugyō Keizai Nenkan* [Pharmaceutical Economics Annual] (Tokyo: Yakuji Nippōsha, 1967), 240.

2.5.4 Product Standards

In anticipation of capital liberalisation – as well as in response to recurrent drug tragedies – the government began to improve Japan’s drug quality standards from the 1960s through administrative guidance.¹⁵⁸ In the “Basic Policies for Drug Manufacturing Approval” in 1967, the government specified drug development guidelines for the first time.¹⁵⁹ While these measures improved the quality of drugs available in Japan, they were different from the standards used overseas. The standards effectively served as a non-tariff trade barrier and excluded foreign pharmaceuticals from the Japanese market. Spurred by government-guaranteed demand for prescription pharmaceuticals and sheltered from foreign competition, Japan’s pharmaceutical industry embarked upon a remarkable period of expansion.¹⁶⁰

This expansion was also fuelled by the relatively low criteria placed on drugs to qualify as a New Chemical Entity (NCE).¹⁶¹ Many of the new drugs launched in Japan during the 1960s and 1970s were not necessarily novel, and were approved with modest improvements such as more suitable doses, convenient forms of administration, or fewer side effects.¹⁶² To a certain extent, the government’s policies

¹⁵⁸ Administrative guidance refers to informal legislation in the form of official or unofficial announcements from the government. The Japanese government used administrative guidance as an instrument of industrial policy to provide guidelines for business. Non-compliant parties could be penalized, for example, by receiving lower quotas or less aid from the government. This included the launch of an adverse reactions monitoring system in 1967 and the adoption of Good Manufacturing Practices (GMP) in 1974. See Kaoru Tabuchi, “GMP no Ayumi to sono Tenbō [History and Prospects of GMP],” *Gekkan Yakujū* 21 (November 1979): 243-247. See also Shinji Nitta, “Iyakuin no Shinsa Gyōsei [Governing the Examination of Pharmaceuticals],” *Gekkan Yakujū* 21 (November 1979): 53-65.

¹⁵⁹ This legislation created the distinction between prescription and OTC drugs by establishing criteria for drug approval in Japan. The 1967 guidelines, for example, specified the necessary documentation required to pursue a new drug application. Among other criteria, the guidelines also asked producers of prescription medicines to disclose adverse effects and provide a stable supply of medicines.

¹⁶⁰ Ministry of Health and Welfare, *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Yakugyō Keizai Kenkyūjo, 1953-1967); Ministry of Health and Welfare, *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Yakugyō Keizai Kenkyūjo, 1968-2000).

¹⁶¹ A New Chemical Entity is a chemical compound that has not been previously been approved for use in humans.

¹⁶² Robert Neimeth, “Japan’s Pharmaceutical Industry Postwar Evolution,” 158-159.

to place a lower threshold on innovation eased the transition from process to product innovations. Under this system, Japanese firms launched many new drugs with incremental innovations and marketed these to physicians who could gain from high pharmaceutical price differentials. While Japan's pharmaceutical sector grew steadily during this period, with minimal innovative value, most Japanese drugs could not be translated into overseas markets.

The gradual liberalisation of capital controls prompted a fresh wave of foreign entrants such as SmithKline, Eli Lilly, and Wellcome.¹⁶³ But foreign firms had yet to put a dent into Japan's antibiotics sector in the 1970s. After all, the product standards introduced in 1967 had placed foreign products out of the Japanese market. In addition, foreign firms were reluctant to enter a market where their large R&D investments for breakthrough drugs would not be rewarded for their innovative value as in their home markets. As well, foreign firms had yet to establish a marketing presence in Japan.¹⁶⁴ It was true that capital liberalisation posed a threat to many Japanese firms. But by the mid 1970s, Japan's firms had largely caught up with the West, and the large pharmaceutical firms that dominated the domestic market were prepared to capture gains from abroad.

2.5.5 1973: a year of welfare for the people – and for industry

Despite its struggles in R&D, production, and distribution, the government's

¹⁶³ Mitsubishi Bank, Ltd., "Nihon Shijō ni Chūryoku suru Iyakuhin Gaishi [Foreign Pharmaceutical Firms Eye the Japanese Market," *Mitsubishi Bank Research Report* 369 (January 1986): 32.

¹⁶⁴ Yakugyō Jihōsha, *Yakuji Handobukku* [Pharmaceutical Affairs Handbook] (Tokyo: Yakugyō Jihōsha, 1968-2000).

sponsorship of demand continued to help the growth of Japan's pharmaceutical industry. The impact of the government's health care policies was particularly evident in the 1973 reforms. Dubbed "The Year of Welfare," in 1973, the government introduced several welfare measures that increased its level of sponsorship of prescription pharmaceuticals. Thirty percent co-payment levels were introduced for family dependants, medical fees were capped for high cost treatments, and free health care was provided for the elderly.¹⁶⁵ The impact of these reforms was immediate, and while production levels had been increasing since 1961, the 1973 reforms added a fresh surge in momentum.

Indeed, from the introduction of universal health care in 1961, the pharmaceutical industry expanded markedly. While it was the fifth largest global producer of pharmaceuticals in 1960, Japan became the second largest producer of pharmaceuticals in 1963. Growth in pharmaceutical production was more rapid in Japan compared to the United States or Europe. Between 1960 and 1965, for example, pharmaceutical production in Japan increased 1.7 fold compared to 1.4 fold in the United Kingdom or 1.3 fold in the United States.¹⁶⁶ Between 1961 and 1975, production almost tripled from 1.1 trillion yen to 3.1 trillion yen.¹⁶⁷

¹⁶⁵ Ministry of Health and Welfare, *Kōsei Hakusho* [White Paper on Health and Welfare] (Tokyo: Ōkurashō Insatsukyoku, 1974).

¹⁶⁶ Yakugyō Keizai Kenkyūjo, *Yakugyō Keizai Nenkan* [Economics of the Pharmaceutical Industry Annual] (Tokyo: Yakuji Nippōsha, 1967), 299.

¹⁶⁷ In nominal terms, production levels rose from 218.1 million yen to 1.8 trillion yen. Ministry of Health and Welfare, *Yakuji Kogyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Yakugyō Keizai Kenkyūjo, 1953-1967); Ministry of Health and Welfare, *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Yakugyō Keizai Kenkyūjo, 1968-2000).

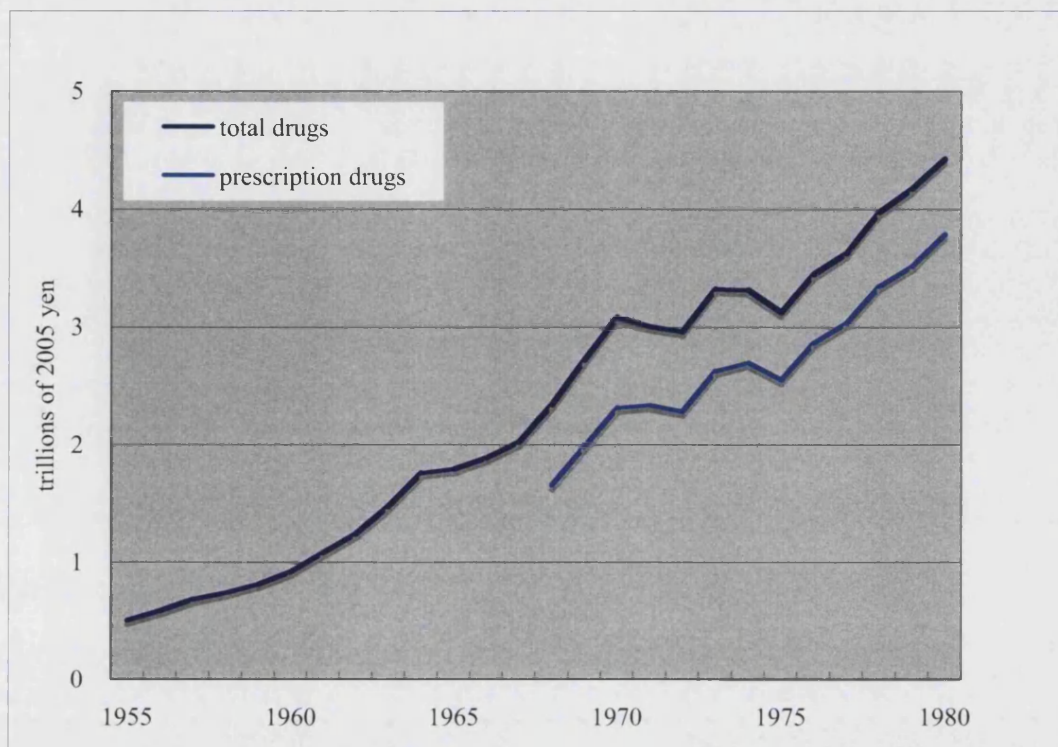


Figure 4. Value of Pharmaceutical Production, 1955-1980¹⁶⁸

Contemporaries expressed concern about the over-production of similar therapeutic products, which led to intense competition. To a certain extent, the lack of a strong intellectual property rights regime prompted the entry of many new firms, which also intensified volume-based expansion through the 1970s.¹⁶⁹ To gain an edge in the market, Japanese firms – which numbered 1,359 in 1975 – continued to engage in dumping and excessive bargaining in the form of bribes or services.¹⁷⁰ Neither administrative guidance nor industry initiatives had much effect in curbing these practices. Some order was restored in 1970, when the government finally threatened to

¹⁶⁸ Ibid. It should be noted that official figures for prescription drugs were not compiled until 1968.. The dip after 1970 is due largely to the oil shock.

¹⁶⁹ Yano Research Institute, "Tasangyō kara no Kigyō Shinshutsu [New Entrants from Other Sectors]," *Iyaku Sangyō Nenkan* (Tokyo: Yano Research Institute, 1975), 78. Between 1970 and 1980, the number of facilities related to pharmaceutical manufacture increased from 20,993 to 22,497. See Ministry of Health and Welfare, "Pharmaceutical Business Facilities (C.Y. 1944--1996, F.Y. 1997--2004)," <http://www.stat.go.jp/data/chouki/24.htm> (accessed 27 July 2008).

¹⁷⁰ *Iyakuhin Sangyō Jittai Chōsa Hōkoku* [Report on the Status of the Pharmaceutical Industry] (Tokyo: Ministry of Health and Welfare, 1988-2000). Reprinted in Japan Pharmaceutical Manufacturers Association, *Data Book* (Tokyo: Japan Pharmaceutical Manufacturers Association, 2007), 2.

de-list the drugs of firms engaged in excessive discounting practices.¹⁷¹

With the launch of universal health care in 1961, the government guaranteed demand for prescription pharmaceuticals and substantially expanded the domestic market. The government's health policies increased demand as it encouraged physicians to prescribe new drugs to benefit from pharmaceutical price differentials. The government's protectionist policies and recognition of process patents also encouraged the development of the pharmaceutical industry by allowing many firms to produce similar products.

At the same time, however, impending plans to liberalise capital controls and introduce product patents in the 1970s encouraged many firms to invest in R&D and seek overseas markets. As in the previous period, links to academic laboratories remained essential for drug development. The threat of capital liberalisation also encouraged firms to invest in central laboratories; some firms also invested more heavily in R&D and launched Japan origin drugs.

2.6 Transitions to quality based growth, 1975-1990

By the 1970s, most Japanese firms were catching up with foreign firms in terms of discovery capacity, if not size or sales. Between 1975 and 1979, 4% of new drugs that were launched in the majority of the G7 countries were discovered in Japan. This was

¹⁷¹ Tokai Bank, Ltd., "Hanbai-mō no Kyōka o Isogu Iyakuinkai [The Pharmaceutical Industry Rushes to Strengthen its Distribution Network]," *Tokai Ginkō Chōsa Geppō* 222 (January 1966): 17-26. See also, Kunihiko Futaba, "Sengo no Iyakuin Ryūtsushi: Iyakuin Kōgyō no Kiki to Dakai e no Mosaku [The History of Distribution in the Pharmaceutical Industry: Seeking Solutions to the Challenges of the Pharmaceutical Industry]," *Iyaku Jānaru* 11 (September 1972): 44-53.

a time when 29% of new global products were discovered in the United States, 18% were discovered in Germany, 11% were discovered in Switzerland, and 1% was discovered in the United Kingdom.¹⁷² Japan's pharmaceutical industry now reached a turning point. Government policies to liberalise capital and strengthen intellectual property protection opened the market and encouraged firms to invest in product innovations.¹⁷³ Under foreign pressure, the government removed barriers to entry and introduced enhanced safety, quality, and efficacy standards that helped improve the quality of drugs available in Japan.

2.6.1 Creating a modern market: opening up and protecting intellectual property

In the mid 1970s, the government introduced two measures that aimed to modernise the market. While intense lobbying by the Japan Pharmaceutical Manufacturers Association (JPMA) with the MITI, MHW, and Keidanren had helped stall deregulation, capital controls were finally liberalised in 1975.¹⁷⁴ Product patents were introduced shortly thereafter, in 1976.¹⁷⁵ Both changes brought an influx of foreign firms, who could now worry less about the imitation of their products. Not only did these measures lead Japanese firms to adopt a more research-intensive orientation to

¹⁷² P.E. Barral, *20 Years of Pharmaceutical Research Results Throughout the World* (Antony: Rohne-Poulenc Rorer Foundation), 24. See also, Elma S. Hawkins and Michael R. Reich, "Japanese-originated Pharmaceutical Products in the United States from 1960 to 1989: An Assessment of Innovation," 1-11.

¹⁷³ Ministry of Health and Welfare, "Iyakuhin Sangyō nado no Genjō to Shomondai [Current Status and Problems in the Pharmaceutical Industry]" in *Kōsei Hakusho* [White Paper on Health] (Tokyo: Ōkurashō Insatsukyoku, 1977).

¹⁷⁴ Japan Pharmaceutical Manufacturers Association, *Seiyakukyō 20-nenshi* [A 20 year History of the Japan Pharmaceutical Manufacturers Association] (Tokyo: Japan Pharmaceutical Manufacturers Association, 1988), 57-58, 63-64. Established in 1946, the Keidanren was one of Japan's four leading economic organizations, along with the Nikkeiren, the Japan Chambers of Commerce and Industry and the Japan Committee for Economic Development. Known to represent the voice of big business toward the government's economic policies, it merged with Nikkeiren into the Nippon Keidanren in 2002. the Japan Pharmaceutical Manufacturers Association's success in bargaining an extension to capital controls between the late 1960s and early 1970s has been discussed in Sōichiro Giga, "Han'ei no Naka no Naiyū Gaikan" *Iyaku Jānaru* 9 (October 1970): 24-31. The experience of Sankyo's former vice president is discussed in an interview with Jūshin Suzuki, "Hanbai ni Kokoro Ubaware Sōyaku Wasureta Seiyaku Sangyō [Caught Up in Sales, the Pharmaceutical Industry Forgot to Develop Drugs]," *Doraggu Magajin* 43 (January 2000): 54-66.

¹⁷⁵ Ministry of Health and Welfare, "Iyakuhin Sangyō nado no Genjō to Shomondai [Current Status and Problems in the Pharmaceutical Industry]" in *Kōsei Hakusho* [White Paper on Health] (Tokyo: Ōkurashō Insatsukyoku, 1977).

compete, they also helped protect new discoveries made by Japanese firms.

2.6.2 The cost of an ageing population

By the 1980s, Japan began to feel the pressures of an ageing population. The proportion of the population aged 65 and over reached 9.1%, more than double the level in 1950.¹⁷⁶ There was higher demand for medicines to treat diseases of affluence, and rising health care costs began to place a burden on Japan's universal health care system, which had been based on a population structure characterized by high birth rates and a large population of workers who split the cost of elderly care.¹⁷⁷

The government responded to the rising health care costs in two major ways. First, it introduced biennial price reductions in 1981, starting with a steep, across-the-board reduction of 18.6%.¹⁷⁸ In 1982, it ended free health care coverage to the elderly under the law, "Healthcare for the Aged." The response was swift, and production levels peaked in 1982. The rate of growth in production had actually stumbled slightly earlier, as the official rates for initial consultation fees and hospitalisation fees were raised in 1980. But combined with a raise in beneficiary co-payment levels from 10% to 20% in 1984, production values fell from 4.0 trillion yen in 1982 to 3.8 trillion yen in 1985. The biennial price reductions also helped stem the pace of increase in production from an average year-on-year growth of 5.2% in the 1970s to 3.8% in the 1980s.¹⁷⁹

¹⁷⁶ Ministry of International Affairs and Communications, "Population by Single Years of Age and Sex (1884—2000)," <http://www.stat.go.jp/data/chouki/02.htm> (accessed 20 March 2007).

¹⁷⁷ Ministry of Health and Welfare, "Patients and Deaths of Infectious Diseases and Food Poisoning (1876 1999)," <http://www.stat.go.jp/data/chouki/02.htm> (accessed 6 May 2008).

¹⁷⁸ Jihō, *Iryō Iyakuhin Gyōkai no Ippan Chishiki* [General Information on the Healthcare and Pharmaceutical Industries] (Tokyo: Jihō, 2005), 60.

¹⁷⁹ In nominal terms, production values fell from 3.40 trillion yen in 1982 to 3.38 trillion yen in 1985. Ministry of Health and

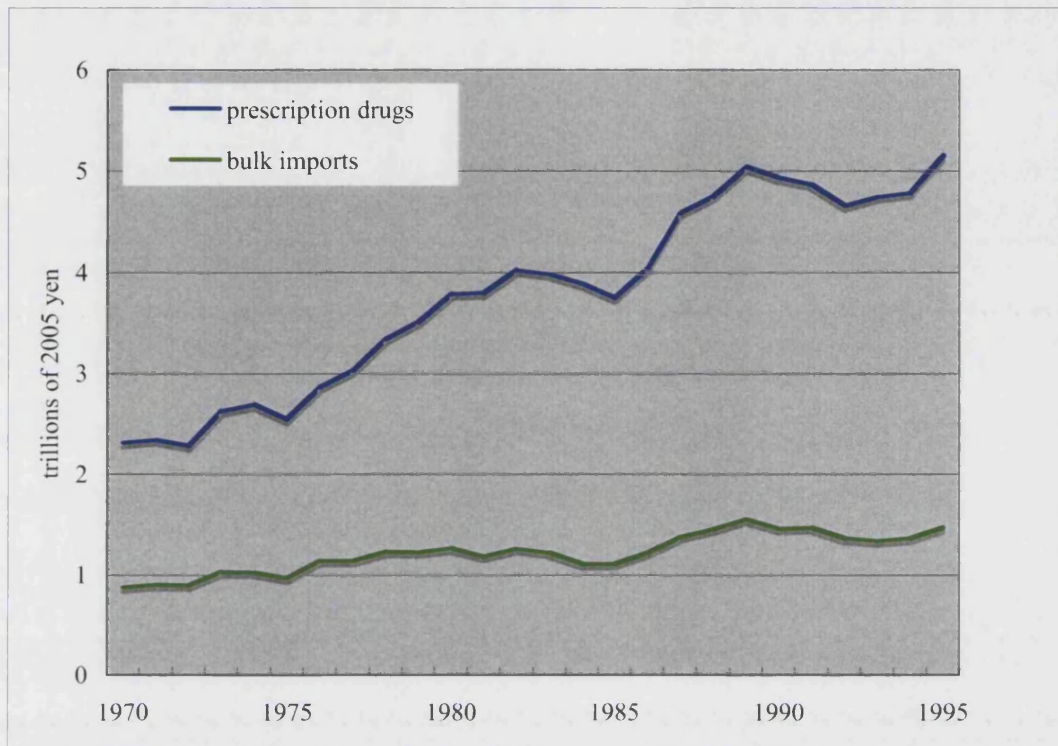


Figure 5. Value of Pharmaceutical Production, 1970-1995¹⁸⁰

The biennial price reductions had a particularly severe impact on Japanese pharmaceutical firms' incentive to invest in R&D. As the graph in figure 6 indicates, drug prices fell 67.9% between 1981 and 1991.¹⁸¹ Drug prices were revised uniformly on a regular basis – regardless of innovative value – throughout the patent protection period. These reductions incentivised Japanese firms to launch a stream of new drugs with short product life and little innovative value that could recoup the costs of R&D, rather than invest in more substantial innovation. After all, the threshold on innovation was much smaller for new drugs in Japan compared to many advanced markets. While

Welfare, *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Yakugyō Keizai Kenkyūjo, 1968-2000).

¹⁸⁰ Ibid. There are three dips in this period. The first is due to the oil shock, the second is due the end of free health care for the elderly in 1982, and the third stems from the burst of Japan's economic bubble of the 1980s.

¹⁸¹ Jihō, *Iryō Iyakuin Gyōkai no Ippan Chishiki* [General Information on the Healthcare and Pharmaceutical Industries] (Tokyo: Jihō, 2005), 60.

the industry did intensify its R&D orientation, most firms invested less than many American and European firms. These trends hindered the industry's prospects of launching breakthrough drugs that would have been more competitive overseas.

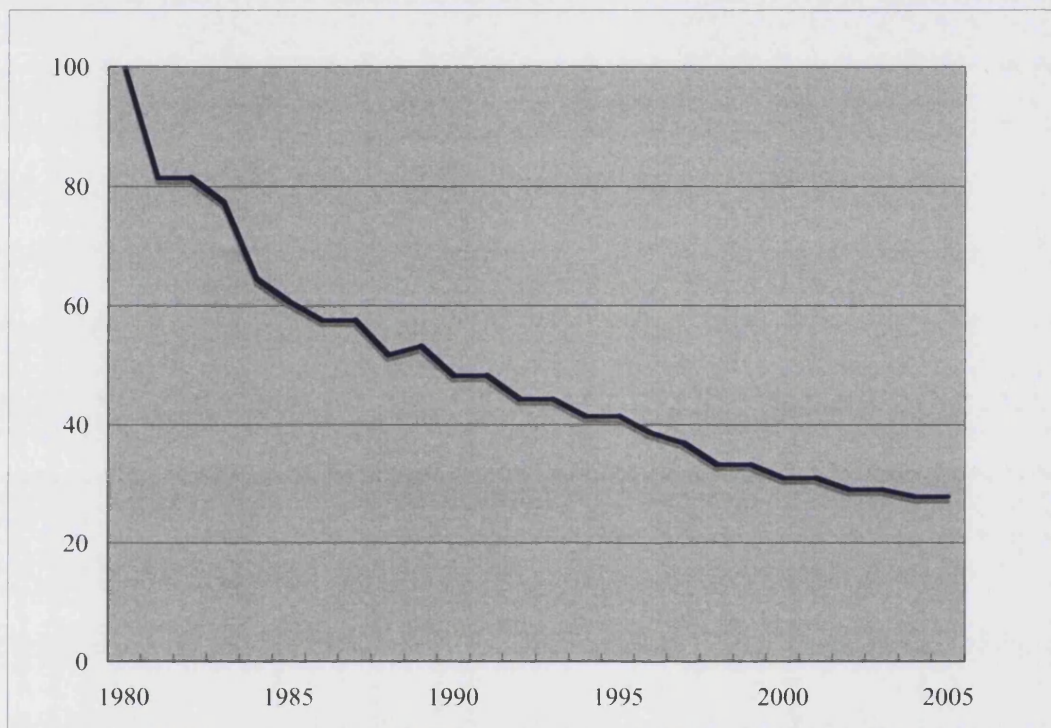


Figure 6. Impact of Price Reductions, 1980-2005 (1980=100)¹⁸²

There were several new entrants into the pharmaceutical sector during this period: foreign firms and Japanese firms from other industries. Capital liberalisation in 1975, of course, had a pronounced effect on increasing the number of foreign firms in Japan. In 1970, there were 74 foreign pharmaceutical firms operating in Japan. By 1980, these figures had risen to 239.¹⁸³ Major firms such as Eli Lilly and Glaxo expanded their operations in Japan. With limited marketing capacities, however, most foreign

¹⁸² Yakuji Kenkyukai, *Saikin no Yakumu Gyōsei* [Recent Trends in Pharmaceutical Administration] (Tokyo: Yakumu Kōhōsha, 2005), 133. See also, Jihō, *Yakuji Handobukku* [Pharmaceutical Affairs Handbook] (Tokyo: Jihō, 2000-2007). Drug prices in 1980 are indexed to 100.

¹⁸³ Mitsubishi Bank, Ltd., "Nihon Shijō ni Chūryoku suru Iyakuhin Gaishi [Foreign Pharmaceutical Firms Eye the Japanese Market]," *Mitsubishi Bank Research Report* 369 (January 1986): 22-32.

firms had yet to make a substantial presence in the Japanese market during this period.¹⁸⁴ For many Japanese firms, Merck's 1983 acquisition of a controlling stake in Banyu highlighted the very threat that they had wished to avoid for decades.¹⁸⁵ While foreign firms had existed in Japan before the 1970s, what changed were the prominence, power, and permanence of these firms.

There were other new entrants from other sectors of the Japanese economy. Since the oil shock of the 1970s, Japan had been unable to check the slowing of its economy. As various industrial sectors matured, firms began to seek opportunities for diversification, particularly in the hope that they would be able to capitalise on the potential of new developments in biotechnology. While funding levels only amounted to a tenth of US levels, government agencies such as the Science and Technology Agency (STA), MITI, and the Ministry of Agriculture, Forestry and Fisheries (MAFF), provided funding for biotechnology research projects. By coordinating research between government, industry, and academia, the government aimed to translate the fruits of this research into commercially viable discoveries.¹⁸⁶

New entrants came from a range of sectors, as evidenced by the textile maker Teijin, milk producers such as Snow Brand Milk Products and Meiji Dairies, and breweries

¹⁸⁴ Yakugyō Jihōsha, *Yakuji Handobukku* [Pharmaceutical Affairs Handbook] (Tokyo: Yakugyō Jihōsha, 1968-1999).

¹⁸⁵ Steve Lohr, "Merck's Big Venture in Japan," *The New York Times*, 13 October 1983. Merck's acquisition of Banyu was one of the first foreign acquisitions of a major Japanese firm. Banyu was then a firm listed on the First Section of the Tokyo Stock Exchange. However, its overreliance on technology imports and lack of investment in R&D had dried up the firm's product offering and profit potentials. By 1980s, it was in dire need of capital and in search of a partner who would acquire the firm.

¹⁸⁶ See for example, Mark D. Dibner, "Biotechnology in Pharmaceuticals: The Japanese Challenge," *Science* 229 (September 1985): 1230-1235.

such as Suntory and Kirin Brewery.¹⁸⁷ Firms with expertise in fermentation techniques were particularly well placed to take advantage of these new technologies. Without a sophisticated distribution network, however, few of the new firms posed a threat to existing firms – even if they could discover breakthrough drugs.

2.6.3 “Gaiatsu” in the Japanese pharmaceutical industry

As frictions grew between Japan and its trading partners in the 1980s, foreign governments began to place additional pressure on the Japanese government to improve access to its market. They argued that non-tariff barriers continued to prevent foreign pharmaceutical firms from competing in the Japanese market. These foreign pressures, or *Gaiatsu*, were particularly pronounced from the United States. In 1985, American and Japanese officials held market-oriented and sector-selective (MOSS) talks that aimed to remove barriers to market access in four sectors – including pharmaceuticals.¹⁸⁸

These demands induced Japanese officials to reduce barriers by accepting foreign clinical data, clarifying the criteria for innovation, and improving transparency in the pricing process. Japanese drug authorities, for example, still required that drugs sold in Japan were to be tested on Japanese patients – and that drug approval applications be filed in Japanese. Moreover, Japan’s complex distribution system for pharmaceuticals

¹⁸⁷ Yano Research Institute, *Iyaku Sangyō Nenkan* (Tokyo: Yano Research Institute, 1980), 12-15; Kinoichi Tsunematsu, “Saihen Katei no Iyakuin Sangyō [The Pharmaceutical Industry under Reorganisation],” *Iyaku Jānaru* 9 (September 1970): 20-23.

¹⁸⁸ United States Department of Commerce, International Trade Administration, Market Access and Compliance, “MOSS Agreement on Medical Equipment and Pharmaceuticals,” United States Department of Commerce, <http://www.mac.doc.gov/japan/source/menu/medpharm/ta860109.html> (accessed 15 May 2007).

still made it extremely difficult for foreign firms to sell drugs in Japan.¹⁸⁹ Business organisations such as the Pharmaceutical Manufacturers Association (PMA) in the United States and the European Business Council (EBC) in Europe also held regular talks with Japanese officials and heavily influenced the process of deregulation.¹⁹⁰ The reforms that followed intensified the competitive pressures in the Japanese pharmaceutical industry.

2.6.4 Responses to change

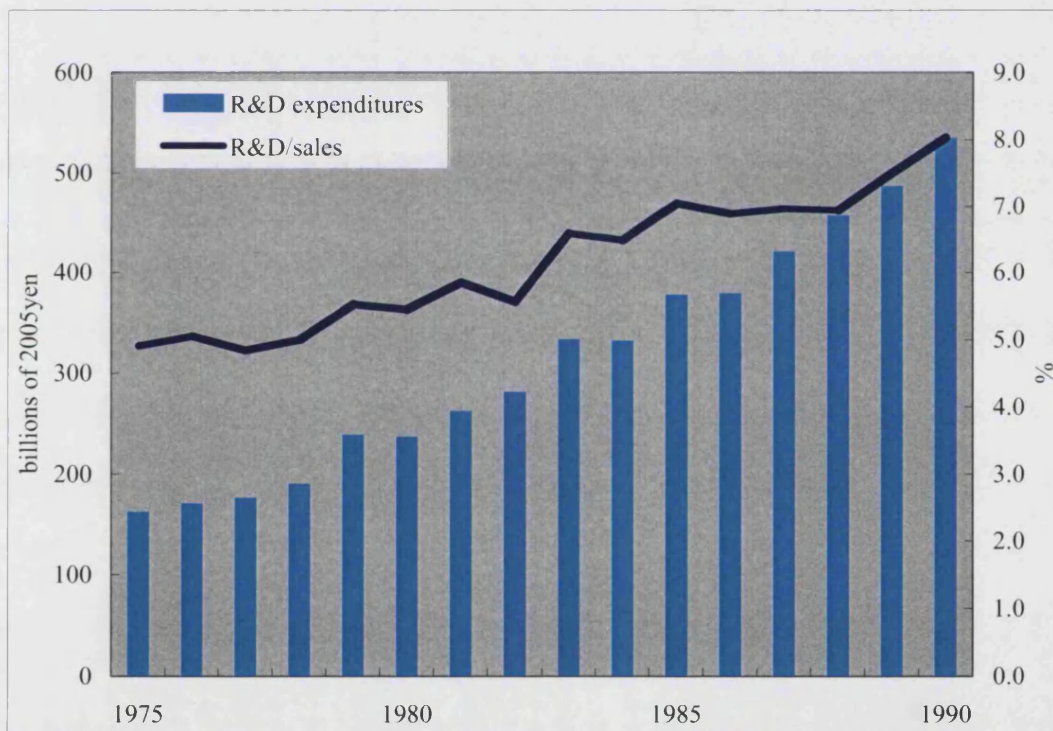


Figure 7. R&D Expenditures, 1975-1990¹⁹¹

While the government’s cost cutting measures did dent incentives to innovate, the

¹⁸⁹ Ibid.

¹⁹⁰ “Yūsei na Kaihatsuryoku de Kyūseicho o Tsuzokeru Zainichi Gaishi [With Stronger Development Capacities, Foreign Firms in Japan Continue to Grow Rapidly],” *Detailman*, (May 1992): 28-35.

¹⁹¹ Office of the Prime Minister, Bureau of Statistics, *Kagaku Gijutsu Kenkyū Chōsa Hōkoku* [Report on the Survey of Research and Development] (Tokyo: Office of the Prime Minister, 1961-1984); Management and Coordination Agency, Statistics Bureau & Statistics Centre, *Kagaku Gijutsu Kenkyū Chōsa Hōkoku* [Report on the Survey of Research and Development] (Tokyo: Management and Coordination Agency, 1985-2000).

rising competition from new Japanese and foreign firms in a more open market urged Japanese firms to intensify their R&D orientation. A 1987 revision in Japan's patent law further encouraged firms to invest in R&D, as it became possible to extend the effective life of a patent and recover the time lost in the drug testing and approval process.¹⁹²

Indeed, between 1975 and 1990, R&D expenditures rose 3.3 fold from 162.4 billion yen to 534.8 billion yen, or from 4.9% to 8.0% in terms of R&D as a proportion of total sales.¹⁹³ The number of regular researchers employed in pharmaceutical firms also increased from 6,854 to 14,932. Technology imports also rose 2.5 fold from 8.8 billion yen to 22.3 billion yen, while technology exports leapt 9.3 fold from 2.1 billion yen to 19.6 billion yen.¹⁹⁴ The number of patents approved in Japan among Japanese firms also rose from 376 in 1980 to 623 in 1990.¹⁹⁵ Over the 1980s, Japan also discovered 24.1% of the world's new therapeutic substances, compared to 26.6% in the United States and 48.7% in Western Europe.¹⁹⁶

Between 1975 and 1990, the key change in Japan's pharmaceutical industry was a shift

¹⁹² The partial revision to the patent law, Law No.27 in 1987, became effective in 1988. See "Iyakuhiin no Kenkyū Kaihatsu no Shien: Gutaiteki na Shiensaku [Supporting R&D in Pharmaceuticals: Specific Support Policies]" in Kōsei Hakusho (Tokyo: Ministry of Health and Welfare, 1988)

<http://www.hakusho.mhlw.go.jp/wpdocs/hpaz198701/b0053.html>; Kazuyuki Motohashi, "Japan's Patent System and Business Innovation: Reassessing Pro-patent Policies," RIETI Discussion Paper Series 03-E-020, http://www.rieti.go.jp/en/publications/act_dp2003.html (accessed 15 May 2008).

¹⁹³ In nominal terms, R&D expenditures between 1975 and 1990 rose from 95.2 billion yen to 516.1 billion yen. Ibid.

¹⁹⁴ In nominal terms, technology imports rose from 5.2 billion yen to 21.5 billion yen, while technology exports rose from 1.3 billion yen to 18.9 billion yen. Ibid. See also, Will Mitchell, Thomas Roehl, and Ronald J. Slattery, "Influences on R&D Growth among Japanese Pharmaceutical Firms," *Journal of High Technology Management Research* 6 (1995): 17-31.

¹⁹⁵ Japan Patent Office. Number of patents approved are reprinted in Japan Pharmaceutical Manufacturers Association, *Data Book* (Tokyo: Japan Pharmaceutical Manufacturers Association, 2007), 45.

¹⁹⁶ This figure does need to be treated with caution, as the criteria for new drug approval was lower in Japan for other countries. The figure is used to indicate that there were advances in drug discovery during this period. See European Federation of Pharmaceutical Industries and Associations (EFPIA), *The Pharmaceutical Industry in Figures* (Brussels: EFPIA, 1997): 12, and EFPIA, *The Pharmaceutical Industry in Figures* (Brussels: EFPIA, 2005), 20.

from a manufacturing-based to a knowledge-based industry. The Japanese market also became more concentrated as firms faced more competition and invested in more R&D.¹⁹⁷ In 1970 Japanese firms invested 3.0% of sales in R&D, but by 1990, these figures had increased to 8.0%.¹⁹⁸ In the meanwhile, the market continued to expand in terms of production and trade. While imports were still 3.6 times the value of exports during this time, Japanese exports increased 1.8 fold from 64.1 billion yen to 116.2 billion yen between 1975 and 1990.¹⁹⁹ Japan's export destinations also shifted from the developing to the developed world.²⁰⁰

Despite the influx of foreign firms, however, the majority of Japanese firms did not venture abroad. Among the 1,123 Japanese pharmaceutical firms in 2000, for example, there were only 245 that had expanded abroad.²⁰¹ To a certain extent this was understandable, as many Japanese firms were not in a position to compete against leading Western firms who had already expanded into these markets.²⁰² Even so, between 1975 and 1990, Japanese firms adopted a more global orientation. Firms with overseas operations rose 3.0 fold from 30 in 1975 to 91 in 1990.²⁰³ But Japanese firms

¹⁹⁷ Japan Fair Trade Commission, *Shuyō Sangyō ni okeru Ruiseki Seisan Shūchūdo* [Concentration Ratio of Main Industries] (Tokyo: Japan Fair Trade Commission, 1975-1994), <http://www.jftc.go.jp/katudo/ruiseki/ruisekidate.html> (accessed 1 June 2008).

¹⁹⁸ Office of the Prime Minister, Bureau of Statistics, *Kagaku Gijutsu Kenkyū Chōsa Hōkoku* [Report on the Survey of Research and Development] (Tokyo: Office of the Prime Minister, 1961-1984); Management and Coordination Agency, Statistics Bureau & Statistics Centre, *Kagaku Gijutsu Kenkyū Chōsa Hōkoku* [Report on the Survey of Research and Development] (Tokyo: Management and Coordination Agency, 1985-2000).

¹⁹⁹ In nominal terms, Japanese exports increased from 36.8 billion yen to 111.1 billion yen. Ministry of International Trade and Industry, *Tsūshō Hakusho* [White Paper on Trade] (Tokyo: Ōkurashō Insatsukyoku, 1958-1973); Ministry of International Trade and Industry, *Tsūshō Hakusho* [White Paper on Trade] (Tokyo: Gyōsei, 1974-2000).

²⁰⁰ Ministry of Health and Welfare, *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Yakugyō Keizai Kenkyūjo, 1968-2000).

²⁰¹ Ministry of Health, Labour and Welfare, *Iyakuhin Sangyō Jittai Chōsa Hōkokusho* [Report on the Pharmaceutical Industry] (Tokyo: Ministry of Health, Labour and Welfare, 2001); Yano Research Institute *Iyaku Sangyō Nenkan* (Tokyo: Yano Research Institute), reprinted in Japan Pharmaceutical Manufacturers Association, *Data Book* (Tokyo: Japan Pharmaceutical Manufacturers Association, 2007), 21.

²⁰² Yakugyō Jihōsha, *Yakuji Handobukku* [Pharmaceutical Affairs Handbook] (Tokyo: Yakugyō Jihōsha, 1968-1999). See also, "Kill or Cure for Japan's Drug Firms," *The Economist*, 29 August 1981, 78.

²⁰³ Yano Research Institute *Iyaku Sangyō Nenkan* (Tokyo: Yano Research Institute), reprinted in Japan Pharmaceutical Manufacturers Association, *Data Book* (Tokyo: Japan Pharmaceutical Manufacturers Association, 2007), 21.

had yet to establish a substantial international presence.²⁰⁴

2.7 Building a R&D intensive, global pharmaceutical industry, 1990-2005

In contrast to previous decades of relative stability, the Japanese pharmaceutical industry underwent a dramatic transformation in the 1990s. The industry experienced a massive reorganisation, and became more global and research-intensive. The 1990s began with reforms to the distribution system, which were followed by the harmonisation of pharmaceutical regulations with Europe and the United States, and other deregulatory measures. These reforms prompted foreign firms to increase their presence in the Japanese market, just as Japanese firms increased their presence abroad. As firms attempted to counter rising R&D costs and intense global competition, and wave of M&A swept across the industry.

But much remained to be addressed. Delays to drug approval following an HIV blood scandal increased R&D costs, while biennial price reductions continued to penalise investments in innovation. Structural problems, such as the lack of qualified reviewers, and the absence of government funding for industrial R&D, also hindered the launch of new drugs in Japan. Seeking more favourable conditions abroad, some Japanese firms began to transfer their core operations out of Japan to the United States and Europe. The industry did continue to expand in terms of production, trade and R&D. But Japan's pharmaceutical industry was still much smaller than global leaders in

²⁰⁴ In 1990, Takeda, Japan's leading pharmaceutical firm, was still the only Japanese company that ranked within the top 25 global pharmaceutical companies (in sales). See PJB Publications, *Scrip: Pharmaceutical Company League Tables 1991* (Richmond: PJB Publications, 1991), 2.

terms of sales, R&D expenditures, or value of exports, and the country remained a net importer of pharmaceuticals.²⁰⁵

2.7.1 The HIV scandal and an enduring drug lag

Just as the thalidomide tragedy coloured the debates over drug approval in the 1960s, the HIV blood scandal in Japan did the same in the 1990s. But unlike the more positive responses to the 1960s drug scandal through better legislation, the 1990s scandal resulted in significant delays to the drug approval process. This led to a serious rise in the cost of R&D and urged some Japanese firms to seek more favourable opportunities abroad.

The HIV blood scandal was a drug accident that came to light in the 1990s after Japanese haemophiliacs contracted HIV from the circulation of untreated blood products. Despite knowledge over the potential dangers of unheated blood products, the MHW had allowed for their circulation to reduce competition for Japan's leading provider of blood products, Green Cross Corp. The Japanese firm was not yet prepared to produce heat-treated blood products that were available abroad. As a pharmaceutical firm to which many MHW bureaucrats also retired, conflicts of interests also prevented MHW bureaucrats from taking actions that might have alienated the firm. Legal proceedings suggested that the MHW had delayed the approval of heat-treated blood products in order to allow Green Cross to catch up with

²⁰⁵ See for example, Bank of Tokyo-Mitsubishi, Ltd., "Honkakuteki na Kyōsō Jidai o Mukaeru Iyakuin Gyōkai [The Pharmaceutical Industry to Enter an era of Real Competition]," *Chōsa Geppō* [Monthly Research Report] 107 (February 2005): 1-9.

foreign rivals.²⁰⁶

The Japanese drug lag since the 1990s originates from this scandal, which left the MHW much more cautious and tentative in the drug approval process. It has also been a major source of contention for firms seeking to introduce new drugs swiftly into the market.²⁰⁷ For many firms, R&D in Japan became less attractive, as longer assessment times raised the cost of drug development for a relatively low priced drug. In 1980, drug approvals in Japan took much less than the 26.3 months in the United States.²⁰⁸ But by 2000, the average time for drug approval in Japan was 28.5 months compared to 16.5 months in the United States.²⁰⁹

While the major response to the drug scandal was a delay in the drug approval process, there was a silver lining. The scandal also cut excess demand for unnecessary medicines and contributed to the fall in production levels over the 1990s. The widely publicised scandal produced better-informed patients more sceptical of medicines, increasingly sensitive to out of pocket drug expenses, and reluctant to spend on minor medicines – particularly under economic recession.

²⁰⁶ See Yakugai Konzetsu Fōramu, *Yakugai Eizu wa Naze Okitaka* [Why the HIV Drug Tragedy Occurred], (Tokyo: Kirishobō, 1996); Eric A. Feldman, "HIV and Blood in Japan, Transforming Private Conflict in Public Scandal," in *Blood Feuds: Aids, Blood and the Politics of Medical Disaster* (Oxford: Oxford University Press, 1999), 59-94; Takao Takahashi, "Medical Business Ethics: The HIV-Tainted Blood Affair in Japan," in *Taking Life and Death Seriously: Bioethics from Japan*, ed. Takao Takahashi (Amsterdam: Elsevier, 2005), 253-273.

²⁰⁷ P. Reed Maurer, interview by author, Tokyo, Japan, 11 July 2007. Kenjirō Nagasaka, interview by author, Osaka, Japan, 15 December 2007.

²⁰⁸ Janice M. Reichert, "Trends in Development and Approval Times for New Therapeutics in the United States," *Nature Reviews Drug Discovery* 2 (September 2003): 697; P. Reed Maurer, interview by author, Tokyo, Japan, 11 July 2007. Kenjirō Nagasaka, interview by author, Osaka, Japan, 15 December 2007.

²⁰⁹ Kuniaki Yasuda, "Nihon ni Okeru Shiniyakuin no Shōnin Shinsa Kikan [Approval Times for New Drugs in Japan]," *Research Paper Series, Office of Pharmaceutical Industry Research, Japan Pharmaceutical Manufacturers Association* 35 (December 2006); Federal Drug Administration, CDER Drug and Biological Approval Reports, <http://www.fda.gov/cder/rdmt/default.htm> (accessed 4 May 2008).

2.7.2 Distribution Reform in 1990: a much needed cleanup

In the Japanese pharmaceutical industry, the supply chain linking manufacturers to patients involved two intermediaries: wholesalers and dispensing physicians. Since 1951, the retail price of prescription drugs had been set by the government. As a result, dispensing physicians increased their margins by bargaining down the price paid to wholesalers. Until 1992, pharmaceutical manufacturers usually entered into resale price maintenance agreements with their wholesalers. Most forms of resale price maintenance were illegal in Japan since 1947. But Japan's antimonopoly statute exempted pharmaceuticals from this prohibition. The resale price maintenance agreements limited the competitive pressure on Japan's many small and inefficient wholesalers. For the manufacturers, this arrangement made it difficult for new entrants to sell drugs to Japanese wholesalers or dispensing physicians.²¹⁰

In 1991, the government introduced several measures to reform the distribution system. These measures were, to a large extent, a response to foreign pressures to reduce barriers to entry into the Japanese market. The sheer complexity and cost involved in pharmaceutical distribution in Japan had deterred many potential firms from making a full entry into the market. The consternation of foreign firms in facing these market barriers, for example, was addressed in state-level talks, such as the Structural Impediments Initiative with the United States between 1989 and 1990.²¹¹

²¹⁰ Problems with this system have been discussed widely. See for example, Shūmei Tanaka, "Iyakuhiin no Ryūtsu o Meguru Mondaiten [Problems in Pharmaceutical Distribution]," in *Shakai Yakugaku Nyūmon* (Tokyo: Nankōdō, 1987), 156-168.

²¹¹ U.S. Department of Commerce, International Trade Administration, Office of Japan Market Access and Compliance, "U.S.-Japan Structural Impediments Initiative (SII)," United States Department of Commerce, <http://www.mac.doc.gov/japan/market-opening/market-opening.htm> (accessed 2 May 2008).

As part of the distribution reforms, resale price maintenance in pharmaceuticals was prohibited.²¹² This measure basically destroyed the vertical groupings that had long persisted between select wholesalers and manufacturers, and lowered barriers to entry.²¹³ Liberated from the control of manufacturers, these reforms sparked a wave of consolidation, and wholesalers swiftly expanded from regional to national coverage.²¹⁴ While there were 403 wholesalers in Japan in 1990, there were only 232 by 2000.²¹⁵ As larger firms, wholesalers were able to increase their bargaining power in dealing with manufacturers.²¹⁶

Another part of distribution reform involved a correction to the government's method of calculating the biennial price reductions, which no longer made it possible for physicians to profit substantially from pharmaceutical price differentials. This resulted in a shift in promotional strategies among pharmaceutical firms. No longer able to provide generous discounts for physicians, pharmaceutical firms invested in the education of marketing representatives to compete on the basis of quality rather than price.

²¹² The new price settlement system was called "Shin-shikirika-sei." See Ministry of Health and Welfare, "Iyakuin, Iryōryōgu no Ryūtsu Kindaika [Modernisation of Distribution in Pharmaceuticals and Medical Equipment]," in *Kōsei Hakusho* [White Paper on Health and Welfare] (Tokyo, Okurashō Insatsukyoku, 1974); Japan, House of Representatives, Health and Welfare Committee, *Official Report of Debates*, 126th Diet, 6th Session, 2 April 1993; Japan, House of Councillors, Health and Welfare Committee, *Official Report of Debates*, 126th Diet, 7th Session, 20 April 1993; Japan, House of Councillors, Health and Welfare Committee, *Official Report of Debates*, 126th Diet, 11th Session, 30 June 1993.

²¹³ See Tadashi Inoue, "Iryōryō Iyakuin Shijō no Tokushusei to Ryūtsū Kaikaku [Special Features of the Prescription Pharmaceutical Market and Distribution Reform]," *Waseda Shakaigaku Kenkyū* 49 (October 1994): 55-65. See also Japan Business History Association, *Banyu Pharmaceutical: 85 Year History* (Tokyo: Banyu Pharmaceutical, 2002): 304-308. Banyu Pharmaceutical's then president Kenjiro Nagasaka spearheaded the industry's reforms in distribution in response to the government's policy reforms.

²¹⁴ P. Reed Maurer, "Why Japanese Pharmaceutical Wholesalers Merge," *Pharma Marketletter*, 4 June 1999; Ministry of Health and Welfare, *Iyakuin Sangyō Jittai Chōsa Hōkoku* [Report on the Status of the Pharmaceutical Industry] (Tokyo: Ministry of Health and Welfare, 1988-2000).

²¹⁵ These figures are in terms of the number of companies who were members of the Federation of Japan Pharmaceutical Wholesalers Association. True figures are expected to be higher, and the fall in the number of wholesalers much more dramatic. Federation of Japan Pharmaceutical Wholesalers Association, "Changes in the Number of Member Firms" <http://www.jpwa.or.jp/jpwa/index.html> (accessed 4 May 2007). Jihō, *Yakuji Handobukku* [Pharmaceutical Affairs Handbook] (Tokyo: Jihō, 2002), 215.

²¹⁶ P. Reed Maurer, "Positive News on 'Dramatic' Wholesaler Restructuring in Japan Overlooked," *Pharma Marketletter*, 20 November 2003.

2.7.3 Sweeping changes in the regulatory environment

Japan's pharmaceutical industry made a major step towards globalisation when the government decided to harmonise its pharmaceutical regulations with the United States and Europe. In 1990, the three regions formed The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) to reduce or eliminate the cost and time involved in duplicating drug development across countries. The harmonisation of regulations meant that Japanese drugs could easily be approved in the United States and Europe, just as European and American drugs could easily be approved in Japan. By using resources efficiently, the ICH also aimed to bring quality drugs more quickly to the market.²¹⁷

For Japanese firms, incentives to innovate improved markedly. The adoption of American and European regulations strengthened the criteria for innovation. As well, Japanese firms were forced to compete with a greater number of foreign firms as harmonisation improved access to the Japanese market.²¹⁸ In 1990, no foreign firms were among the top ten Japanese pharmaceutical firms.²¹⁹ By 2005, there were two: Pfizer and Novartis.²²⁰ At the same time, harmonisation made it much easier for Japanese firms to access the large markets of Europe and the United States. In 1990, 91

²¹⁷ The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, <http://www.ich.org>, (accessed 15 May 2007).

²¹⁸ "Better and Stronger Brands: Brand Managers are Focusing on Launching Products Globally, Aiming to Make Patients and Physicians All Over the World Aware of their Products and in the Process Build Powerful Brands," *Med Ad News* 1 October 2002, S16 (4); "Entering Japan: Deregulation Transforms the Third-largest Pharmaceutical Market into a Friendlier Place for Business," *Med Ad News* 1 March 2003, 1 (3).

²¹⁹ PJB Publications, *Scrip: Pharmaceutical Company League Tables 1991* (Richmond: PJB Publications, 1991), 42.

²²⁰ Jihō, *Yakuji Handobukku* [Pharmaceutical Affairs Handbook] (Tokyo: Jihō, 2007), 473. This excludes firms solely dedicated to the bulk production of drugs.

firms had expanded into overseas markets; by 2005, there were 284.²²¹ ICH also helped raise the profile of Japanese firms, as they developed more innovative and effective drugs that were recognised and successful in world markets.²²²

This momentum for reform continued into the late 1990s. For example, Japanese authorities lowered barriers to foreign entry by dismissing the Japanese language requirement in filing patent applications, disposing of the requirement to conduct clinical trials on Japanese subjects, eliminating the local manufacturing requirement for foreign firms, and creating tax incentives for R&D.²²³ In 1997, the government added more flexibility to the market by recognising the use of contract research organisations to improve efficiency in drug development.²²⁴

In Japan, academics at national and public universities in Japan were considered to be civil servants.²²⁵ Until 1998, Japanese academics were not allowed to take outside employment. This rule discouraged academics working on pharmaceuticals from

²²¹ Yano Research Institute, *Iyaku Sangyō Nenkan* (Tokyo: Yano Research Institute), reprinted in Japan Pharmaceutical Manufacturers Association, *Data Book* (Tokyo: Japan Pharmaceutical Manufacturers Association, 2007), 21. In 1990, for example, there were 37 manufacturing facilities and 44 sales offices abroad. In 2005, there were 102 manufacturing facilities and 206 sales offices abroad.

²²² Established in 1990, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a project which aims to harmonize the pharmaceutical regulations of Europe, Japan and the United States. See <http://www.ich.org>. The impact of foreign firms on the Japanese pharmaceutical industry has been reported in Mizuho Corporate Bank, Ltd., “Ōbei Seiyaku Kigyō no Saihen Dōkō to Wagakuni Seiyakigyōkai no Inpurikēshon,” *Mizuho Sangyō Chōsa* 17 (March 2005): 1-42.

²²³ Yakugyō Jihōsha, *Yakuji Handobukku* [Pharmaceutical Affairs Handbook] (Tokyo: Yakugyō Jihōsha, 1968-1999); Jihō, *Yakuji Handobukku* [Pharmaceutical Affairs Handbook] (Tokyo: Jihō, 2000-2007).

²²⁴ Ministry of Health and Welfare, “Standards for the Implementation of Clinical Trials on Pharmaceutical Products,” MHW Ordinance No. 28, 27 March 1997; and Ministry of Health and Welfare, “Application of Standards for the Implementation of Clinical Trials on Pharmaceutical Products,” Notification No. 445 of Pharmaceuticals and Cosmetics Division/Notification No. 68 of the Safety Division, Pharmaceutical Affairs Bureau, 29 May 1997. Information on contract research organizations in Japan may be found at, Japan CRO Association, <http://www.jcroa.gr.jp/> (accessed 4 May 2008).

²²⁵ This status changed with the incorporation of national universities in Japan in April 2004. See Ministry of Education, Culture, Sports, Science and Technology, “Incorporation of National Universities,” in *FY2003 White Paper on Education, Culture, Sports, Science and Technology* (Tokyo: Ministry of Education, Culture, Sports, Science and Technology, 2004), http://211.120.54.153/b_menu/hakusho/html/hpac200301/hpac200301_2_021.html

commercializing their research.²²⁶ In 2000, the government also made it possible for academics to establish companies and made it easier for academics to move between academia and industry.²²⁷ In so doing, the Japanese government hoped that, as in other countries, university start-ups might help translate the fruits of academic research into commercial products.²²⁸

2.7.4 The impact of a greying population and cost containment policies

Over the 1990s, Japan's ageing population intensified the financial pressures on the national health insurance system. The proportion of the population aged 65 and over increased from 12.0% to 17.8% between 1990 and 2000.²²⁹ In response to the rising financial pressures, the government continued to legislate reductions in the price of prescription drugs. As the government subsidised the purchase of prescription drugs in Japan, it was strongly incentivised to contain the prices of these drugs.²³⁰

The government's policy of containing drug prices undermined the ability and willingness of firms to make substantial reinvestments in R&D. The potential profits of developing a new drug in Japan were much smaller than the United States, for

²²⁶ See Steven Collins and Hikoji Wakoh, "Universities and Technology Transfer in Japan: Recent Reforms in Historical Perspective," *The Journal of Technology Transfer* 25 (June 2000): 213-222; Kenji Kushida, "Japanese Entrepreneurship: Changing Incentives in the Context of Developing a New Economic Model," *Stanford Journal of East Asian Affairs* 1 (Spring 2001): 86-95.

²²⁷ Barriers to entrepreneurship has been discussed in Yoshiaki Nakamura and Hiroyuki Odagiri, "Nihon no Baiobenchā Kigyō: Sono Igi to Jittai [Japanese Bioventures: Meaning and Current Status]," *REITI Discussion Paper Series* 02-J-007 (June 2002). An assessment of recent changes in legislation has been written by Michael Lynskey "The Commercialisation of Biotechnology in Japan: Bioventures as a Mechanism of Knowledge Transfer from Universities," *International Journal of Biotechnology* 6 (2004): 155-185. Limitations on relying predominantly on in-house R&D has also been discussed in Robert Kneller, "Autarkic Drug Discovery in Japanese Pharmaceutical Companies: Insights into National Differences in Industrial Innovation," *Research Policy* 32 (2003): 1805-1827.

²²⁸ Steven W. Collins, *The Race to Commercialize Biotechnology: Molecules, Markets, and the State in the United States and Japan* (London: RoutledgeCurzon, 2004), 151.

²²⁹ Ministry of International Affairs and Communications, "Nenrei Kakusai Danjobetsu Jinkō [Population by Single Years of Age and Sex] (1884—2000)," <http://www.stat.go.jp/data/chouki/02.htm> (accessed 20 March 2007).

²³⁰ The impact of the regular price reductions has been widely discussed. See for example, Tsuruhiko Nanbu, "Iyakuin no Sangyō Soshiki: Yakka Kisei no Keizaiteki Kōka [Industrial Organisation of Pharmaceuticals: The Consequences of Price Regulation in Japan]," *Iryō to Shakai* 7 (January 1997): 1-15.

example, where there were no price restrictions on drugs. This had a heavy impact on Japanese pharmaceutical firms who, unlike their American counterparts, could not rely on government funding for industrial R&D.²³¹ It was particularly crucial at a time when R&D processes were becoming increasingly costly and sophisticated. The limited ability to invest in research technologies such as genomics, combinatorial chemistry and high throughput screening, placed firms in Japan at further disadvantage.²³² As well, the inability to grow meant that many Japanese firms lacked the capital to acquire foreign firms and expand.

Another effect of the government's policy of reducing official drug prices was that physicians could no longer benefit from the pharmaceutical price differentials. After 1990, many physicians began to abandon the business of dispensing drugs to patients. In 1990, 87.2% of physicians dispensed drugs; by 2005, 45.9% of physicians still continued to do so.²³³ With the separation of prescribing and dispensing functions, firms could no longer profit from high priced drugs with minimal innovative value. Instead, firms were incentivised to develop high priced drugs with greater innovative value.

2.7.5 The impact of globalisation

The Japanese pharmaceutical industry continued to develop over the 1990s. In the

²³¹ Government funds for pharmaceutical R&D are provided to universities. Firms are therefore indirectly subsidised through joint projects conducted with universities.

²³² Developments in drug discovery technologies has been written by Leland J. Gershell and Joshua H. Atkins, "A Brief History of Novel Drug Discovery Technologies," *Nature Reviews Drug Discovery* 2 (April 2003): 321-327. See also, James R. Broach and Jeremy Thorner, "High-throughput Screening for Drug Discovery," *Nature* 384 (November 1996): 14-16.

²³³ Japan Pharmaceutical Association, "Iyakuhin Bungyō Shinchoku Jōkyō [Progress on the Separation on the Prescribing and Dispensing of Medicines]," Japan Pharmaceutical Association, <http://www.nichiyaku.or.jp/contents/bungyo/default.html> (accessed 20 April 2008).

1990s, production values grew 1.1 fold from 4.9 trillion yen to 5.2 trillion yen.²³⁴

While the momentum for growth slowed to an average of 0.4% a year compared to 3.7% a year during the previous decade, the country maintained its position as the second largest market in the world.²³⁵ Facing more rigorous standards and sophisticated technologies in R&D as well as greater competition from foreign firms, Japanese firms intensified their R&D orientation after 1990. Between 1990 and 2005, R&D expenditures almost doubled while R&D expenditures as a percentage of sales rose from 8.02% to 10.01%.²³⁶ Japanese firms also became a net exporter of pharmaceutical technology after 1997, recording a surplus of \$1.4 million dollars by 2005.²³⁷ The number of researchers also increased from 14,900 to 20,800 during this period.²³⁸ But in a global context, these figures remained much smaller than the leading pharmaceutical markets. For example, the average R&D budgets of the top 10 Japanese firms were still about one-fifth of the average of the top Western companies in 2000.²³⁹

²³⁴ In nominal terms, production values grew from 4.7 trillion yen to 5.4 trillion yen between 1990 and 1999.

²³⁵ *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Yakugyō Keizai Kenkyūjo, 1968-2000); Yakugyō Jihōsha, *Yakuji Handobukku* [Pharmaceutical Affairs Handbook] (Tokyo: Yakugyō Jihōsha, 1968-1999).

²³⁶ Management and Coordination Agency, Statistics Bureau & Statistics Centre, *Kagaku Gijutsu Kenkyū Chōsa Hōkoku* [Report on the Survey of Research and Development] (Tokyo: Management and Coordination Agency, 1985-2000); Ministry of Internal Affairs and Communications, Statistics Bureau, *Kagaku Gijutsu Kenkyū Chōsa Hōkoku* [Report on the Survey of Research and Development] (Tokyo: Ministry of Internal Affairs and Communications, 2001-2006).

²³⁷ *Ibid.* It is recognised that these figures do not accurately represent the strength of Japanese firms. The figures, for example, obscure the number of foreign pharmaceutical firms who, rather than licensing out to Japanese firms, marketed their drugs through their own distribution networks in Japan.

²³⁸ *Ibid.*

²³⁹ Jihō, *Yakuji Handobukku* [Pharmaceutical Affairs Handbook] (Tokyo: Jihō, 2002), 159.

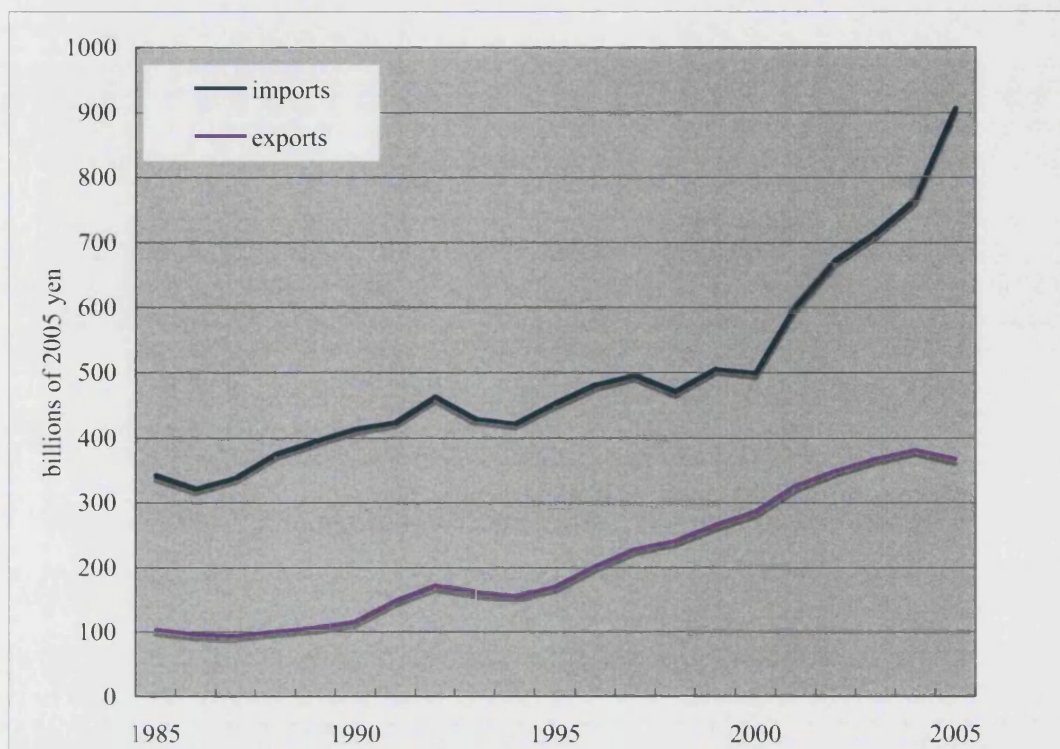


Figure 8. Value of Pharmaceutical Trade, 1985-2005²⁴⁰

Japan's pharmaceutical industry remained a net importer of pharmaceuticals. In 2005, Japan still imported 2.5 times more drugs than it exported, with imports of 538 billion yen (or approximately \$4.9 billion).²⁴¹ While these figures were smaller than the US trade deficit in pharmaceuticals of around \$11 billion, far fewer Japanese drugs were recognised globally compared to those produced by American or European firms. In 1999, only one eighth of NCEs launched by Japanese firms became international, compared to more than one third among US and European firms. In addition, although foreign sales among Japanese firms increased, they still accounted for only around a fifth of those among US and European firms.²⁴² While the nominal gap in R&D

²⁴⁰ Ministry of International Trade and Industry, *Tsūshō Hakusho* [White Paper on Trade] (Tokyo: Gyōsei, 1974-2000); Ministry of Economy Trade and Industry, *Bōeki Dōkō Dētabēsu* [Database on Trends in Trade], http://www.meti.go.jp/policy/trade_policy/trade_db/html/01.html

²⁴¹ Ministry of Economy Trade and Industry, *Bōeki Dōkō Dētabēsu* [Database on Trends in Trade], http://www.meti.go.jp/policy/trade_policy/trade_db/html/01.html

²⁴² Centre for Medicines Research International, "Japan in Focus: Strategies for Innovation and Global Drug Development, What Differentiates Japanese Pharma Companies from their Western Counterparts," *R&D Briefing* 28 (1999): 4.

expenditures widened between Japanese firms and leading Western firms in the 1990s, figures for the proportion of foreign sales to total sales did narrow. In 2005, Japan's top three pharmaceutical firms Takeda, Astellas and Eisai derived 44.3%, 45.3%, and 57.2% of their sales from overseas markets, respectively. In the meanwhile the top three global firms, Pfizer, GlaxoSmithKline, and Sanofi-Aventis derived 48.0%, 68.2%, and 55.6% of sales from overseas markets, respectively.²⁴³

2.7.6 Dramatic reorganisation since the millennium

Prompted by the dramatic changes to the regulatory environment, and in response to the rising sophistication and costs of R&D, Japanese firms reorganised and globalised. The performance gap also widened between Japanese firms that were globally competitive and those that were domestically oriented.²⁴⁴ Leading Japanese firms gained more as they increasingly transferred their core operations abroad where there were both larger markets and greater reward for innovation – such as the United States. These trends are reflected in the decline of clinical trials conducted in Japan versus the rise of clinical trials conducted abroad.²⁴⁵ This was because of the higher cost and longer duration of clinical trials conducted in Japan in comparison to the United States or Europe.²⁴⁶ Drug approval times also took longer, not only because of the reluctance

²⁴³ Japan Pharmaceutical Manufacturers Association, *JPMA Databook* (Tokyo: Japan Pharmaceutical Manufacturers Association, 2007); It is also important to note that Japanese firms that derive a substantial portion of sales from abroad is still very limited.

²⁴⁴ See Yakugyo Jihōsha, *Yakuji Handobukku* [Pharmaceutical Affairs Handbook] (Tokyo: Yakugyo Jihōsha, 1968-1999); Jihō, *Yakuji Handobukku*, [Pharmaceutical Affairs Handbook] (Tokyo: Jihō, 2000-2007). The experience of globally successful Japanese firms are documented in “Kokusaiteki Hitto Shōhin no Jōken [The Criteria for a Internationally Successful Drug],” *Detailman* (September 1991): 29-45; and “Kaigai de Katsuyaku suru Kokusan Shinyaku no Genjō [The Current Status of Japan-origin Drugs Abroad],” *Gekkan Mix* (June 1996): 44-62.

²⁴⁵ See Eiji Ueda, “Wagakuni no Chiken no Genjō to Mondaiten [The Current Environment and Issues around Clinical Trials in Japan],” *Modan Media* 50, no. 2 (2004): 12; Office of Pharmaceutical Industry Research, “Sōyaku no Ba to shite no Kyōsōryoku Kyōka ni Mukete [Creating a Stronger, More Competitive Environment for Drug Discovery],” *Office of Pharmaceutical Industry Research, Japan Pharmaceutical Manufacturers Association* (November 2005), 75.

²⁴⁶ Office of Pharmaceutical Industry Research, “Sōyaku no Ba to shite no Kyōsōryoku Kyōka ni Mukete [Creating a Stronger, More Competitive Environment for Drug Discovery],” *Office of Pharmaceutical Industry Research, Japan Pharmaceutical Manufacturers Association* (November 2005), 75-78.

to approve new drugs after the HIV blood tragedy, but also because of the dispersion of clinical trials across many hospitals, the adoption of more rigorous clinical trial standards, and severe lack of qualified personnel to evaluate new drugs relative to the United States or Europe.²⁴⁷ The nationality of these globally-oriented Japanese firms become increasingly questionable, as while management was located in Japan, both the sources of innovation and potential for growth were located overseas.

From the late 1990s, a massive wave of M&A swept the Japanese pharmaceutical industry as firms began to grasp the urgent need to achieve scale economies and strengthen R&D operations to survive global competition. This began with the merger of Mitsubishi Chemicals with Tokyo Tanabe into Tokyo Mitsubishi Pharmaceutical in 1999, and its merger with Welfide in 2001.²⁴⁸ Several other mergers followed, including those of Japan's leading pharmaceutical firm such as Yamanouchi and Fujisawa into Astellas, Dainippon and Sumitomo into Dainippon Sumitomo, and Daiichi and Sankyo into Daiichi Sankyo – all in 2005.²⁴⁹

At the same time, foreign firms raised their profile, as the harmonisation of pharmaceutical regulations facilitated their entry into the Japanese market. Foreign firms launched many new products, developed their own distribution networks, and

²⁴⁷ Even in 2006, Japan had 197 personnel to evaluate drug approvals, compared to 2,200 in the United States (FDA), 693 in the United Kingdom (MHRA), and 1,100 in Germany. See Office of Pharmaceutical Industry Research, "Seiyaku Sangyō no Shōrai-zō [The Future Image of the Pharmaceutical Industry]," Office of Pharmaceutical Industry Research, Japan Pharmaceutical Manufacturers Association (May 2007), 113-114. See also, Robert Kneller, "University-Industry Collaboration in Biomedical Research in Japan and the United States: Implications for Biomedical Industries," in *Industrializing Knowledge: University-Industry Linkages in Japan and the United States*, eds. Lewis M. Branscomb, Fumio Kodama, and Richard L. Florida (Cambridge: MIT Press, 1999), 410-438.

²⁴⁸ Mitsubishi Pharma Corp., *Yūka Shōken Hōkokusho* (Tokyo: Ōkurashō Insatsukyoku, 2006), 4.

²⁴⁹ Astellas Pharma Inc., *Yūka Shōken Hōkokusho* (Tokyo: Ōkurashō Insatsukyoku, 2006), 4; Dainippon Sumitomo Pharma Co., "Kaisha Enkaku [Company History]," <http://www.ds-pharma.co.jp/profile/history.html> (accessed 28 July 2008); Daiichi Sankyo Co., *Yūka Shōken Hōkokusho* (Tokyo: Ōkurashō Insatsukyoku, 2006): 3.

increased their sales in Japan. Indeed, between 1996 and 2005, foreign firms accounted for more than 70% of Japan's new drug approvals and were a major source of growth in Japan's pharmaceutical industry.²⁵⁰ Several foreign firms even made high profile acquisitions, such as Roche's purchase of Chugai in 2002, Abbott's purchase of Hokuriku Seiyaku and Merck's purchase of Banyu in 2003.²⁵¹

Japan's pharmaceutical industry at the turn of the twenty-first century presented a mixed picture. Japanese firms after the 1990s were stronger and dynamic, more R&D intensive and global. The industry continued to grow in terms of production, R&D investments, sales, and overseas operations. But economic recession, combined with rigid and outdated institutional structures also dampened growth prospects. The number of NCEs discovered in Japan declined relative to other countries in the 1990s, and Japan no longer led NCE launches after 1995.²⁵² Biennial price reductions also discouraged new entries into the Japanese market.²⁵³ Even with the M&A boom, the size of Japanese firms remained far too small to rival the sales, profits, R&D, human resources, or marketing capacity of leading Western pharmaceutical firms. For decades, Japan's pharmaceutical industry had been a highly successful domestic industry. But it had yet to prove success in the global market.

²⁵⁰ Office of Pharmaceutical Industry Research, "Seiyaku Sangyō no Shōraizō [The Future Image of the Pharmaceutical Industry]" *Office of Pharmaceutical Industry Research, Japan Pharmaceutical Manufacturers Association* (May 2007), 52. See also, Michiyo Nakamoto and David Pilling, "Drugs Market Set for Change: Japan's Pharma Industry is Slowly Opening Up," *Financial Times* 3 April 2002.

²⁵¹ Chugai Pharmaceutical Co., "History," Chugai Pharmaceutical Co., <http://www.chugai-pharm.co.jp/profile/about/history.html> (accessed 4 May 2008); Abbott Japan Co., "History," Abbott Japan Co. <http://www.abbott.co.jp/company/history.asp> (accessed 4 May 2008); Banyu Pharmaceutical Co., "The History of Banyu," Banyu Pharmaceutical Co. <http://www.banyu.co.jp/content/corporate/about/history/index.html> (accessed 4 May 2008). These events were widely publicised. See for example, Christopher Bowe and Michiyo Nakamoto "Merck Bids for the Rest of Banyu" *Financial Times*, 10 January 2003.

²⁵² Centre for Medicines Research International, "Japan in Focus: Strategies for Innovation and Global Drug Development. What Differentiates Japanese Pharma Companies from their Western Counterparts," *R&D Briefing* 28 (1999): 2.

²⁵³ ACCJ, FDI Task Force, "Pharmaceuticals," *Specific Policy Recommendation*, February 2004.

2.8 Analysis of the overview chapter

In the early 21st century, the Japanese pharmaceutical industry remained weak compared to pharmaceutical industries in the United States, Britain or Switzerland. For example, Japan's largest and most profitable pharmaceutical firm, Takeda, ranked only 14th in global pharmaceutical sales in 2004. The next largest Japanese drug companies, Eisai and Sankyo, ranked 19th and 21st, respectively.²⁵⁴ In the fiscal year ending March 2006, Takeda recorded revenues of \$10.3 billion, followed by Daiichi Sankyo's \$7.9 billion and Eisai's \$5.1 billion.²⁵⁵ By comparison, Pfizer (US), GlaxoSmithKline (UK) and Merck (US) recorded revenues of \$51.3 billion, \$39.4 billion, and \$22.0 billion, respectively.²⁵⁶ In terms of firm size, Japan's leading pharmaceutical firms, Takeda, Daiichi Sankyo and Eisai employed about 15,000, 18,000 and 9,000 workers in 2005, respectively.²⁵⁷ This was only a fraction of the leading global firms such as Pfizer, GlaxoSmithKline and Merck, for example, who employed about 106,000, 100,000, and 61,500 workers, respectively.²⁵⁸ In an industry where scale economies mattered, the prospects for Japanese firms of becoming global leaders appeared dim.

²⁵⁴ PJB Publications, *Scrip: Pharmaceutical Company League Tables 2005* (Richmond: PJB Publications, 2005), 33-34.

²⁵⁵ Japanese yen have been converted into US dollar amounts at the rate of 117 yen = US\$ 1.00, the approximate exchange rate prevailing on March 31, 2006. Takeda Pharmaceutical Co., *Annual Report 2006*, 3; Daiichi Sankyo Co., *Annual Report 2006*, 2; Eisai, Co., "Business Performance Highlights," Eisai, Co., <http://www.eisai.co.jp/eir/achievements1.html> (accessed 10 June 2007).

²⁵⁶ GlaxoSmithKline's sales of £21.7 billion were converted into US dollars at the exchange rate of \$1.82 = £1. Pfizer, Inc. *2005 Annual Review* (New York: Pfizer Inc., 2006), 12; GlaxoSmithKline plc. *Annual Report 2005* (Brentford: GlaxoSmithKline, 2006), 4; Merck & Co., *2005 Annual Report* (Whitehouse Station: Merck & Co., 2006), 68.

²⁵⁷ Takeda Pharmaceutical Co., *Annual Report 2006*, 3; Daiichi Sankyo Co., *Annual Report 2006*, 65; Eisai, Co., "Corporate Profile," Eisai, Co., <http://www.eisai.co.jp/ecompany/eprofile/eprofile.html> (accessed 10 June 2007).

²⁵⁸ Pfizer, Inc. *2005 Annual Review* (New York: Pfizer Inc., 2006), 26; GlaxoSmithKline plc. *Annual Report 2005* (Brentford: GlaxoSmithKline, 2006), 16; Merck & Co., *2005 Annual Report* (Whitehouse Station: Merck & Co., 2006), 68.

Japanese firms were still less responsive to changing market conditions compared to their American or European counterparts. With the escalating costs of R&D and increasing competition from globalisation, the first wave of mergers among Western pharmaceutical firms occurred in the late 1980s. These mergers began with SmithKline Beecham (from SmithKline and Beecham) and Bristol Myers Squibb (from Bristol Myers and Squibb) in 1989.²⁵⁹ Consolidation continued into the millennium, with mergers such as Pfizer (from Warner-Lambert in 2000 and Pharmacia in 2003) and Sanofi-Aventis (from Sanofi-Synthelabo and Aventis) in 2004.²⁶⁰ But the first mergers in Japan occurred only a decade later, with Mitsubishi Chemicals and Tokyo Tanabe in 1999.²⁶¹ The belated responses of Japanese firms to exploit commercial opportunities undermined the potentials for growth.

	USA	Japan	Germany	Switzerland	UK
1980-84	29%	16%	15%	13%	4%
1985-89	35%	9%	15%	3%	6%
1990-94	40%	9%	7%	11%	11%

Table 1: Main Countries where International Drugs have Originated²⁶²

Moreover, while Japan had managed to discover almost a tenth of the world's drugs, it failed to develop a pharmaceutical industry with global presence. Given Japan's industrial leadership in other research-intensive sectors, the inability to become a

²⁵⁹ "Drugs Mergers; Everybody Get Together," *The Economist*, 8 April 1989, 78; "Drug Company Mergers; Love Potion No. 9," *The Economist*, 5 August 1989, 58.

²⁶⁰ Adrian Michaels, "Warner Bows to Pfizer Demand for Merger Talks," *Financial Times*, 14 January 2000; Christopher Bowe, "Pfizer set to Complete Pharmacia Purchase," *Financial Times*, 14 April 2003; "Abandoned at the Altar; Drug Mergers," *The Economist*, 1 May 2004, 75.

²⁶¹ "Barbarians at the Gate," *The Economist*, 3 April 1999, 73-74.

²⁶² P. E. Barral, *20 Years of Pharmaceutical Research Results Throughout the World (1975-94)* (Antony: Rohne-Poulenc Rorer Foundation), 24.

leader in pharmaceuticals was striking. An international drug has been defined as a drug that has been launched in at least four of the G7 countries. According to this definition, between 1975 and 2000, 86% of international drugs were discovered by the G7 countries: 33% were discovered in the United States, 14% in Germany, and 10 % each in Japan and Switzerland.²⁶³ Despite its capacity to discover drugs, Japan's pharmaceutical industry remained much smaller compared to the United States, Germany or Switzerland. Despite its acquisition of scientific and technological capacities, Japan did not make the transition into a globally competitive pharmaceutical industry.

Explanations for the relative weakness of Japan's pharmaceutical industry

This overview chapter suggests that Japan's pharmaceutical industry remained relatively weak for several reasons. In the following section, five possible explanations will be considered. Together, these factors help to account for the relative weakness of Japan's pharmaceutical industry.

The first cause of the relative weakness of Japan's pharmaceutical industry stems from the industry's historical origins. German pharmaceutical firms were export oriented from a very early stage. The origins of Japan's pharmaceutical industry, in contrast, lay in the import business. Japan's oldest drug companies began as import houses in Osaka and only later branched out into manufacturing Western-style pharmaceuticals for the domestic market. Adopting an international orientation did not occur naturally

²⁶³ Ibid.

to Japanese firms. Moreover, many of the licensing agreements that allowed Japanese firms to produce foreign-discovered drugs in the post-war period prohibited exports of these products.

The second cause behind the weak performance of Japanese pharmaceutical firms lay in industrial structure. In the pharmaceutical industry, larger firms have a crucial advantage in achieving economies of scale in R&D, manufacturing and marketing. Japanese pharmaceutical firms have historically been much smaller than their American and European counterparts. In addition, while there are several major R&D-oriented pharmaceutical firms that dominate the US and UK markets, a greater number of these firms dominate the Japanese market. For example, while the UK pharmaceutical industry is comprised of seven major companies, there are roughly 20 significant firms in Japan.²⁶⁴

The smaller size of Japanese firms compromised their ability to compete with larger Western firms.²⁶⁵ Lacking capital, expertise and technology. Japanese firms concentrated on acquiring extensive manufacturing capacities through incremental innovation until the 1970s. In the meanwhile, American, British and German pharmaceutical firms developed robust R&D capacities through more radical innovations that required larger investments and developing global distribution

²⁶⁴ Jeremy Howells and Ian Neary, *Intervention and Technological Innovation: Government and the Pharmaceutical Industry in the UK and Japan* (Basingstoke: Macmillan, 1995), 17, 233-234. See also, Robert Neimeth, "Japan's Pharmaceutical Industry Postwar Evolution," 117; "Japanese Drug Market; Weak Enough to Work Together," *The Economist*, 13 August 1983, 66; "Japan's Sickly Drug Firms," *The Economist*, 19 October 1996, 65; Yakugyō Jihōsha, *Yakuji Handobukku* [Pharmaceutical Affairs Handbook] (Tokyo: Yakugyō Jihōsha, 1968-1999); Jihō, *Yakuji Handobukku* [Pharmaceutical Affairs Handbook] (Tokyo: Jihō, 2000-2007).

²⁶⁵ Robert Tulloch, *Pharmaceutical Markets in the Pacific Rim*, Scrip Reports (Richmond: PJB Publications, 1995), 46.

networks.²⁶⁶ It is true that larger firms outsourced many of their business operations to smaller firms – and that smaller firms have been an important source of pharmaceutical innovation. But growth in the pharmaceutical industry was channelled by larger firms who managed to coordinate and gain from the operations outsourced to smaller firms.

As well, with limited resources, R&D in Japan took place in academia, where knowledge was transferred through informal networks. By comparison, industrial research had become the norm in German and American pharmaceutical firms by the early 20th century. Because R&D in Japan was conducted in academic laboratories, the research was not as responsive to industry conditions. By contrast, industrial laboratories in the United States and Germany could align their R&D goals more closely with marketing, distribution and sales agendas that would support industrial growth.

The third reason why Japan was not able to develop a globally competitive industry was due to factors that incentivised Japanese firms to launch numerous new drugs of minimal innovative value that would neither be approved nor commercially viable overseas. To begin with, Japanese drug authorities approved new drugs with relatively low criteria for innovation. In addition, as Japanese pharmaceutical firms were not able to profit from free market prices for pharmaceutical innovations, many firms preferred to minimise their investments in R&D. Moreover, most Japanese physicians

²⁶⁶ Jon Sigurdson, *Future Advantage Japan?: Technology Strategies for Pharmaceutical and Chemical Corporations* (London: Cartermill, 1996).

continued to adhere to traditional practices of both prescribing and dispensing drugs. To profit from the difference between wholesale and retail drug prices, physicians were incentivised to prescribe newer and higher priced drugs that tended to have the steepest price differential.

Indeed, the profit incentives created by Japanese physicians' dual prescribing and dispensing practices heavily shaped the industry. In 1989, for example, the Ministry of Health and Welfare revealed that pharmaceutical price differentials averaged around 25% of official drug prices and amounted to 1.3 trillion yen a year.²⁶⁷ Physician demand for a particular drug translated easily into patient demand in a hierarchical society where patients did not question the authority of physicians, where few explanations were made of the medicines prescribed, and in a market where consumers were price insensitive.²⁶⁸ The generous criteria for drug approval, low reward for innovation, and endurance of this dual prescribing and dispensing practice led Japanese firms to launch drugs that were only profitable in the Japanese market. Furthermore, as Robert Neimeth has noted, the stark dissimilarities between the Japanese and overseas markets, generated reluctance among Japanese firms to make the immense investments necessary to expand into America or Europe.²⁶⁹

Perhaps the most powerful explanation for the relative weakness of Japan's

²⁶⁷ See "Yakka Saeki Nen ni 1-chō 3-zen-oku en: Kusuridai Sōgaku no 4-bun no 1 [Pharmaceutical Price Differentials amount to 1.3 Trillion Yen a Year, or a Quarter of Drug Prices]," *Asahi Shimbun*, 9 November 1989.

²⁶⁸ Eric Feldman, "Medical Ethics the Japanese Way," *The Hastings Center Report* 15, no. 5 (1985): 21-24. It is, however, difficult to assess the degree to which a more hierarchical relationship might have mattered. See William E. Steslicke, "Doctors, Patients, and Government in Modern Japan," *Asian Survey* 12, no. 11 (1972): 913-931.

²⁶⁹ Robert Neimeth, letter to author, 31 March 2006.

pharmaceutical industry was the endurance of the government's developmental health policies, which was suitable for a low-income country, but became outdated over the decades. With its governance by the MHW rather than the MITI, government policies tended to prioritise domestic health agendas over industrial development. The government's developmental health policies were essentially guided by an overarching goal to provide universal access to drugs for Japanese citizens. To do so, the government set drug prices at fixed rate, subsidised patients who purchased prescription drugs, and reduced drug prices regularly to contain costs. These policies were appropriate in the early post-war period when Japanese consumers were still poor and infectious diseases were rampant. The government was able to afford essential medicines to treat acute, life threatening diseases that required medication for only a short period of time. But these policies persisted into the late 20th century when chronic diseases of affluence became the norm.

The MHW's tendency to prioritise the needs of consumers over industry reduced incentives among firms to innovate and develop drugs that would succeed in global markets. The capping of drug prices not only resulted in smaller profits, but also limited the ability of firms to pursue riskier, costly, or sophisticated investments in R&D. Japanese pharmaceutical firms attempted to maximise their gains by continuously launching new drugs with minimal innovative value. By comparison, policies in the countries that had developed pharmaceutical industries earlier, such as the United States, Germany and Britain, were designed to penalise imitations and encourage pioneering innovations that would be accepted worldwide.

The fifth reason for the weak performance of Japan's pharmaceutical industry lay in the government's developmental industrial policies, which protected Japanese firms from foreign competition long after it was necessary or desirable. For decades, the government adopted an import-substitution policy, and Japanese firms relied on technology imports to develop or modify foreign-discovered products rather than pursue research for therapeutic breakthroughs. In a protected market, the government's policies essentially enabled firms to remain highly profitable without launching highly original drugs that could be translated into foreign markets.

Even while Japanese firms acquired manufacturing capacities over the 1960s and developed substantial discovery capacities by the 1970s, various layers of protection remained. Until 1975, for example, foreign pharmaceutical firms were explicitly prohibited from establishing wholly-owned subsidiaries in Japan. In addition, distribution networks for pharmaceuticals remained highly complex and opaque until the 1990s, making it very costly and difficult for foreign companies to penetrate the Japanese market. Japan's drug standards and classifications created another entry barrier, as they made drugs in the Japanese market a very different product from drugs abroad. It was only in the 1990s, when Japanese pharmaceutical regulations were harmonised with those in the United States and Europe, that foreign drugs were more easily recognised in Japan. Other regulations that protected Japanese firms included requirements to conduct clinical trials on Japanese subjects and to file drug approval documents in Japanese.

As well, the lack of explicit industrial policy for the pharmaceutical sector meant that government policies tended to be reactive, ad-hoc, and short sighted. This was particularly visible in official responses to drug tragedies or escalating health care costs. The government was generally slow to enforce reforms, and usually guided industry through a prolonged period of administrative guidance before establishing legislation. An earlier implementation of comprehensive, long-term strategies and strong legislation to strengthen the industry would likely have facilitated the development of a more research intensive and global pharmaceutical industry well before the 1990s.

It is true that other regulations and the absence of certain institutional factors also weakened the ability of Japanese firms to produce globally competitive drugs. For example, regulation that forbade the entrepreneurship of university academics long stifled the translation of university research into viable commercial therapies. The absence of a structured clinical trial system and lack of qualified reviewers also made both drug development and approval in Japan a much more costly, inefficient, and time-consuming affair. Rather than the lack of reward, it was more the penalties to investments in innovation that deterred Japanese firms from developing therapies and from pursuing drugs that might be globally competitive.

The final factor behind the relative weakness of Japan's pharmaceutical industry was the lack of entrepreneurial initiative among Japanese firms. Many firms were also

short-termist, and were content to profit from a domestic market so long as it was protected from foreign competition. Few firms planned or actively sought to take advantage of international markets by for example, investing in R&D or developing overseas marketing networks from an earlier period. Most firms only began to do so as a response to government deregulation in the 1970s. While the pharmaceutical industries of Germany or Switzerland have historically prioritised foreign markets for growth, it was not until the 1990s that some Japanese firms began to circumvent inferior incentives within Japan by seeking more favourable opportunities abroad.

At the turn of the 21st century, the performance of Japan's pharmaceutical industry remained mixed. Japan's pharmaceutical industry experienced phenomenal growth from a small, insular domestic industry into a larger, more open, and global industry. It achieved spectacular growth in production, sales, trade and R&D. With the harmonisation of pharmaceutical regulation and research-intensive orientation, many features in Japan converged with the leading global pharmaceutical industries. But Japan's pharmaceutical industry was not a global leader. Too little had been done too late.

3 Antibiotics chapter

This thesis argues that Japanese pharmaceutical firms were historically much smaller, less R&D intensive, and more domestically-oriented in comparison with other developed countries such as the United States, the United Kingdom, and Switzerland. Japan's pharmaceutical industry also remained relatively weak in comparison with the country's leading industries such as automobiles and electronics. Japan was a net importer of pharmaceuticals, and Japanese firms generally remained uncompetitive in the global pharmaceutical industry.

But some sectors of the Japanese pharmaceutical industry were much stronger than others. This was particularly true of Japan's antibiotics sector. Antibiotics have been Japan's leading pharmaceutical export.²⁷⁰ At times, Japan was also able to record a trade surplus in antibiotics.²⁷¹

This chapter examines the history of the Japanese antibiotics sector and provides several explanations for its strong performance. The antibiotics sector emerged in the late 1940s under the guidance of the American Occupation forces. By the early 1980s, foreign observers remarked that Japanese firms had become global leaders in antibiotics.²⁷² In the mid 1980s, antibiotics developed in Japan and produced under licence by American firms accounted for 20% of the US antibiotics market.²⁷³

²⁷⁰ *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Yakugyō Keizai Kenkyūjo, 1968-2000); Ministry of Health, Labour and Welfare, *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Jihō, 2001-2006).

²⁷¹ Japan recorded a trade surplus in antibiotics in 1993, 1994 and 1998. Ministry of International Trade and Industry, *Tsūshō Hakusho* [White Paper on Trade] (Tokyo: Gyōsei, 1974-2000).

²⁷² N.R. Kleinfeld, "Intense Battle for Antibiotics," *The New York Times*, 13 June 1983.

²⁷³ Eric Schmitt, "What's Hot in Imported Products; Antibiotics Made Jointly," *The New York Times*, 30 November 1986.

Japanese pharmaceutical firms demonstrated their capacity to discover innovative antibiotics from the early post-war period. In fact, some of the antibiotics discovered and developed by Japanese firms in the 1950s remain in worldwide use to date. In the 1990s, the majority of firms involved in antibiotic research were still Japanese or American.²⁷⁴ Japanese firms have also dominated the domestic market with their own products – even after the government’s protectionist policies were lifted in the mid 1970s.²⁷⁵

This chapter examines the development of the antibiotics sector over five phases. In the first phase between 1945 and 1949, the antibiotics sector emerged under the American Occupation. This was followed by the rise of Japanese antibiotic discoveries and the acquisition of production capacities in a protected market via technology imports between 1950 and 1961. During the third phase between 1961 and 1975, the antibiotics sector experienced volume-based expansion under universal health care while developing R&D capacities through process innovation. This was followed by a phase of government deregulation, which encouraged R&D capacities in product innovation via capital liberalisation and a new product patent regime between 1975 and 1990. Since the burst of the bubble in 1990 to 2005, the industry matured alongside efforts to harmonise regulatory guidelines with international standards under ICH.²⁷⁶ The chapter concludes by providing an explanation for why

²⁷⁴ Jenny Wilson, *Antibacterial Products and Markets, Scrip Reports* (Richmond: PJB Publications, 1997), 137.

²⁷⁵ Datamonitor, “Japan – Antibacterial Drugs,” *Industry Profile* (London: Datamonitor, 2002), 9.

²⁷⁶ ICH refers to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. See, The International Conference on Harmonisation of Technical Requirements for Registration of

the performance of the Japanese antibiotics sector has been relatively strong.

3.1 Japan's antibiotics sector during the Allied Occupation period

The creation of the antibiotics sector after 1945 was important for several reasons. First, antibiotics dramatically improved public health conditions in Japan, where many were suffering from infectious diseases. Second, antibiotics were the foundation of the modern Japanese pharmaceutical industry. Penicillin was a groundbreaking therapy that played a central role in building Japan's post-war pharmaceutical industry. Japanese firms also produced other drugs in the Occupation period such as DDT, sulfa drugs and vitamins.²⁷⁷ This section follows the experience of Japanese firms in establishing the antibiotics sector through the first antibiotic, penicillin – and later, streptomycin. It considers the reasons behind the remarkable rise of Japan's antibiotics sector over the late 1940s.

3.1.1 Early Efforts to Produce Antibiotics, 1944-1945

Antibiotics are a substance that kills or inhibits the growth of other microbes. The age of antibiotics began with the discovery of penicillin by Alexander Fleming in 1929. Fleming, a bacteriologist at the University of London, accidentally discovered penicillin when he noticed that a mould that had contaminated one of his bacterial cultures had caused the bacteria to deteriorate.²⁷⁸ With its remarkable efficacy in

Pharmaceuticals for Human Use, <http://www.ich.org>, (accessed 15 May 2007). See also overview chapter.

²⁷⁷ See "Gyōkai Tenbō: Seiyaku Kōgyōkai [Industry Prospects: The Pharmaceutical Industry]," *Kigyō Chōsa* 63 (September 1948): 3.

²⁷⁸ Alexander Fleming, "On the Antibacterial Action of Cultures of a Penicillium, with Special Reference to Their Use in the Isolation of H. Influenzae," *British Journal of Experimental Pathology* 10 (June 1929): 226-236.

treating infectious disease, penicillin revolutionised the practice of medicine.²⁷⁹ While scientists had developed other antibacterials such as alkaloids and sulfa drugs in the first half of the 20th century, it was penicillin that gave birth to the modern antibiotics era.

Although British scientists had discovered penicillin, it was the US firms such as Merck, Squibb, Lederle and Pfizer who were able to commercialise penicillin during World War II.²⁸⁰ Fleming had abandoned research on penicillin in 1929 after he found it difficult to isolate the substance and grew increasingly sceptical of its viability as an actual drug.²⁸¹ While Oxford scientists led by Howard Florey, Ernest Chain and Norman Heatley took up penicillin research in the late 1930s, they could not interest British firms such as ICI or Boots in commercialising the drug. Indeed, it was only after Florey and Heatley brought penicillin to the attention to the United States in 1941 that the US government and the leading American firms, working together, were able to mass-produce penicillin in 1943.²⁸²

The Japanese Army learned of penicillin in late 1943. Since 1942, the Ministry of Foreign Affairs and the Ministry of Education had operated an information service that

²⁷⁹ For a general history on the development of penicillin, see for example, Gladys L. Hobby and Milton Wainwright, *Penicillin: Meeting the Challenge* (New Haven: Yale University Press, 1985); John Parascandola, ed., *History of Antibiotics* (Madison: American Institute of the History of Pharmacy, 1980); David Wilson, *Penicillin in Perspective* (London: Faber, 1976). Textbooks generally define antibacterials as synthetic chemicals more toxic to bacteria than to mammals while antibiotics are defined as substances produced by microorganisms that are toxic to bacteria. The distinction between these two categories have, however, blurred over the years as scientists developed synthetic means to produce antibiotics.

²⁸⁰ See W. H. Helfand, H.B. Woodruff, K.M.H. Coleman and D.L. Owen, "Wartime Industrial Development of Penicillin in the United States, in John Parascandola, ed., *The History of Antibiotics: A Symposium* (Madison: American Institute of the History of Pharmacy, 1980): 31-55.

²⁸¹ Gwyn Macfarlane, *Alexander Fleming: The Man and the Myth* (Oxford: Oxford University Press, 1984), 139.

²⁸² See for example, Jonathan Liebenau, "The British Success with Penicillin," *Social Studies of Science* 17, no. 1 (1987): 69-86; M. Lawrence Podolsky and Daniel E. Koshland, "The Oxford Incidents," in *Cures out of Chaos: How Unexpected Discoveries Led to Breakthroughs in Medicine and Health* (Amsterdam: Harwood, 1997), 177-224.

dispatched recent Western medical journals from Germany via submarine. These publications heightened the Army's interest in penicillin production.²⁸³ One article in the *Klinische Wochenschrift* was of particular interest, as it contained abstracts of penicillin related papers published by the Oxford Group between 1940 and 1943.²⁸⁴

Upon reading these articles, surgeon major Katsuhiko Inagaki of the Army Medical School established a small research group in January 1944 to explore penicillin production in Japan. Inagaki called upon leading scientists such as Yūsuke Sumiki and Hamao Umezawa at his alma mater, the University of Tokyo, to collaborate on this project.²⁸⁵ But what truly jumpstarted penicillin production in Japan was a newspaper article published in 28 January 1944. The *Asahi Shimbun* erroneously reported that Winston Churchill had been cured of pneumonia with a new drug called penicillin.²⁸⁶ While later reports clarified that the British premier had actually been cured by sulfa drugs, the Japanese Army immediately requested its medical school to organise a production committee within two to three days, and to supply the Army with penicillin by August 1944.²⁸⁷ The first Penicillin Committee convened on 1 February 1944 under military command. There, members of the Army Military School and scientists

²⁸³ Details of this discovery have been written in Fuksako Tsunoda, *Hekiso: Nihon Penishirin Monogatari* [Hekiso: The Story of Penicillin in Japan] (Tokyo: Shinchōsha, 1978): 3-22. A brief overview of Japan's wartime penicillin project was also written by a scientist involved in the project: Hamao Umezawa, "Kōsei Busshitsu no Kenkyūshi (1) [A History of Research in Antibiotics (1)]," *Shizen* 17, no.2 (1962): 83-89.

²⁸⁴ Manfred Kiese, "Chemotherapie mit Antibakteriellen Stoffen aus Niederen Pilzen und Bakterien," *Journal of Molecular Medicine* 22 (1943): 505-511.

²⁸⁵ Katsuhiko Inagaki, interview by Nihon Penishirin Kyōkai, "Penishirin no Nihon Inyū [The Transfer of Penicillin into Japan], in Nihon Penishirin Kyōkai [Japan Penicillin Association]," *Penishirin no Ayumi: 1946-1961* [The History of Penicillin: 1946-1961]; Katsuhiko Inagaki, interview by Kihachirō Shimizu, "Nihon ni Okeru Penishirin Kaihatsu no Keii [The Development of Penicillin in Japan]," *Today's Therapy* 19, no.2 (1995): 26-34. Inagaki's involvement in the development of penicillin in Japan was later published by Haruhiko Inagaki, *Hekiso: Kokusan Penishirin Kaihatsu no Hatafuri, Inagaki Gun'i Shōsa to Ichikōsei Gakuto Dōin* [Hekiso: Pioneering the Development of Penicillin in Japan, Lieutenant Medic Inagaki and the Mobilised Students of the Imperial University] (Tokyo: Nikkei Jigyō Shuppan Sentā, 2005).

²⁸⁶ Chāchiru Inochi Biroi, *Zuruhon zai o Oginau Penishirin* [Churchill's Life is Saved: Penicillin, instead of Sulfa Drugs, are the Drug of Choice], *Asahi Shimbun*, 27 January 1944.

²⁸⁷ Yukimasa Yagisawa, "Early History of Antibiotics in Japan," in *The History of Antibiotics: A Symposium*, ed. John Parascandola (Madison: American Institute of the History of Pharmacy, 1980), 69-90.

at Japanese universities decided upon how to pursue penicillin production.²⁸⁸

Headed by Inagaki, Japan's wartime penicillin project was run by the Army Medical School. The Army organised several research groups comprised of Japanese academic scientists and requested them to inform the Army of their research results through detailed reports.²⁸⁹ By international standards, it was a small-scale project: a mere 1.9 billion yen project compared to the 63.5 billion yen spent to develop penicillin by the United States.²⁹⁰ But it was also a successful project. Despite the desperate scarcity of supplies in a war-stricken economy, Japanese scientists were able to produce penicillin by December 1944.²⁹¹

The two facilities to produce penicillin were selected by members of the Penicillin Committee. Inagaki, who found striking similarities between milk production plants and images of penicillin production plants abroad, contacted Morinaga president Hanzsaburō Matsuzaki, and requested that the confectioner and milk producer cooperate in penicillin production. Morinaga produced its first batch of penicillin under the guidance of Penicillin Committee scientists in December 1944. The sulfa drug maker Banyu Pharmaceuticals followed shortly thereafter, with its first batch of penicillin in February 1945.²⁹² The Army Medical School then distributed the

²⁸⁸ Katsuhiko Inagaki, *Penishirin Iinkai no Kotodomo* [Notes on the Penicillin Committee], 16 November 1944, Naito Museum of Pharmaceutical Science and Industry, Kagamihara, Japan. See also, *Penishirin Iinkai, Penishirin Iinkai Gijiroku* [Minutes of the Penicillin Committee], February to December 1944, Naito Museum of Pharmaceutical Science and Industry, Kagamihara, Japan.

²⁸⁹ *Ibid.*

²⁹⁰ See Hamao Umezawa "Kōsei Busshitsu o Motomete (1) [Searching for Antibiotics (1)]" *Shokun* 1, no. 1 (1980): 294. Umezawa estimated that the development of penicillin in the 1940s cost the Japanese 1.5 billion yen while it cost the United States 50 billion yen in 1980 values. This article discusses the development of penicillin in Japan during the Second World War.

²⁹¹ Katsuhiko Inagaki, *Penishirin Iinkai no Kotodomo* [Notes on the Penicillin Committee], 11.

²⁹² Katsuhiko Inagaki, *Penishirin Iinkai no Kotodomo* [Notes on the Penicillin Committee] and *Penishirin Iinkai, Penishirin Iinkai Gijiroku* [Minutes of the Penicillin Committee].

penicillin vials produced. The penicillin produced during this time was still low in volume, of limited efficacy, and reached few patients. But Japanese firms were able to produce some penicillin under the guidance of the Army and university scientists for military purposes during the Second World War.²⁹³

3.1.2 The First year of the Occupation

The rise of Japan's post-war antibiotics sector began with the rebuilding of penicillin production capacities that began during the Second World War. As mentioned earlier, penicillin production in Japan began in late 1944.²⁹⁴ To a certain extent, the rapid rise of Japan's penicillin industry was possible because Japan's antibiotics makers had sustained relatively little damage during the war.²⁹⁵

In the immediate post-war period, Japanese firms faced high demand for therapies that might cure infectious disease. The lack of foodstuffs and unsanitary conditions heightened morbidity and mortality levels for a range of infectious diseases, including tuberculosis, dysentery and diphtheria.²⁹⁶ While death rates from infectious disease did fall along with improvements in food supply and public health standards in the immediate post-war period, repatriated soldiers brought a fresh surge in morbidity levels as they carried infectious diseases from foreign lands.²⁹⁷

²⁹³ Ibid. Both firms had been linked to key members of the Penicillin Committee. President Hanzaburō Matsuzaki of Morinaga and Katsuhiko Inagaki were fellow alumni of the University of Tokyo. President Kōichi Iwadare of Banyu and Hamao Umezawa's (one of the lead scientists of the project) were also alumni of the University of Tokyo.

²⁹⁴ "Trade and Industry: Penicillin," *The Oriental Economist*, 13 September 1947, 749.

²⁹⁵ This is well documented in the company security filings in the late 1940s. See also, Chōbei Takeda, "Wagakuni no Iyakuin Kōgyō to Bōeki [Pharmaceutical Industry and Trade in Our Country]," *Kankeiren* 16 (January 1949): 19-21.

²⁹⁶ Ministry of Health and Welfare, *Densenbyō Oyobi Shokuchūdoku no Kanjasū to Shibōshasū* [Patients and Deaths of Infectious Diseases and Food Poisoning] (Tokyo, 1876 -1999)," <http://www.stat.go.jp/data/chouki/24.htm> (accessed 20 March 2007).

²⁹⁷ Eiji Takemae, *Inside GHQ: The Allied Occupation of Japan and Its Legacy* (London: Continuum, 2002), 409. See also Crawford F. Sams and Zabelle Zakarian, "Medic": *The Mission of an American Military Doctor in Occupied Japan and Wartorn Korea* (London: M.E. Sharpe, 1998), 81.

As the pre-war producers and new entrants began to produce penicillin, the Occupation authorities were confronted with the need to control the quality and prices of penicillin in Japan. Unapproved, counterfeit, or mislabelled products were rife, and a large volume of penicillin of dubious quality was traded on the black market.²⁹⁸ In an attempt to regulate penicillin available in Japan, the Ministry of Health introduced official drug prices for several standards of penicillin in 18 January 1946.²⁹⁹ Much to the surprise of Japanese officials and firms, however, the GHQ banned sales of penicillin shortly after this announcement because of the limited efficacy and heavy side effects of penicillin produced in Japan.³⁰⁰ The Occupation authorities decided to improve penicillin production in Japan – both for the Japanese and the American Army stationed in Japan.

The Allies' decision to improve penicillin production in Japan was not entirely based on altruistic motives. For the GHQ, enabling Japanese firms to mass-produce antibiotics offered a more cost-effective means of public health administration and of providing antibiotics to American troops in Japan.³⁰¹ Indeed, approximately 60% of the first penicillin ration was distributed to treat syphilis in the American Army at the Recreation and Amusement Association (RAA) and Yoshiwara hospitals, while

²⁹⁸ "Furyō Iyakuin Torishimari Kyōka: Yamitorihiki wa Genbatsu [Strengthening Regulations over Unauthentic Medicines: Strict Penalties for Black Market Transactions]," *Iji Tsūshin* 1 (November 1946): 3; "Yami no Penishirin wa Inchiki [Black Market Penicillin is Fraudulent]," *Directives and Important Releases of G.H.Q.* 26 (December 1946): 10.

²⁹⁹ Yukimasa Yagisawa, "Early History of Antibiotics in Japan," 77.

³⁰⁰ "Penishirin Saihanbai Kyōka [Penicillin Resale Approval]," *Nihon Iji Shinpo* 10 (May 1946): 11.

³⁰¹ General Headquarters, Supreme Commander for the Allied Powers, Public Health and Welfare Section, *Public Health and Welfare in Japan* (Tokyo: Supreme Commander for the Allied Powers, Public Health and Welfare Section, 1949), 190. See also General Headquarters, Supreme Commander for the Allied Powers, Public Health and Welfare Section, *Mission and Accomplishments of the Occupation in the Public Health and Welfare Fields* (Tokyo: Supreme Commander for the Allied Powers, Public Health and Welfare Section, 1949), 32.

another 30% were used to treat bronchitis in Japanese civilians.³⁰²

Given the costs involved in communication, transport and time, it was much cheaper and convenient to produce antibiotics in Japan using improved domestic facilities, than import antibiotics from the United States. Inadequate supplies were supplemented with imports from the American Red Cross, UNICEF, Licensed Agencies for Relief in Asia (LARA) and CARE, but these could not sufficiently satisfy domestic demand.³⁰³ Production in Japan could also be more easily monitored and adjusted to fluctuations in demand. As well, improving public health conditions was expected to win the loyalty of the Japanese, and help the Occupation authorities achieve their broader agendas to democratise and demilitarise Japan – and prevent the country from becoming Communist.³⁰⁴

As an occupying power, the GHQ had absolute authority. The Occupation forces were able to build an antibiotics sector in Japan without heavy opposition from vested interests in Japan. The early Japanese antibiotics sector therefore caught up quickly, equipped with modern technology, regulatory standards, and the expertise necessary for subsequent development.

³⁰² “Penishirin no Daiikkai Haikyū [The First Ration of Penicillin]” *Iyaku Tsūshin* 1 (July 1946): 3. The Recreation and Amusement Association (RAA) was an organisation established by the Japanese government to form brothels and provide prostitution services to the Occupation forces. Yoshiwara was a red-light district in Tokyo.

³⁰³ General Headquarters, Supreme Commander for the Allied Powers, Public Health and Welfare Section, *Public Health and Welfare in Japan* (Tokyo: Supreme Commander for the Allied Powers, Public Health and Welfare Section, 1949), 121. LARA was an American volunteer organisation established in April 1946 under the American Council of Voluntary Agencies for Foreign Service to provide aid to the impoverished regions of Asia (particularly Japan, Korea, and Okinawa) after the Second World War. CARE was also an American humanitarian aid organisation founded in 1945 to provide relief to survivors of World War II.

³⁰⁴ See Sey Nishimura, “Censorship of Medical Journals in Occupied Japan” *Journal of the American Medical Association* 274 (August 1995): 456. See also overview chapter.

The GHQ introduced several measures to improve the conditions of Japan's penicillin market during the first year of the Occupation. In January 1946, the Occupation authorities requested scientists at the University of Tokyo to evaluate the quality of penicillin submitted by potential manufacturers to the government for manufacturing approval.³⁰⁵ A Penicillin Ration Committee comprised of university professors was formed in June 1946 to help coordinate the distribution of scarce penicillin supplies.³⁰⁶ The distribution routes were based on Japan's wartime rationing organisations, such as the Medicines Control Company (*Iyakuhin Tōsei Kabushiki Kaisha*).³⁰⁷ It was true that distribution failures did occur, and that penicillin of dubious quality was traded on the black market. But the creation of formal transfer mechanisms helped restore some order to the chaos of the distribution routes in the immediate post-war period.

The GHQ also requested the formation of the Japan Penicillin Association (*Nihon Penishirin Kyōkai*) as a forum to exchange information on penicillin production between government, industry, and academia.³⁰⁸ The association was established on 15 August 1946, only a year after the bombing of Hiroshima, and was led by the early penicillin makers Banyu, Morinaga, Wakamoto, and Yaesu. An academic organisation, the Japan Penicillin Research Association (*Nihon Penishirin Gakujutsu Kyōgikai*) was established a few weeks later – a successor to the wartime Japan Antibiotic Penicillin

³⁰⁵ Japan Business History Association, ed., *Banyu Pharmaceutical: 85 Year History* (Tokyo: Banyu Pharmaceutical, 2002): 95-96.

³⁰⁶ See for example, "Penishirin no Seisankeikaku [Production Plan for Penicillin] *Akarui Bōeki* 2, no.2 (1947): 11. Penicillin, along with other medicines – such as antibiotics and vaccines – were mostly rationed via "purchasing passbooks" to dealers authorized by the prefectural government, such as clinics, veterinary hospitals, pharmacies, and other retailers.

³⁰⁷ Yakugyō Keizai Kenkyūjo, *Yakuji Nenkan* [Pharmaceutical Annual] (Osaka: Nihon Yakugyō Shimbunsha, 1951), 247.

³⁰⁸ Nihon Penishirin Kyōkai [Japan Penicillin Association], *Penishirin no Ayumi: 1946-1961* [The History of Penicillin: 1946-1961], 58-67.

Research Committee that was dissolved in 1945.³⁰⁹ But what truly transformed penicillin production in Japan were a series of technology transfers provided through Jackson Foster, a scientific consultant appointed by the GHQ.

3.1.3 Crawford Sams and Jackson Foster

I have sent back for a technician who will show your manufacturers how to make high potency penicillin and we and we are working with both your manufacturers and the Ministry to produce good penicillin, which will be sold in adequate doses.

Crawford F. Sams, "Address to Tokyo Pharmacists," 7 March 1946³¹⁰

During the Occupation, Japan's pharmaceutical industry was regulated by the Public Health and Welfare Section led by Colonel Crawford F. Sams.³¹¹ Under Sams' administration, the Occupation played a crucial role in the building of Japan's antibiotics industry by orchestrating the direct transfer of penicillin technology. The most important technology transfers were made between October 1946 and February 1947, when Jackson Foster visited Japan.³¹² Foster was an industrial scientist who had been involved in the commercialisation of penicillin at Merck in the United States during the Second World War.³¹³ The American scientist's direct transfer of penicillin technology to the Japanese was crucial to the eventual mass production of penicillin in

³⁰⁹ Nihon Penishirin Kyōkai [Japan Penicillin Association], *Penishirin no Ayumi: 1946-1961* [The History of Penicillin: 1946-1961], 68-69. See also, Japan Antibiotics Research Association, "Honkai no Gaiyō [About Us]," <http://www.antibiotics.or.jp/jara/news/jara.htm> (accessed 28 April 2008). The Japan Penicillin Research Association was renamed as the Japan Antibiotics Research Association (JARA) in 1951. JARA currently operates under the Ministry of Health, Labour and Welfare, Pharmaceutical and Food Safety Bureau, Evaluation and Licensing Division. It continues to support antibiotic research to date.

³¹⁰ Crawford F. Sams, "Address to Tokyo Pharmacists," 7 March 1946 Declassified EO 12065 Section 3-402/NNDG no. 775024, 3 (NDL).

³¹¹ Eiji Takemae, *Inside GHQ: The Allied Occupation of Japan and Its Legacy* (London: Continuum, 2002), 49. See also, Crawford F. Sams, interview by Darryl Podoll, 3 May 1979.

³¹² Yukimasa Yagisawa, "Early History of Antibiotics in Japan," 79-80.

³¹³ Barry Woodruff, "A Soil Microbiologist's Odyssey," *Annual Review of Microbiology* 35 (1981): 8.

Japan.

Foster not only imparted his knowledge of penicillin to the Japanese, but also offered the strains of bacteria found to be effective in producing penicillin in the United States. Perhaps the most significant event was a three-day symposium on penicillin production held from 13 to 15 November 1946.³¹⁴ The event was attended by 380 leading figures in Japan, including 120 academics, 6 government officials, and 120 workers from 47 firms.³¹⁵ Foster's lectures were reproduced as the first article in the first issue of the Japanese Journal of Antibiotics, the scholarly journal published by the Japan Antibiotics Research Association (JARA).³¹⁶ After the lectures, Foster provided Professor Kin'ichirō Sakaguchi of the University of Tokyo with B21 strains for surface culture production, Q176 strains for deep-tank production, and a petroleum can full of corn steep liquor – which were then distributed to researchers throughout Japan. During his five-month stay, Foster also provided direct guidance at various production plants across Japan.³¹⁷

The Occupation authorities further nurtured the development of penicillin production in Japan by establishing central research laboratories, which promoted the diffusion of developments in penicillin technology – not only across government, industry, and

³¹⁴ Jackson W. Foster, "Three Days' Symposium on Penicillin Production, Held at Welfare Ministry, Tokyo, Japan, November 13-15, 1946," *Journal of Antibiotics* 1 (March 1947): 1-28.

³¹⁵ Yukimasa Yagisawa, "Early History of Antibiotics in Japan," 79.

³¹⁶ Jackson W. Foster, "Three Days' Symposium on Penicillin Production, Held at Welfare Ministry, Tokyo, Japan, November 13-15, 1946," *Journal of Antibiotics* 1 (March 1947): 1-28. Prior to 1951, the Japan Antibiotics Research Association was known as the Japan Penicillin Research Association.

³¹⁷ Yukimasa Yagisawa, "Early History of Antibiotics in Japan," 80.

academia, but also across the various regions of Japan.³¹⁸ The GHQ's decision to enable Japanese firms to produce penicillin was a windfall for the Japanese. After all, the United States had invested six years and 20 million of dollars in research to develop penicillin technology.³¹⁹ The direct transfer of this technology enabled Japan to leapfrog over investments and accomplishments that would have been impossible for a war-torn economy.

3.1.4 Putting Foster's Gift to Work

Helped by the interventions of the Occupation forces, Japan's antibiotics sector grew quickly during the Occupation period. While Japanese firms had not been able to produce commercially viable doses at the end of the War, it produced 147 million units by 1951.³²⁰ Penicillin production rose, both as existing firms acquired mass-production capacities, and as new firms began to produce penicillin. While "shortages of critical raw materials, fuel, and power" remained a problem, distribution controls were removed in 1948, and the country was the third country after the United States and the United Kingdom to become self-sufficient in penicillin.³²¹

³¹⁸ Nihon Yakushi Gakkai, *Nihon Iyakuhin Sangyōshi* [A History of the Japanese Pharmaceutical Industry], 113.

³¹⁹ Nippon Kayaku Co., *Nihon Kayaku no Ayumi: Kono 10-nen o Chūshin to shite* [The History of Nippon Kayaku: With Special Attention to the Past 10 Years] (Tokyo: Nippon Kayaku Co., 1976), 186; Junichi Aoyagi, *Inochi o Kangaete 85-nen: Banyu Seiyaku no Ayumi* [85 Years for Life: The History of Banyu] (Tokyo: Banyu Pharmaceutical, Co. 2000), 153.

³²⁰ General Headquarters, Supreme Commander for the Allied Powers, Public Health and Welfare Section, *Public Health and Welfare in Japan* (Tokyo: Supreme Commander for the Allied Powers, Public Health and Welfare Section, 1950), 83.

³²¹ Joichi Kumazawa and Morimasa Yagisawa, "The History of Antibiotics: The Japanese Story," *Journal of Infection and Chemotherapy* 8, no.2 (2002): 125. See also, General Headquarters, Supreme Commander for the Allied Powers, Public Health and Welfare Section, *Public Health and Welfare in Japan* (Tokyo: Supreme Commander for the Allied Powers, Public Health and Welfare Section, 1952): 123; and Crawford F. Sams and Zabelle Zakarian, "Medic": *The Mission of an American Military Doctor in Occupied Japan and Wartorn Korea*, 136.

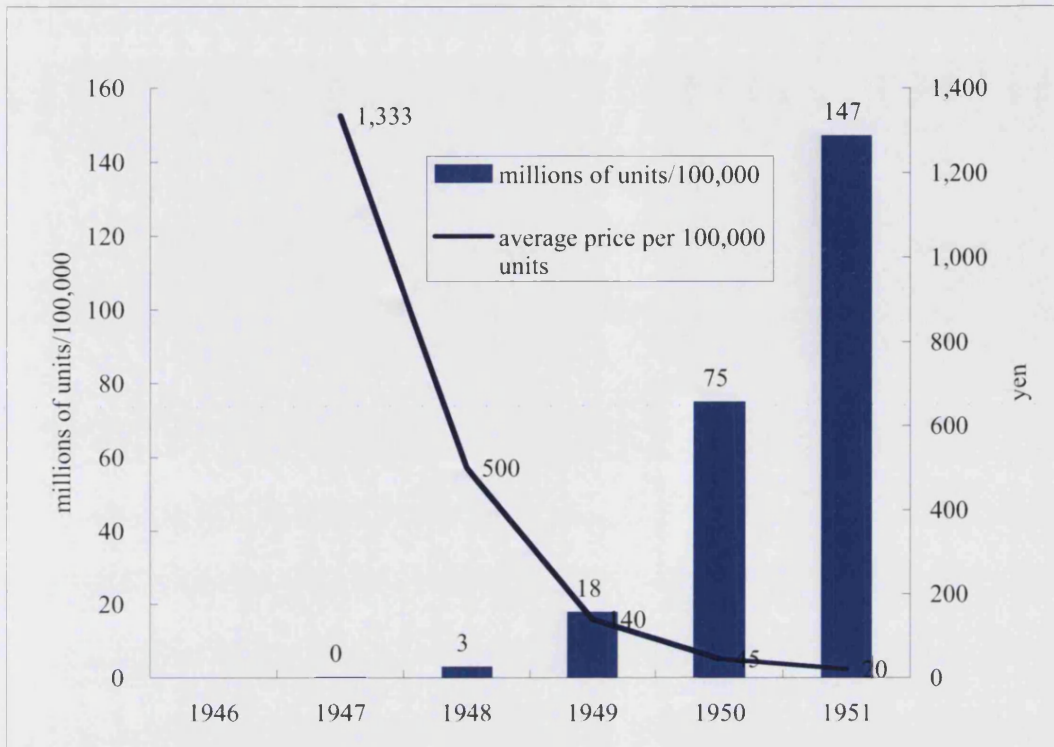


Figure 9. Penicillin Production and Prices, 1946-1951 (nominal)³²²

A major turning point occurred in 1948, when Japanese firms acquired mass production capacities.³²³ Until that time, Japanese firms produced penicillin via surface culture, rather than deep-tank fermentation. In the early post-war period, Japanese firms produced penicillin from surface grown cultures in thousands of glass bottles. While Japanese scientists did manage to increase yields between 1944 and 1948 by improving culture media and penicillin strains, this did not lead to a substantial rise in production levels.³²⁴ It was only after milk bottles were replaced with 1,000-4,000 litre fermentation tanks that Japanese firms were to mass-produce penicillin and production levels actually began to satisfy domestic demand.³²⁵ Indeed,

³²² General Headquarters, Supreme Commander for the Allied Powers, Public Health and Welfare Section, *Public Health and Welfare in Japan* (Tokyo: Supreme Commander for the Allied Powers, Public Health and Welfare Section, 1949), 123. These are nominal prices.

³²³ "Trade and Industry: Penicillin," *The Oriental Economist*, 1 May 1948, 352-353.

³²⁴ Kuniaki Tatsuta and Morimasa Yagisawa, *Kōseibusshitsu: Seisan no Kagaku* [Antibiotics: The Science of Production] (Tokyo, Nihon Kagakukai, 1994), 9.

³²⁵ "Trade and Industry: Penicillin," *The Oriental Economist*, 13 September 1947, 749; "Trade and Industry: Penicillin," *The*

between 1947 and 1948, penicillin production increased 21 fold. In 1949, Japanese firms were finally able to produce penicillin with the 40,000 litre tanks used in the United States.³²⁶

The mass production of penicillin prompted a dramatic fall in prices – and expanded access to penicillin for Japanese citizens.³²⁷ Despite general inflation, penicillin prices plummeted 62% from 1,333 yen to 500 yen in 1948. In fact, as production levels rose and penicillin was removed from ration distribution controls in 1949, penicillin prices fell by approximately 70% in both 1949 and 1950, and by 56% in 1951. As prices fell, penicillin became more affordable to a greater number of patients. By 1949, Japan had gained both capacity and self-sufficiency in penicillin production.³²⁸

The growth of Japan's penicillin industry continued to be supported by several measures implemented by the Occupation authorities. In January 1947, for example, the government introduced a rule to secure production materials for specific products, such as medicines.³²⁹ The Occupation forces also imported equipment and machinery necessary "to aid in indigenous pharmaceutical production and to provide high standard testing equipment" for the National Institute of Health.³³⁰

Oriental Economist, 1 May 1948, 352-353.

³²⁶ "Trade and Industry: Penicillin," *The Oriental Economist*, 3 September 1949, 863; Hamao Umezawa, "Kōsei Busshitsu no Kenkyūshi (2) [A History of Research in Antibiotics (2)]," *Shizen* 17, no.3 (1962): 86, 87.

³²⁷ Penicillin was out of reach of ordinary citizens in the early post-war period. In 1946, for example, the smallest dose of 10,000 unit penicillin priced at 450 yen at a time when ordinary citizens could only withdraw 500 yen for living expenses from blocked deposits. See Yukimasa Yagisawa, "Early History of Antibiotics in Japan," 77.

³²⁸ General Headquarters, Supreme Commander for the Allied Powers, Public Health and Welfare Section, *Public Health and Welfare in Japan* (Tokyo: Supreme Commander for the Allied Powers. Public Health and Welfare Section, 1949), 123.

³²⁹ This rule refers to the Shitei Seisan Shizai Wariate Kisoku. See Takeda Pharmaceutical Co., *Takeda 200-nen* [200 Years of Takeda] (Osaka: Takeda Pharmaceutical Co., 1984), 128-129.

³³⁰ *Ibid.*

3.1.5 Thinning Out

Attracted to the low risk, yet high profit potentials of penicillin manufacture, many Japanese firms began to produce antibiotics in the late 1940s. In fact, the entry of so many firms made Japan's antibiotics sector intensely competitive in the late 1940s. This reduced profits and the number of firms peaked around 1947, when membership in the Japan Penicillin Research Association reached 72 members. Thereafter, the number of penicillin producers declined, and only the strongest remained. Top penicillin makers changed hands rapidly, and once leading firms such as Morinaga, Wakamoto and Toyo Jozo began to close their penicillin operations.³³¹

Table 2. Members of the Japan Penicillin Research Association, 1946-1956³³²

Year	Number of Firms
Start	39
1946	55
1947	72
1948	54
1949	34
1950	21
1951	19
1952	19
1953	19
1954	18
1955	16
1956	15

While the intense competition and massive increase in production levels led to a swift

³³¹ Nihon Penishirin Kyōkai [Japan Penicillin Association], *Penishirin no Ayumi: 1946-1961* [The History of Penicillin: 1946-1961], 170.

³³² *Ibid.*

decline in penicillin prices and a peaking in the number of penicillin producers, these developments also led to considerable progress in the quality of penicillin available. In addition, there was a marked change in the leading producers of penicillin. In 1946, the top five penicillin makers were Banyu, Meiji Seika, Yashima Kagaku, Daito Shokusan, and Showa Yakuhin. In 1951, the top five were Nippon Kayaku, Takeda, Meiji Dairies, Meiji Seika, and Banyu.³³³ By the end of the Occupation, leading penicillin makers such as Banyu, Meiji Seika, and Takeda had survived industry clear out and had established their position in the Japanese market.³³⁴ A similar clear-out of industry was observed in the United States, where in 1950, 12 firms remained of the 20 firms engaged in penicillin production during World War II.³³⁵

In addition to the technology transfers and the creation of new institutions and organisations, the Occupation authorities added several layers of protection from foreign firms to nurture the Japanese antibiotics sector. This measure was significant, as strong competition from advanced foreign firms might have decimated the emerging industry. In the early post-war period, for example, imports were subject to approval by the SCAP, who would purchase “all pharmaceutical products considered necessary for import to Japan on a disease and unrest basis ... through normal procurement channels in the United States.”³³⁶ Deregulation of bulk imports to the private sector occurred in 1947, but finished products were imported by the

³³³ Ibid., 166.

³³⁴ Ibid., 170.

³³⁵ Federal Trade Commission, United States, *Economic Report on Antibiotics Manufacture* (Washington: Government Printing Office, 1958), 82.

³³⁶ Public Health and Welfare Section, ESS/FT, Chemicals Branch, “Visit of Mr. C. A. Scherer, Foreign Trade Representative of Kremers-Urban Company,” 4 December 1947. Declassified EO 12065 Section 3-402/NNDG no. 775024, 4 (NDL).

government until January 1950.³³⁷

Almost all FDI was banned from Japan until 1949.³³⁸ The Occupation authorities restricted FDI because foreign capital was viewed as an unnecessary complication that might retard the administration of the Occupation as well as undermine the economic recovery of Japan.³³⁹ Japan experienced dramatic inflation after the war. It was believed that, if FDI were permitted, foreign firms could take over undervalued Japanese firms and dominate the domestic market and deplete Japan's foreign reserves. Under the GHQ's strict capital controls, Japan's antibiotic sector remained protected from foreign competition. Had the GHQ allowed foreign antibiotics firms into Japan during the Occupation period, Japan's budding industry might have been destroyed.

What was remarkable about Japan's antibiotics sector was not only the scale of progress made, but also the speed of progress made so soon after the war. Japanese firms were able produce enough penicillin to meet domestic demand before the end of the decade, in which scarcity "was of historical significance only."³⁴⁰ As Japanese manufacturers became confident of their capacity to produce penicillin, they began to improve upon the quality of penicillin produced. They also made new attempts at streptomycin manufacture – and even drug discovery.³⁴¹

³³⁷ Kunihiko Futaba, "Sengo no Iyakuhi Ryūtsushi: Haisen ni yoru Shijō Ryūtsu no Konran to Saiken [The History of Distribution in the Pharmaceutical Industry: Chaos and the Rebuilding of a War-devastated Market and Distribution System]," *Iyaku Jānaru* 11 (May 1972): 42-58.

³³⁸ General Headquarters, Supreme Commander for the Allied Powers, Public Health and Welfare Section, *Public Health and Welfare in Japan* (Tokyo: Supreme Commander for the Allied Powers, Public Health and Welfare Section, 1950), 89.

³³⁹ See Mark Mason, *American Multinationals in Japan: The Political Economy of Japanese Capital Controls* (Cambridge: Harvard University Press, 1992), 105-109.

³⁴⁰ General Headquarters, Supreme Commander for the Allied Powers, Public Health and Welfare Section, *Public Health and Welfare in Japan* (Tokyo: Supreme Commander for the Allied Powers, Public Health and Welfare Section, 1949), 118.

³⁴¹ Yukimasa Yagisawa, "Kōseibusshitsu no Kaihatsu: Rekishi to Genjō [Antibiotic Development: History and Current Status]," *Sōgō Rinsho* 21, no. 12 (1972): 2751-2757.

3.1.6 Diversification and Streptomycin: Branching Out

In the late 1940s, a second antibiotic, streptomycin, began to interest authorities in Japan. Mass production of streptomycin in the United States had begun in 1946, three years after its discovery by Selman Waksman at Rutgers University.³⁴² As a therapy that could cure tuberculosis, the leading cause of death in Japan, several firms began to develop an interest in producing streptomycin. With streptomycin, Japan's antibiotics sector entered a new phase of development.

As a stopgap measure to reduce demand pressures, the Occupation authorities imported streptomycin via the Government and Relief in Occupied Areas (GARIOA) programme and commercial funds from 1949.³⁴³ But the extremely high incidence of tuberculosis in Japan meant that sufficient dollar funds were not available for the level of imports necessary to meet demand.³⁴⁴ Because of this, the Occupation authorities were keen to enable Japanese firms to achieve self-sufficiency.

To assist in making streptomycin, the Occupation authorities helped provide supplies of raw materials for streptomycin production. The Public Health and Welfare Section requested and received the bacterial strain that would enable commercial streptomycin

³⁴² "Drug Production Begun: Two Plants Now Devoted to Making of Streptomycin," *The New York Times*, 21 August 1946; Albert Schatz, Elizabeth Bugie, and Selman Waksman, "Streptomycin, A Substance Exhibiting Antibiotic Activity against Gram-positive and Gram-negative Bacteria," *Proceedings of the Society for Experimental Biology and Medicine* 55 (1944): 66-69.

³⁴³ GARIOA was a U.S. government aid programme for American occupied territories after World War II. U.S. government aid through this programme provided mainly foodstuffs, fertilisers and pharmaceuticals to Japan between 1947 and 1951.

³⁴⁴ General Headquarters, Supreme Commander for the Allied Powers, Public Health and Welfare Section, *Public Health and Welfare in Japan* (Tokyo: Supreme Commander for the Allied Powers. Public Health and Welfare Section, 1949), 128-129.

production from Selman Waksman via the Department of the Army.³⁴⁵ These cultures were transferred to the Japanese government and distributed by the National Institute of health to researchers interested in commercial production.³⁴⁶ The Occupation forces also encouraged Japanese firms to produce streptomycin by: emphasising its therapeutic value, outlining the preparations required for domestic production, and guaranteeing the procurement of any streptomycin produced. But unlike the case of penicillin, Japanese requests for a technical consultant to facilitate the transition from laboratory to industrial production were frustrated.³⁴⁷ As the end of the Occupation neared, the Allied forces transferred more responsibilities to the Japanese. Technology transfers were increasingly arranged between Japanese and foreign firms without mediation by the authorities. But not only was the Occupation regime less interested in enabling Japanese firms to produce streptomycin compared to penicillin, the Japanese had much less clout in negotiating with foreign firms or universities.³⁴⁸

While the Occupation authorities were much less interventionist than in the transfer of penicillin technology, they were still instrumental in the transfer of streptomycin technology to Japan. The Central Streptomycin Research Council, comprised of members of the Occupation forces, Japanese government officials and university professors, was established in late 1949.³⁴⁹ This council helped coordinate technology

³⁴⁵ Stuart G. Smith to Selman A. Waksman, 19 July 1948, Personal Correspondence; Selman A. Waksman to W. Fujita, 15 March 1949, Personal Correspondence, Selman A. Waksman Papers, Box 20, Folder 1, Rutgers University.

³⁴⁶ General Headquarters, Supreme Commander for the Allied Powers, Public Health and Welfare Section, *Public Health and Welfare in Japan* (Tokyo: Supreme Commander for the Allied Powers, Public Health and Welfare Section, 1949), 122-123.

³⁴⁷ *Ibid.*

³⁴⁸ See for example, Yusuke Sumiki to Selman A. Waksman, 28 November 1950 and 14 February 1950, Personal Correspondence, Selman A. Waksman Papers, Box 20, Folder 1, Rutgers University; Selman A. Waksman to Yusuke Sumiki, 4 December 1950, 6 February 1951 and 18 June 1951, Personal Correspondence, Selman A. Waksman Papers, Box 20, Folder 1, Rutgers University.

³⁴⁹ General Headquarters, Supreme Commander for the Allied Powers, Public Health and Welfare Section, *Public Health and Welfare in Japan* (Tokyo: Supreme Commander for the Allied Powers, Public Health and Welfare Section, 1949), 122. This

transfers between firms in Japan and the United States. Indeed, the council orchestrated two contractual agreements made between Merck and Meiji Seika and Kyowa Hakko. In exchange for royalty payments, Merck supplied its patent rights, technical data, strains, and plant design.³⁵⁰ During May and June 1949, the American firm also sent two scientists, Addinall and Colin, to provide technological guidance to the Japanese firms.³⁵¹ Whereas penicillin technology had been transferred to many firms, universities, and research organisations throughout Japan, streptomycin was initially transferred to only a handful of firms.³⁵²

The first commercial batch of streptomycin was made available in July 1951.³⁵³ Production levels grew quickly as Meiji Seika, Kyowa Hakko, the Institute of Science, Shimane Chemical, and Japan Seibutsu Kagaku became its first licensed producers in October 1951.³⁵⁴ As with penicillin, the first manufacturers of streptomycin were new entrants such as confectioners, brewers, and chemical firms rather than the traditional pharmaceutical firms. By placing streptomycin on the ration control list until 1952, the Occupation ensured streptomycin producers of profits. With the aid of supplies, technology transfers, protectionist policies, and distribution routes secured by the government, production levels rose from 1.7 kg in July 1950 to 416.8 kg in

council was comprised of officials from the GHQ's Public Health and Welfare Section, Japan's Ministry of Health, university professors, and hospital directors.

³⁵⁰ General Headquarters, Supreme Commander for the Allied Powers, Public Health and Welfare Section, *Public Health and Welfare in Japan* (Tokyo: Supreme Commander for the Allied Powers, Public Health and Welfare Section, 1950), 81; General Headquarters, Supreme Commander for the Allied Powers, Public Health and Welfare Section, *Public Health and Welfare in Japan* (Tokyo: Supreme Commander for the Allied Powers, Public Health and Welfare Section, 1952), 123-124.

³⁵¹ Yukimasa Yagisawa, "Early History of Antibiotics in Japan," 82.

³⁵² Selman A. Waksman to Russel E. Watson, 12 October 1951, Personal Correspondence, Selman A. Waksman Papers, Box 20, Folder 1, Rutgers University.

³⁵³ Yukimasa Yagisawa, "Early History of Antibiotics in Japan," 82.

³⁵⁴ Russell E. Watson to Selman A. Waksman, 18 October 1951, Personal Correspondence, Selman A. Waksman Papers, Box 20, Folder 1, Rutgers University.

December 1951.³⁵⁵

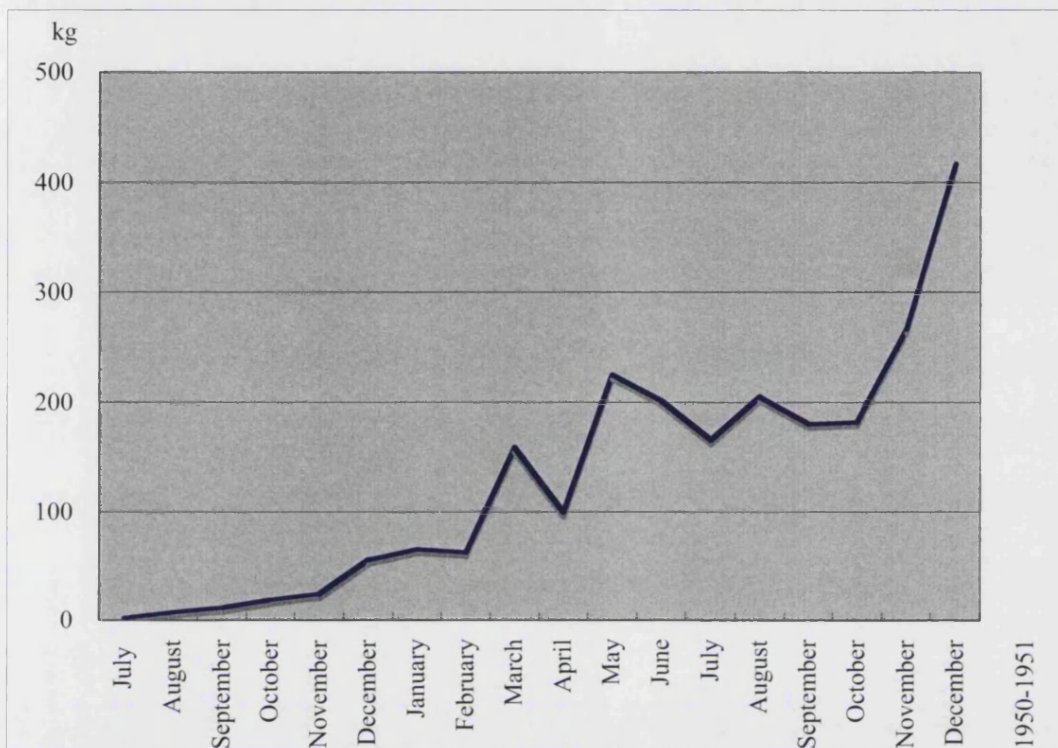


Figure 10. Volume of Streptomycin Production, July 1950-December 1951³⁵⁶

Meiji and Kyowa's streptomycin alliance with Merck marked the first of numerous technology imports of antibiotics during the 1950s. As one of the most novel therapeutic discoveries of the times, antibiotics comprised the majority of the technology imports in the 1950s – although imports ranged from sulfa drugs, antihistamines, to hormonal preparations. Major transfers of antibiotic technologies over the following decade would include Sankyo's alliance with Parke Davis for chloramphenicol in 1951, Banyu's alliance with Bristol Laboratories in 1953 for procaine penicillin and 1955 for tetracycline, and Yamanouchi's alliance with

³⁵⁵ General Headquarters, Supreme Commander for the Allied Powers, Public Health and Welfare Section, *Public Health and Welfare in Japan* (Tokyo: Supreme Commander for the Allied Powers, Public Health and Welfare Section, 1952), 124.

³⁵⁶ *Ibid.*

Boehringer in 1954 for chloramphenicol.³⁵⁷

3.1.7 Summary of the Occupation period

In less than half a decade after 1945, Japan became self-sufficient in antibiotics. Japanese firms managed to develop, produce, and distribute quality antibiotics within an extraordinarily short period of time. This was largely due to the guidance provided by the Occupation authorities. The Occupation forces supplied the necessary raw materials, provided technical assistance in antibiotic production, and stimulated demand by purchasing antibiotics for the use of American forces stationed in Japan. The Occupation authorities also introduced protectionist policies that eliminated foreign competition in Japan. The very existence of Japan's antibiotics sector owes itself to the policies of the Allied forces.

The technology transfers arranged by the American authorities were able to create a modern pharmaceutical industry because Japanese firms were capable of adopting the knowledge provided. Two types of firms produced antibiotics in Occupied Japan: the traditional pharmaceutical firms and new entrants such as confectioners and brewers.³⁵⁸ Neither had been heavily damaged from the bombings during the Second World War. Brewers and confectioners were particularly well positioned to use their idle facilities to produce antibiotics, as there was little demand for non-essential foodstuffs after the War. As such, the rebuilding of Japan's pharmaceutical industry in

³⁵⁷ Yakugyō Keizai Kenkyūjo, *Yakuji Nenkan* [Pharmaceutical Annual] (Osaka: Nihon Yakugyō Shimbunsha, 1957), 59-60.

³⁵⁸ Japan's older, more traditional firms such as Takeda, Daiichi, and Sankyo often produced drugs such as hexyresourcinol, DDT, and sulfa drugs.

the Occupation period was not as difficult as in other sectors that had been devastated by the war. Moreover, the human capital and connections with universities that had survived the war proved crucial in rebuilding the pharmaceutical industry. Towards the end of the Allied Occupation of Japan, technology transfers took place between individual firms, with less intervention by government.

It is also worth noting that the development of the antibiotics sector was also encouraged by the high therapeutic demand in Japan. Infectious diseases such as tuberculosis were rife and the leading causes of death. For many, penicillin and streptomycin offered a life-saving cure.

3.2 Building production capacities and discovering new antibiotics, 1951-1961

Prompted by the discoveries of penicillin and streptomycin, the 1950s evolved into an era of antibiotic discovery. While the government became less interventionist than it had been during the Occupation, it extended a strong degree of protection to enable Japanese firms to catch up with those in the West. As with other sectors of the Japanese economy, strong demand from the American Army during the Korean War (1951-1953) fuelled the growth of the antibiotics sector. Other reasons for growth included enduring therapeutic demand and strong informal networks between government, industry and academia.

But as in the Occupation era, the major reason for the growth of the antibiotics sector in the 1950s lay in the policies made by government. The government's protectionist

policies, for example, to control foreign exchange and restrict foreign capital while promoting process patents allowed for the rapid dissemination of technology – and catch up – among Japanese firms. The government also fostered the development of the antibiotic sector through research funding. This section shows how the government's industrial policies continued to shape the development of Japan's antibiotics sector after the Occupation era.

3.2.1 Japan's first antibiotic discovery

Japanese scientists began to search for new types of antibiotics in the late 1940s. Discovering new antibiotics involved sifting through numerous soil samples to locate bacteria that might produce antibacterial substances. The process was also labour-intensive and required little expensive equipment. As such, antibiotics R&D was suited to a developing economy.

The first Japan-origin antibiotic was discovered by a team of researchers led by Yasuo Koyama and Akio Kurosawa of the Kobayashi Bacteriological Laboratory, which was affiliated with the Lion Pharmaceutical Company.³⁵⁹ Since 1946, researchers at the Kobayashi Bacteriological Laboratory had screened approximately 140 strains of bacteria from soil samples collected across Japan. An effective strain, No 70B, was discovered out of a soil sample from Fukushima Prefecture in 1950. Found effective toward gram-negative bacteria, colistin was valued for its potential application against

³⁵⁹ Katsuichi Matsuo, "Korisuchin oyobi Korisuchin Metan Suruhonsan Natoriumu no Kaihatsu [The Development of Colistin and Colistin Methanesulfonate]," in *Sangyō Gijutsu no Rekishi no Shūtaisei-Taikeika o Okonaukoto ni Yoru Inobēshon Sōshutsu no Kankyō Seibi ni Kansuru Chōsa Kenkyū Hōkokusho* [Investigation and Research Report on the Compilation and Organisation on the History of Industrial Technology to Develop an Environment more Suitable for Innovation], ed. Japan Machinery Federation (Tokyo: Japan Machinery Federation, 2006), 74-80, 242-275.

dysentery and whooping cough, for which no effective therapies existed.³⁶⁰

The commercialisation of colistin was a joint project between academia and industry. Research on manufacturing processes were conducted at the Lion Pharmaceutical, while basic animal tests on toxicity, absorption and excretion were outsourced to several research teams at Tohoku University and Tohoku Pharmaceutical University.³⁶¹ After favourable results were obtained from the laboratory and preliminary tests at local hospitals, clinical trials were carried out in collaboration with Keio University, Tokyo University and Teishin Hospital. In 1951, initial attempts at mass production were conducted at Snow Brand Milk Products.

Colistin was approved for use in 1951. Lion Kinyaku Kogyo (Lion Antibiotic Industry) – a firm established and operated by Kobayashi laboratory scientists – produced colistin, while Tokyo Iyakuhin – a pharmaceutical distributor – marketed the drug.³⁶² Colistin's therapeutic effects were recognised internationally, and it became the first Japan-origin antibiotic to be licensed overseas. While colistin was not approved in the United States until 1962, the drug was approved in Europe via Laboratories Roger Bellon (France) in 1959.³⁶³ For Lion, colistin proved commercially successful, and in 1969, the firm was recognised by the Ministry of

³⁶⁰ Yasuo Koyama, Akio Kurosasa, Atsushi Tsuchiya, and Kinsuke Takakuta, "A New Antibiotic "Colistin" Produced by Spore-forming Soil Bacteria," *Journal of Antibiotics* 3, no. 7 (1950): 457-459.

³⁶¹ One of the scientists, Masahito Fujimasa established Lion Kinyaku specifically for this purpose in 1949.

³⁶² Yakuji Nippōsha, "Colistin," in *Saikin no Shinyaku* [New Drugs in Japan] (Tokyo, Yakuji Nippōsha, 1952), 21-23.

³⁶³ FDA/Center for Drug Evaluation and Research, "Label and Approval History: Coly-mycin S," *Drugs@FDA*, FDA Approved Drug Products,

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist (accessed 8 May 2008). Seiyaku Kigyō Kondankai [Council of Pharmaceutical Firms], *Seiyaku Kigyō no Genjō to Kōsatsu* [An Evaluation of the Current Status of Pharmaceutical Firms] (Tokyo: Seiyaku Kigyō Kondankai, 1965).

International Trade and Industry (MITI) for its contribution toward Japanese exports.³⁶⁴

3.2.2 Import substitution and growth

While Japanese scientists began to discover and develop antibiotics, the Japanese antibiotics market in the 1950s was mostly comprised of antibiotics imported in finished form. In the second half of the decade, these were replaced by domestically-produced antibiotics based on imported technology. As in the Occupation era, the major players in the early 1950s remained the non-traditional pharmaceutical firms equipped with fermentation facilities. Many of these were confectioners and brewers who had been unable to maintain their existing business in non-essential goods under destitute post-war conditions.

But the traditional pharmaceutical firms – wholesalers of Western medicines – began to regain their footing in the market in the mid 1950s, as they began to produce antibiotics under foreign licenses. Sankyo, for example, shifted its focus from the production and sale of anthelmintics, DDT and BHC to the import, production and sale of antibiotics. By 1960, antibiotics comprised almost a quarter of Sankyo's total pharmaceutical sales of 18.1 billion yen, mainly via licenses from Parke Davis, Løvens Kemiske, Sando, and Squibb.³⁶⁵ Shionogi also formed alliances with Eli Lilly to launch antibiotics such as erythromycin. By 1960, antibiotics comprised 12.7% of

³⁶⁴ Katsuichi Matsuo, "Korisuchin oyobi Korisuchin Metan Suruhon san Natoriumu no Kaihatsu [The Development of Colistin and Colistin Methanesulfonate]," 74.

³⁶⁵ Sankyo Co., *Yūka Shōken Hōkokusho* [Annual Securities Report] (Tokyo: Ōkurashō Insatsukyoku, 1960).

production at Shionogi.³⁶⁶ Even Takeda, primarily a vitamins producer, launched antibiotics such as tetracycline and kanamycin in 1956 and 1959, respectively.³⁶⁷ Many of the antibiotics marketed in Japan originated from large American firms such as Parke Davis, Bristol, Squibb, Beecham, Pfizer, Upjohn and Eli Lilly.

In the 1950s, Japan's leading pharmaceutical firms from the pre-war era regained their dominance in the antibiotics market through these imports of technology.³⁶⁸ Larger firms had greater capital to borrow technology from foreign firms. In addition, Japan's larger, traditional pharmaceutical manufacturers began to form vertical *keiretsu* groupings with wholesalers in the 1950s. These alliances helped the traditional pharmaceutical firms to strengthen their marketing capacities and deter the entry of new firms.

³⁶⁶ Shionogi & Co., *Yūka Shōken Hōkokusho* [Annual Securities Report] (Tokyo: Ōkurashō Insatsukyoku, 1960).

³⁶⁷ Takeda Pharmaceutical Co., *Yūka Shōken Hōkokusho* [Annual Securities Report] (Tokyo: Ōkurashō Insatsukyoku, 1960).

³⁶⁸ Minoru Aizawa and United Nations Industrial Development Organization, *Review of the Development of Antibiotic Industry in Selected Countries: Technical Report: Antibiotic Industry in Japan, History and Development* (Vienna: United Nations Industrial Development Organization, 1985), 74.

Product	Length of Contract	Companies
Procaine penicillin	1953 (15 years)	Banyu-Bristol Laboratories
Streptomycin	1951 (15 years)	Merck-Kyowa Hakko, Meiji
Chloramphenicol	1951 (15 years)	Sankyo-Parke Davis
	1954 (10 years)	Yamanouchi-Boehringer
Chlortetracycline	1953 (15 years)	Japan Lederle- American Cyanamid
Oxytetracycline	1953 (15 years)	Taito Pfizer-Pfizer
Tetracycline	1953 (15 years)	Japan Lederle- American Cyanamid
	1954 (15 years)	Taito Pfizer-Pfizer
	1955 (14 years 4 months)	Banyu-Bristol Laboratories
Penicillin Aminoethyl	1954 (5 years)	Sankyo-Løvens Kemiske
Dypenicillin	1953 (15 years)	Banyu-Wyeth International

Table 3 Significant Imports of Antibiotic Technology after the Occupation³⁶⁹

Indeed, the government's import substitution strategies were central to the development of Japan's antibiotics sector in the 1950s. Japanese firms imported technologies as a rapid, efficient, and cost-effective means to catch up with more advanced countries. In fact, technology imports of antibiotics far outweighed any other therapeutic sector, accounting for 21 of the 70 technology imports for pharmaceuticals between 1951 and 1960.³⁷⁰ By restricting imports to products that remained unavailable in Japan or production processes that remained undeveloped in Japan, Japanese firms were protected from foreign competition. As a process patent regime, the government lowered barriers to entry and promoted the diffusion of new

³⁶⁹ Yakugyō Keizai Kenkyūjo, *Yakuji Nenkan* [Pharmaceutical Annual] (Osaka: Nihon Yakugyō Shimbunsha, 1957), 59-60.

³⁷⁰ Yakugyō Keizai Kenkyūjo, *Yakuji Nenkan* [Pharmaceutical Annual] (Osaka: Nihon Yakugyō Shimbunsha, 1961), 123.

technologies across many firms.

Many Japanese firms took advantage of this environment to develop antibiotics through the reverse engineering of foreign products. While firms such as Roche and Taito-Pfizer had established operations in Japan, the few foreign firms in Japan did not pose a threat to domestic firms.³⁷¹ This was because foreign firms were few in number, affiliated with Japanese firms, and had yet to establish their own distribution routes. It was true that the government's protectionist measures encouraged the growth of an imitation – rather than innovation – industry during the 1950s, and the market began to bear signs of over-competition. Yet the government's import-substitution policies in the 1950s were crucial to offering Japanese firms a chance to catch up with the West.

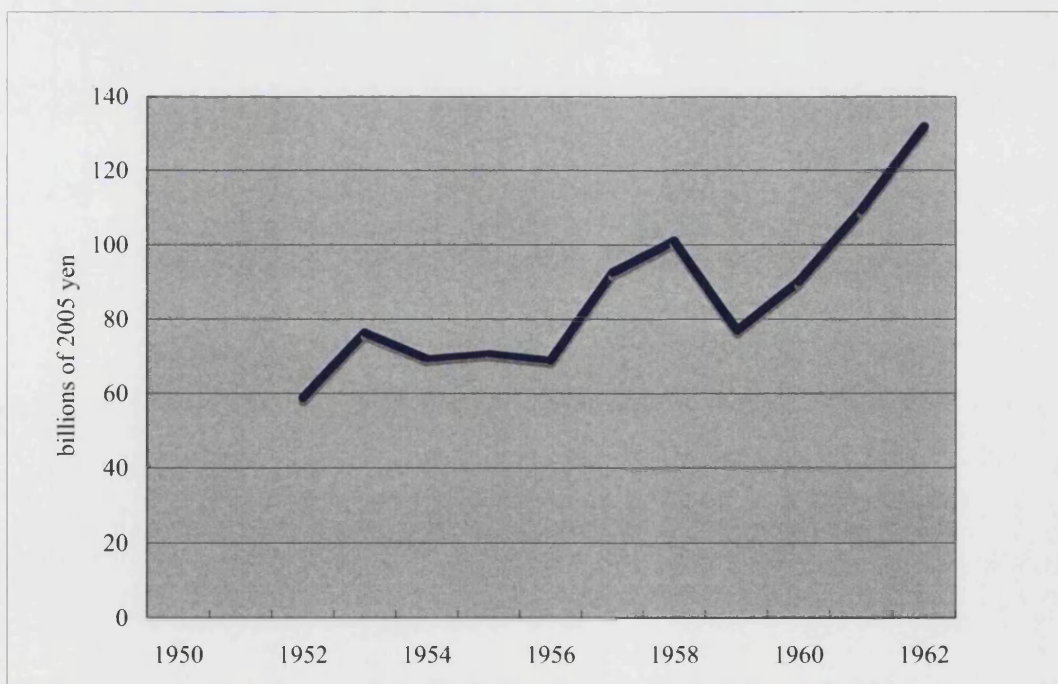


Figure 11. Value of Antibiotic Production, 1952-1962³⁷²

³⁷¹ Ibid, 124-145.

³⁷² Yakugyō Keizai Kenkyūjo, *Yakuji Nenkan* [Pharmaceutical Annual] (Osaka: Nihon Yakugyō Shimbunsha, 1957), 289; Ministry of Health and Welfare, *Yakuji Kogyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical

As Japanese firms imported new technologies and established new production plants, the antibiotics sector grew steadily over the 1950s. Japan's rapid economic growth since the 1950s also had a strong impact on the growth of industry, as production levels correlated closely with macroeconomic performance. For example, while production grew rapidly during the Jinmu and Iwato economic booms from 1955 to 1957, and from 1959 to 1961, respectively, production fell during the recession between 1957 and 1959. In the mean time, the importance of the antibiotics to Japan's pharmaceutical industry lessened, as more firms diversified out of antibiotics. Antibiotics were the leading therapy in 1952, comprising almost 16% of total production. A decade later, however, antibiotics comprised less than 10% of total production, and vitamins overtook antibiotics as the leading therapeutic sector between 1958 and 1969. While its market share relative to Japan's overall pharmaceutical industry may have declined, the antibiotics sector experienced stable growth over the 1950s.³⁷³

Industry] (Tokyo: Yakugyō Keizai Kenkyūjo, 1953-1967); Ministry of Health and Welfare, *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Yakugyō Keizai Kenkyūjo, 1968-2000).

³⁷³ Ibid.

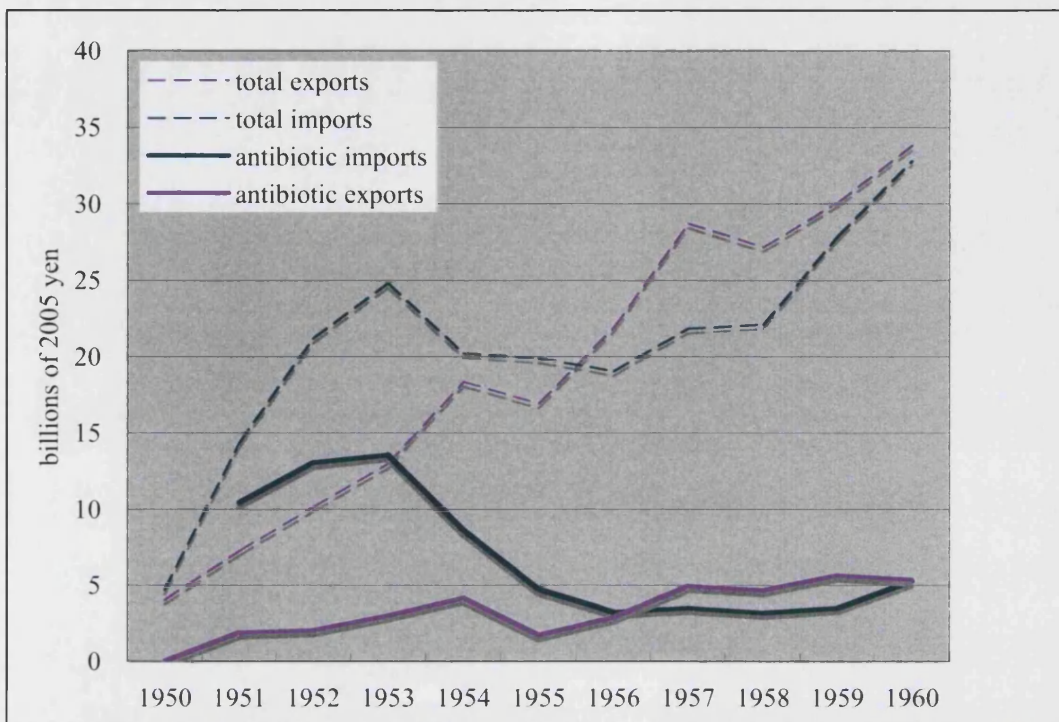


Figure 12. Value of Antibiotic Trade, 1950-1960³⁷⁴

Japan's imports of antibiotics declined during the 1950s both as special procurements by the US Army came to an end, and as imports were replaced by antibiotics produced in Japan. Antibiotic trade also declined in significance relative to total pharmaceutical trade.³⁷⁵ While antibiotics had comprised almost half of total pharmaceutical trade at the beginning of the decade, figures dropped to only 6% by the end of the decade. Antibiotics had comprised a significant proportion of both imports and exports of total pharmaceuticals in the early 1950s. In 1951, imports and exports of antibiotics comprised 72.7% and 25.8% of imports and exports of total pharmaceuticals, respectively.³⁷⁶ But by the end of the decade, imports and exports of antibiotics had

³⁷⁴ Yakugyō Keizai Kenkyūjo, *Yakuji Nenkan* [Pharmaceutical Annual] (Osaka: Nihon Yakugyō Shimbunsha, 1957), 292-293, 300-301; Yakugyō Keizai Kenkyūjo, *Yakuji Nenkan* [Pharmaceutical Annual] (Osaka: Nihon Yakugyō Shimbunsha, 1961), 42.

³⁷⁵ Trade in this context refers to the sum of imports and exports.

³⁷⁶ Yakugyō Keizai Kenkyūjo, *Yakuji Nenkan* [Pharmaceutical Annual] (Osaka: Nihon Yakugyō Shimbunsha, 1957), 292-293, 300-301.

dropped to 8.0% and 4.8% of total pharmaceuticals, respectively.³⁷⁷ Antibiotic exports did increase as Japanese firms became capable of producing antibiotics, particularly as leading firms began to recapture some of the South East and East Asian markets that it had lost during the War.³⁷⁸ But as the rise of exports was much smaller than the fall of imports, total trade in antibiotics declined over the 1950s.³⁷⁹

In terms of trading partners, Japan exported older antibiotics to the developing world while the country imported newer antibiotics from the developed world. In the late 1950s, antibiotics comprised approximately 17% of pharmaceutical exports and 15% of pharmaceutical imports in Japan.³⁸⁰ Japan exported older antibiotics such as streptomycin and penicillin to India, Taiwan, Okinawa, and Italy, while Japan imported newer antibiotics such as chloramphenicol and viomycin, from the United States, the United Kingdom and Germany.³⁸¹

3.2.3 Kanamycin and internationalisation

As Japanese firms acquired the capacity to produce leading antibiotics, and competed to develop better drugs, more firms attempted to discover their own original drugs. Between 1950 and 1960, Japanese firms discovered five of the 22 antibiotics (23%) marketed in Japan. These included colistin by Lion Kinyaku in 1951, sarkomycin by Meiji Seika in 1954, kitasamycin by Toyo Jozo in 1956, kanamycin by Meiji Seika in

³⁷⁷ Yakūgyō Keizai Kenkyūjo, *Yakuji Nenkan* [Pharmaceutical Annual] (Osaka: Nihon Yakūgyō Shimbunsha, 1961), 37-38.

³⁷⁸ *Ibid.*, 44-45.

³⁷⁹ *Ibid.*, 42.

³⁸⁰ *Ibid.*, 37-38.

³⁸¹ *Ibid.*, 44-45.

1958, and mitomycin by Kyowa Hakko in 1959.³⁸² Four of the five antibiotics originated out of small-scale confectionery or brewery firms, reflecting the importance of fermentation capacities and non-traditional pharmaceutical firms in the development of Japan's antibiotics sector in the 1950s.

Government funding of antibiotic R&D played an important role in the discovery and development of Japanese antibiotics. Since 1946, the Ministry of Health and the Ministry of Education had supported research on antibiotics. The Ministry of Health, for example, provided funding through the Japan Antibiotic Research Association, which not only supported academic research but also promoted its dissemination through the publication of the *Journal of Antibiotics* – which remains the leading journal on antibiotic research in Japan to date.³⁸³ Partly because government funding was given to academic institutions, antibiotic discoveries in Japan evolved out of the academic laboratory. While a few industrial laboratories were established by firms such as Takeda, Fujisawa, and Daiichi in the 1950s, industrial laboratories did not take root in most of Japanese pharmaceutical firms until the 1960s.³⁸⁴ Where they did exist, industrial research concentrated primarily on process innovation rather than product

³⁸² Minoru Aizawa and United Nations Industrial Development Organization, *Review of the Development of Antibiotic Industry in Selected Countries: Technical Report: Antibiotic Industry in Japan, History and Development*, 74. Two of the five are actually anticancer antibiotics sarkomycin and mitomycin), which reflect the expansion of antibiotic science toward cancer therapy. It is worth noting discrepancies between discovery figures reported by the United Nations, the Science and Technology Agency (STA), and the JARA. For example, the UN reports 5 Japan-origin discoveries over the 50s while the STA and the JARA report 9 and 12, respectively. This is likely due to differences in methods of calculation, and the criteria for evaluating the significance for a given discovery. STA and JARA figures also suggest the growing importance of Japan-origin discoveries. For example, the STA reports that 25 antibiotic discoveries were made between 1950 and 1960, out of which 9 (36%) were Japanese, 12 (48%) American, 1 (4%) British, French, Belgian, and Swiss. Yagisawa's JARA figures suggest that half of the 12 Japan origin antibiotics between 1950 and 1960 (inclusive) were available overseas. While Japan-origin discoveries gained greater importance in the domestic market, antibiotics with smaller margins of innovation may have been recognised as new therapeutic substances in Japan compared to other industrialised countries.

³⁸³ See Japan Antibiotics Research Association, "Honkai no Gaiyō [About Us]," <http://www.antibiotics.or.jp/jara/news/jara.htm> (accessed 28 April 2008). See also, Yukimasa Yagisawa, "Early History of Antibiotics in Japan," 88.

³⁸⁴ This is documented in various company histories. See for example, Takeda Pharmaceutical Co., *Takeda 200-nen* [200 Years of Takeda] (Osaka: Takeda Pharmaceutical Co., 1984); Fujisawa Pharmaceutical Co., *Fujisawa 100-nenshi* [Fujisawa Pharmaceutical, a 100 Year History] (Osaka: Fujisawa Pharmaceutical Co., 1995); and Daiichi Pharmaceutical Co., *Daiichi Seiyaku 80-nenshi* [Daiichi Pharmaceutical, a 80 Year History] (Tokyo: Daiichi Pharmaceutical Co., 1998).

innovation. Government funding for antibiotic R&D provided the impetus for the discovery of antibiotics through academic laboratories in Japan.

The rise of antibiotic resistance also began to encourage firms to invest in R&D. Before the 1950s, the purpose of antibiotic R&D was to locate any naturally occurring substance effective toward bacterial infections. But the rise of antibiotic resistance and realisation of significant side effects over the decade renewed demand for antibiotics where similar therapies were already available.

One of the major antibiotic discoveries in the mid 1950s was kanamycin. Kanamycin had been discovered by a scientific team led by one of Japan's leading scientists, Hamao Umezawa, who had led antibiotics research in Japan since World War II.³⁸⁵ Since 1952, Umezawa had developed a systematic approach to antibiotic R&D, and studied antibiotic agents that: derived from actinomycetes; halted bacterial growth; were water-soluble; basic; and of low toxicity.³⁸⁶

Umezawa developed kanamycin working in collaboration with Meiji Seika, a firm with which he had been connected since the Occupation era. Meiji Seika had been established in 1916 as one of the first Western-style confectionery firms in Japan. In the pre-war era, the firm developed its confectionery business in caramels and biscuits as it branched out into the production of canned foods. Faced with scarce food supplies

³⁸⁵ Hamao Umezawa was one of the central scientific researchers in Japan's wartime penicillin project. See for example, Katsuhiko Inagaki, *Penishirin Iinkai no Kotodomo* [Notes on the Penicillin Committee], 16 November 1944, Naito Museum of Pharmaceutical Science and Industry, Kagamihara, Japan.

³⁸⁶ Hamao Umezawa, "Kōseibusshitsu o Motomete (2): Kanamaishin no Hakken [Searching for Antibiotics (2): The Discovery of Kanamycin]," *Shokun* 12, no.2 (1980): 294-305.

and a limited market for sweets after the War, however, Meiji Seika saw an urgent need to diversify its operations. The firm entered the antibiotics sector in 1946 as a venture that would build upon its fermentation capacities and where profits were ensured through the government's procurements of penicillin.³⁸⁷ By 1958, Meiji Seika had become one of the leading antibiotics makers in Japan, and one of 13 firms to survive the intense competition in the penicillin market.³⁸⁸ Meiji Seika's involvement in developing kanamycin was a natural extension of its business in antibiotics.³⁸⁹

Much like colistin, kanamycin's development was a joint project between academia and industry, both within and beyond Japan. Basic research, for example, was carried out at Tokyo University, Meiji Seika, and Bristol Laboratories, while Merck joined during the clinical testing phase. While the scale of laboratory tests was small by today's standards, they had become more sophisticated since colistin. After test-production at Meiji Seika's Kawasaki plant – a facility affiliated with Umezawa's research efforts since the penicillin era – clinical tests on patients were led by Tokyo University professor Tokuji Ichikawa, who reported favourable results in tuberculosis, dysentery, and other infectious diseases.³⁹⁰ As in other substances, however, the crystal structure was identified much later, in 1967.³⁹¹

³⁸⁷ Takeshi Nakagawa, interview by Shōzō Tsunabuchi in "Meiji Seika: Ishokudōgen Baio o Mezasu [Meiji Seika Aims to Develop Biotechnology Business]," *Will* (December 1982): 48-51.

³⁸⁸ Nihon Penishirin Kyōkai [Japan Penicillin Association], *Penishirin no Ayumi: 1946-1961* [The History of Penicillin: 1946-1961], 170.

³⁸⁹ For a history of Meiji Seika, see Meiji Seika Kaisha, Ltd., *Meiji Seika no Ayumi: Kaukide Tsukutte 60-nen* [A History of Meiji Seika: Selling What We Want to Buy for 60 Years] (Tokyo: Meiji Seika Kaisha, Ltd., 1977); Meiji Seika Kaisha, Ltd., *Meiji Seika no Ayumi: Sōgyō kara 70-nen* [A History of Meiji Seika: 70 Years since Establishment] (Tokyo: Meiji Seika Kaisha, Ltd., 1987).

³⁹⁰ Hamao Umezawa, "Kanamycin," in *Saikin no Shinyaku* [New Drugs in Japan] (Tokyo, Yakuji Nippōsha, 1959), 13-17.

³⁹¹ The synthetic production of antibiotics usually occurred much later after discovery, after the chemical structure was identified. See K. Maeda and H. Umezawa, "The Crystal Structure of Kanamycin," *Tetrahedron Letters* 15 (1968): 1875-1879.

Kanamycin's discovery, while inexpensive, had been extremely labour intensive – and required the cooperation of scientists from all over Japan. The substance was discovered in early 1955 out of a strain of actinomycetes (K-2J) found in a soil sample from Nagano prefecture. Regional collaborations in antibiotic research was essential to this process, as Umezawa's scientific team laboriously examined between 50 and 100 strains each week. These strains were provided by schools, community health centres, and regional offices throughout Japan, who collected and sent soil samples to the National Institute of Health – where Umezawa was based. After delivery to the institute, these strains were cultivated and examined for any antibacterial substances produced. In 1955, scientists were able to identify kanamycin and its effective range of bacteria, as well as isolate the substance.³⁹²

Kanamycin was valued for its low toxicity and its effectiveness against strains of bacteria that had become resistant to earlier antibiotics. In Japan, for example, kanamycin helped to contain dysentery and tuberculosis, which had increasingly become resistant to existing antibiotics.³⁹³ Kanamycin also proved effective in relatively low doses, and was found suitable to mass production in tank cultures.³⁹⁴

Kanamycin was launched by Meiji Seika in May 1958.³⁹⁵ While discovered a few years later than colistin, kanamycin became a more successful drug because of its

³⁹² Hamao Umezawa, Masahiro Ueda, Kenji Maeda, Koki Yagishita, Shinichi Kondo, Yoshiro Okami, Ryozo Itahara, Yasuke Osato, Kazuo Nitta, and Tomio Takeuchi, "Production and Isolation of a New Antibiotic, Kanamycin," *Journal of Antibiotics Series A* 10 (September 1957): 181-188.

³⁹³ Hamao Umezawa, "Kōsei Busshitsu o Motomete (2) [Searching for Antibiotics (2)]," 301.

³⁹⁴ Ibid., and Hamao Umezawa, "Kanamycin," in *Saikin no Shinyaku* [New Drugs in Japan] (Tokyo, Yakuji Nippōsha, 1959), 13-17. Hamao Umezawa, "Kanamycin: Its Discovery," *Annals of the New York Academy of Sciences* 76, no. 2 (1958): 20-26.

³⁹⁵ Yakuji Nippōsha, *Saikin no Shinyaku* [New Drugs in Japan] (Tokyo, Yakuji Nippōsha, 1959), 22.

ability to treat tuberculosis and ease of use.³⁹⁶ For Meiji Seika, kanamycin proved to be a tremendously successful drug that became one of Japan's top antibiotics exports and remains in use to date.³⁹⁷ The experience of Meiji Seika demonstrates that the capacity among Japanese firms to develop new antibiotics came to be recognised abroad in the 1950s. The presentation of kanamycin at the New York Academy of Science on 10-11 July 1958 was widely documented in Western publications.³⁹⁸

Kanamycin also showed how Japan's process patent regime penalised innovative drug discoveries. Process patents allowed firms to reverse engineer drugs and did not protect the discoveries of innovative firms. Meiji Seika had risked 200 million yen to pursue R&D of kanamycin at a time when the firm had a capital of 840 million yen.³⁹⁹ Despite its successful discovery, Meiji Seika faced an environment that did not generously reward or protect innovation. After kanamycin's approval in April 1958, Meiji Seika had a monopoly in the Japanese market for less than five months. Banyu and Yamanouchi launched their own versions of kanamycin on 15 September 1958, followed by Tanabe three days later.⁴⁰⁰ For many firms, the lack of government protection or support for product innovation undermined incentives to discover new drugs.

³⁹⁶ See for example, Kōichi Nakazawa, "Kekkaku no Kagaku Ryōho to Kanamaishin [Chemotherapeutic Approaches to Tuberculosis and Kanamycin]," *Kenkō Hoken* 14 (November 1960): 46-48. Yasuhisa Chiba, "Kanamaishin to wa [What is Kanamycin?]" *Kyōsai Shinpō* 2 (March 1961): 54-57.

³⁹⁷ Meiji Seika Kaisha, Ltd., *Meiji Seika no Ayumi: Sōgyō kara 80-nen* [The History of Meiji Seika: 80 Years from Establishment] (Tokyo: Meiji Seika Kaisha, Ltd., 1997), 20. See for example, Meiji Seika Kaisha, Ltd., *Yūka Shōken Hōkokusho* [Annual Securities Report] (Tokyo: Ōkurashō Insatsukyoku, 1960). By fiscal 1960, Meiji Seika derived 20% of sales, or 16.2 yen (in 2005yen) from pharmaceuticals, with most of its sales from penicillin, streptomycin, and kanamycin.

³⁹⁸ See for example, "From a Japanese Garden," *Time Magazine*, 21 July 1958. See also, Hamao Umezawa, "Kanamycin: Its Discovery," *Annals of the New York Academy of Sciences* 76, no.2 (1958): 20-26. This article documents Umezawa's speech on "The Basic and Clinical Research of the New Antibiotic Kanamycin" at a conference, held jointly by the New York Academy of Sciences and Bristol Laboratories.

³⁹⁹ Takeshi Nakagawa, interview by Shōzō Tsunabuchi in "Meiji Seika: Ishokudōgen Baio o Mezasu [Meiji Seika Aims to Develop Biotechnology Business]," 48. These are nominal values. In 2005 values, Meiji Seika had risked 1.09 billion yen to pursue R&D of kanamycin at a time when the firm had a capital of 4.57 billion yen.

⁴⁰⁰ Yakuji Nippōsha, *Saikin no Shiriyaku* [New Drugs in Japan] (Tokyo, Yakuji Nippōsha, 1959), 22.

3.2.4 Summary of the period between 1950 to 1961

As in the Occupation period, the major reason for the development of the antibiotics sector between 1950 and 1961 was government policies. As foreign firms were prevented from entering the Japanese market, Japanese antibiotics makers were protected from foreign competition. In addition, Japan's process patent regime encouraged firms to reverse engineer drugs discovered abroad, find another method to manufacture the drug, and launch this drug as a "new" product in Japan. This discouraged investments in R&D.⁴⁰¹ Still, some Japanese drug companies did begin to invest in antibiotic R&D and discover new therapies that were licensed overseas. The search for new antibiotics involved little equipment and was a labour-intensive and serendipitous process – and was a form of pharmaceutical R&D conducive to firms in a developing economy. The discovery of antibiotics was also facilitated by the collaborative links between academia, government and industry.

But unlike the United States, for example, where most research had been transferred to pharmaceutical firms by 1950, antibiotic research in Japan remained in universities and public research institutes.⁴⁰² Antibiotic research in the industrial laboratory would gradually take root over the following decades, as Japanese firms strengthened their capacity to produce and discover global antibiotics.⁴⁰³

⁴⁰¹ Nihon Yakushi Gakkai, *Nihon Iyakuin Sangyōshi* [The History of the Japanese Pharmaceutical Industry], 110.

⁴⁰² Hamao Umezawa, "Kōsei Busshitsu o Motomete (2) [Searching for Antibiotics (2)]," 297.

⁴⁰³ This is evident in the various drug development processes. See Yakuji Nippōsha, *Saikin no Shinyaku* [New Drugs in Japan] (Tokyo: Yakuji Nippōsha, 1950-2006).

3.3 Nurturing industry through process innovations and domestic demand, 1961-1975

Between 1961 and 1975, Japan's antibiotics sector saw a phenomenal expansion in terms of production, trade, and R&D. In 1961, antibiotics accounted for 10% of total drug production and this increased to more than 20% by 1975.⁴⁰⁴ Antibiotics were, in fact, the largest therapeutic sector in Japan between 1970 and 1988.⁴⁰⁵ While the dominance of antibiotics in the pharmaceutical market was echoed in most other developed countries around the globe, the rate and extent of expansion in Japan was distinct.⁴⁰⁶ Confectioners and brewers such as Meiji Seika and Toyo Jozo continued to compete alongside the more traditional pharmaceutical firms such as Takeda, Yamanouchi and Fujisawa into the mid 1970s.⁴⁰⁷

3.3.1 Building a domestically oriented antibiotics sector

Japan's antibiotics sector began to evolve as a domestic oriented industry from the 1960s. This was mainly because the government introduced universal health care, created distinct product standards, allowed physicians to dispense medicines, and set modest criteria for drug approval. In 1961, the government effectively underwrote demand for prescription pharmaceuticals when it launched universal health care. When the government established new product standards for Japanese drugs in 1967, it essentially excluded foreign drugs from the domestic market. Japan's antibiotics

⁴⁰⁴ Ministry of Health and Welfare, *Yakuji Kogyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Yakugyo Keizai Kenkyūjo, 1953-1967); Ministry of Health and Welfare, *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Yakugyō Keizai Kenkyūjo, 1968-2000).

⁴⁰⁵ Ibid.

⁴⁰⁶ See Organisation for Economic Co-operation and Development, *Pharmaceuticals: Gaps in Technology*, 32, 69; and Yakugyō Keizai Kenkyūjo, *Yakugyō Keizai Nenkan* [Pharmaceutical Economics Annual] (Tokyo: Yakuji Nippōsha, 1967), 132-299.

⁴⁰⁷ Minoru Aizawa and United Nations Industrial Development Organization, *Review of the Development of Antibiotic Industry in Selected Countries: Technical Report: Antibiotic Industry in Japan, History and Development*, 74-75.

sector began to expand rapidly within this highly protected environment – where the government also sponsored demand.

In addition, Japanese physicians both prescribed and dispensed antibiotics.⁴⁰⁸ They bargained down the price at which they purchased their drugs from wholesalers, and profited from the difference between the official drug prices at which they resold their drugs to patients. Japanese physicians were particularly incentivised to over-prescribe antibiotics because official drug prices were high, and they could negotiate a steeper discount for wholesale prices. In addition, antibiotics could be prescribed to a large patient population. Infections were common complaints, antibiotics had relatively few side effects, and as a short-term therapy, the total cost of medicines was much lower than in chronic diseases. Furthermore, in 1967, the government established modest criteria for a substance to qualify as a new drug in Japan. The Japanese antibiotics sector expanded rapidly in an environment with strong demand for high priced antibiotics, and where incremental innovations easily qualified as new drugs. At the same time, however, the antibiotics sector became heavily domestically oriented, as both the demand structure and drug approval criteria were specific only to Japan.

3.3.2 A shift in antibiotic R&D

There was a major transition in antibiotic R&D over the 1960s, in terms of both the approaches used and the ability demonstrated by Japanese firms to discover new antibiotics. Antibiotics were no longer discovered out of serendipity from naturally

⁴⁰⁸ Michael Reich, “Why the Japanese Don’t Export More Pharmaceuticals: Health Policy as Industrial Policy,” 135.

occurring substances, but from semisynthetic compounds where new drugs were developed from compounds of known chemical structure and potential therapeutic value. The quality of antibiotics also improved during this time, as the newer drugs offered greater potency, wider antibacterial spectra, and lower toxicity. R&D methods also became more sophisticated, and entailed greater risk, cost, scale, and complexity.⁴⁰⁹

It is true that many Japanese firms continued to produce new antibiotics based on foreign technologies in a highly protected environment. After all, new discoveries were also relatively easy to commercialise using existing networks of collaboration maintained by pharmaceutical firms.⁴¹⁰ Faced with numerous incentives to launch new antibiotics and supported by collaborations with university scientists, many Japanese drug makers were also content to build upon past successes to bolster the growth of the Japanese antibiotics market.⁴¹¹

But Japanese firms proved increasingly successful in the discovery and launch of globally competitive antibiotics as they acquired the capacity to pursue advanced methods of R&D. As in other Japanese industries, many firms established central research laboratories in the 1960s. The government's new quality standards – such as GCP (Good Clinical Practice) and GPMSP (Good Post-Marketing Surveillance

⁴⁰⁹ See for example, Yukimasa Yagisawa, "Shinbunya o Kirihiraita Kōseibusshitsu [A New Field Created by Antibiotics]," *Iyaku Jānaru* 9 (February 1970): 20-23.

⁴¹⁰ The importance of collaborative networks in enabling pharmaceutical innovation has been discussed, for example, in Louis Galambos and Jane Eliot Sewell, *Networks of Innovation: Vaccine Development at Merck, Sharp & Dohme, and Mulford, 1895-1995*.

⁴¹¹ Yukimasa Yagisawa, "Atarashī Kōseibusshitsu no Dōkō [Trends in New Antibiotics]," *Iyaku Jānaru* 8 (February 1969): 31-34.

Practice) – introduced during this time, also helped Japanese firms strengthen their development capacities.⁴¹² Indeed, a total of 22 Japan-origin antibiotics, or 22% of post-war discoveries, were discovered between 1961 and 1975.⁴¹³ Of these, approximately a third were eventually distributed worldwide. These transitions in antibiotic R&D in Japan are well illustrated in the experiences at Yamanouchi and Fujisawa.

Yamanouchi

In 1970, Yamanouchi Pharmaceutical launched a new antibiotic that was recognised around the world. The new antibiotic, josamycin, was a drug that not only cemented the firm's strong position in the domestic market, but also prompted its internationalisation.

Founded by Kenji Yamanouchi in 1923, Yamanouchi prospered in the pre-war era as Japan's first manufacturer of sulfa drugs. By the 1940s, the firm had captured 30% of Japan's sulfa drug market.⁴¹⁴ In the years after the war, Yamanouchi diversified into a variety of medicines, including anthelmintics, penicillin and diuretics. Similar to many Japanese firms, Yamanouchi licensed-in antibiotic technologies, such as chloramphenicol and trichomycin, to develop its antibiotics business in the 1950s.⁴¹⁵

⁴¹² GCP refers to quality standards for pharmaceutical R&D in the laboratory. GPMSP refers to quality standards to monitor drugs in a clinical setting after marketing.

⁴¹³ Joichi Kumazawa and Morimasa Yagisawa, "The History of Antibiotics: The Japanese Story," 125-133; Morimasa Yagisawa, unpublished document, "Antibiotics, Chemotherapeutics and Other Microbial Products Originated from Japan," sent to author. This includes 2 antifungal antibiotics, 2 bioactive microbial substances and 4 anticancer antibiotics.

⁴¹⁴ Yamanouchi Pharmaceutical Co., Ltd., *Yūka Shōken Hōkokusho* [Annual Securities Report] (Tokyo: Ōkurashō Insatsukyoku, 1950), 8.

⁴¹⁵ Yamanouchi Pharmaceutical Co., Ltd., *Yūka Shōken Hōkokusho* [Annual Securities Report] (Tokyo: Ōkurashō Insatsukyoku, 1961), 7.

But unlike many Japanese firms, antibiotics did not constitute the pillar of Yamanouchi's operations. In 1960, Yamanouchi still derived over a quarter of its sales from sulfa drugs, followed by antibiotics and diuretics, which comprised 18% and 11% of sales, respectively. The proportion of antibiotic sales did not change markedly over the 1960s, although antibiotics did begin contribute substantially to the firm's business. In fact, antibiotic sales grew from 3.78 billion yen in 1960 to 15.2 billion yen in 1970.⁴¹⁶

The search for Yamanouchi's new antibiotic evolved amidst market conditions highly favourable to antibiotics. Josamycin was discovered in 1967 from a soil sample in Kōchi Prefecture, out of numerous samples collected from Yamanouchi offices across Japan.⁴¹⁷ The drug was developed by Takashi Osono at Yamanouchi's central research laboratory in collaboration with Yoshiro Okami and Hamao Umezawa at the Institute of Microbial Chemistry. Clinical trials were outsourced to the School of Medicine at Juntendo University.⁴¹⁸ While the drug's development was much less rigorous compared to contemporary standards, the government's new guidelines had prompted firms to modernise facilities, revise procedures, and write much more detailed reports compared to previous decades. Indeed, josamycin developed a better profile than its predecessors and was valued for lower toxicity levels, better absorption levels, and improved efficacy for a wider range of infections – including several strains of

⁴¹⁶ In nominal terms, Yamanouchi's antibiotic sales grew from 722 million yen to 5.1 billion yen between 1960 and 1970. Ibid, 17. Yamanouchi Pharmaceutical Co., Ltd., *Yūka Shōken Hōkokusho* [Annual Securities Report] (Tokyo: Ōkurashō Insatsukyoku, 1971), 18. The firm's history has been documented in Yamanouchi Pharmaceutical Co., *Yamanouchi Seiyaku 50-nenshi* [A 50 Year History of Yamanouchi Pharmaceutical Co.] (Tokyo, Yamanouchi Pharmaceutical Co., 1975).

⁴¹⁷ Yamanouchi Pharmaceutical Co., *Yamanouchi Seiyaku 50-nenshi* [A 50 Year History of Yamanouchi Pharmaceutical Co.] (Tokyo, Yamanouchi Pharmaceutical Co., 1975), 221.

⁴¹⁸ Yakuji Nippōsha "Josamycin," in *Saikin no Shinyaku* [New Drugs in Japan] (Tokyo: Yakuji Nippōsha, 1970), 86-87.

bacteria found to be resistant toward existing antibiotics.⁴¹⁹

Josamycin recorded strong domestic sales following its launch in February 1970.⁴²⁰ For Yamanouchi, josamycin also prompted the firm's expansion into overseas markets, as the drug gained patent approval for countries ranging from the United States, Britain, West Germany to Switzerland.⁴²¹ The drug's first global launch was through EI du Pont Nemours in 1974.⁴²² For Yamanouchi, the drug was a success, and contributed to its increase in antibiotic sales from 15.2 billion yen in 1970 to 19.8 billion yen in 1980.⁴²³ Josamycin's discovery was a product of Japan's strengths in antibiotic science and strong collaboration between industry and academia – and led to its success in overseas markets. The drug's strong performance in the Japanese market was very much helped by government policy, which created a highly profitable environment for antibiotics makers.

Fujisawa

Around the same time, Fujisawa also launched a new antibiotic that proved tremendously successful in both domestic and international markets. The drug,

⁴¹⁹ Takashi Osono, Yoshihiko Oka, Shunichi Watanabe, Yōzō Numazaki, Kiruko Moriyama, Hitoshi Ishida, Kiyoshi Suzuki, Yoshirō Okami and Hamao Umezawa, "A New Antibiotic Josamycin I: Isolation and Physicochemical Characteristics," *Journal of Antibiotics Series A* 20, no.3 (1967): 174-180; and Kazuo Nitta, Kuniichiro Yano, Fumio Miyamoto, Yoshiharu Hasegawa, Toshihisa Sato, Noriko Kamoto and Shintaro Matsumoto, "A New Antibiotic, Josamycin. II: Biological Studies," *Journal of Antibiotics Series A* 20 no.3 (1967): 181-187.

⁴²⁰ Yakuji Nippōsha "Josamycin," in *Saikin no Shinyaku* [New Drugs in Japan] (Tokyo: Yakuji Nippōsha, 1970), 86-87.

⁴²¹ Yamanouchi Pharmaceutical Co., *Yamanouchi Seiyaku 50-nenshi* [A 50 Year History of Yamanouchi Pharmaceutical Co.] (Tokyo, Yamanouchi Pharmaceutical Co., 1975), 311-312.

⁴²² Yamanouchi Pharmaceutical Co., *Yūka Shōken Hōkokusho* [Annual Securities Report] (Tokyo: Ōkurashō Insatsukyoku, 1976), 7.

⁴²³ In nominal terms, Yamanouchi's antibiotic sales grew from 5.1 billion yen to 15.9 billion yen between 1970 and 1980. Yamanouchi Pharmaceutical Co., *Yūka Shōken Hōkokusho* [Annual Securities Report] (Tokyo: Ōkurashō Insatsukyoku, 1971), 18; Yamanouchi Pharmaceutical Co., *Yūka Shōken Hōkokusho* [Annual Securities Report] (Tokyo: Ōkurashō Insatsukyoku, 1981), 12.

cefazolin, belonged to a new category of antibiotics called cephalosporins, which were stronger and more widely effective compared to earlier antibiotics. Whereas scientists had previously discovered antibiotics by screening countless soil samples, cefazolin was a semisynthetic compound that was developed out of a known chemical structure that held the promise of a potential antibiotic. This was a marked transition from previous methods of antibiotic R&D.

While Fujisawa had launched antibiotics in the past, its decision to invest heavily in antibiotic R&D was a new phenomenon. Fujisawa was founded in 1894 by Tomokichi Fujisawa, and grew quickly in the pre-war period through the production of widely used therapies such as tonics and anthelmintics like camphor and santonin. In the post-war period, Fujisawa developed by importing foreign technologies from firms such as Geigy of Switzerland and Astra of Sweden. In the field of antibiotics, for example, a 1953 alliance with the Italian firm Carlo Erba enabled the firm to launch chloramphenicol as Kemicetine in Japan.⁴²⁴ By the early 1960s, Fujisawa derived around 15% of sales from antibiotics and had become known as one of Japan's leading antibiotics makers.⁴²⁵ The success of these ventures prompted Fujisawa to invest in its own antibiotic R&D.

Fujisawa's cefazolin venture reflected the firm's strategic shift toward developing its own antibiotics. In 1961, Fujisawa signed a licensing agreement with the National

⁴²⁴ Fujisawa Pharmaceutical Co., *Yūka Shōken Hōkokusho* [Annual Securities Report] (Tokyo: Ōkurashō Insatsukyoku, 1963), 7.

⁴²⁵ Fujisawa Pharmaceutical Co., *Yūka Shōken Hōkokusho* [Annual Securities Report] (Tokyo: Ōkurashō Insatsukyoku, 1960-1965). For a history of Fujisawa, see Fujisawa Pharmaceutical Co., *Fujisawa Yakuhin 80-nenshi* [Fujisawa Pharmaceutical, a 80 Year History] (Osaka: Fujisawa Pharmaceutical Co., 1976); Fujisawa Pharmaceutical Co., *Fujisawa Yakuhin 100-nenshi* [Fujisawa Pharmaceutical, a 100 Year History] (Osaka: Fujisawa Pharmaceutical Co., 1995).

Research and Development Corporation (NRDC) of the United Kingdom to develop a substance called cephalosporin C into a potential therapy.⁴²⁶ Cephalosporin C had been identified out of a culture from the coast of Sardinia by the bacteriologist Giuseppe Brotsu of the University of Cagliari in 1945. Subsequent research at the NRDC led to the discovery that part of cephalosporin C, a chemical structure 7-ACA, could be isolated and chemically manipulated to locate new antibiotic substances. Compared to existing antibiotics, the cephalosporins held the promise of greater potency, a wider effective spectrum, less toxicity, greater stability, and less probability of causing allergic reactions.⁴²⁷

Fujisawa spent approximately 7.7% of its annual research costs to import cephalosporin C technology.⁴²⁸ Industrial scientists at Takeda and academic scientists at Toho University then worked together to build upon this imported knowledge. Using existing procedures to modify bacterial strains for production, Fujisawa scientists searched for productive strains through exposure to ultraviolet radiation, x-rays and chemical manipulation. To substitute for Fujisawa's lack of laboratory capacities, researchers at Toho University offered their own facilities. After isolating 7-ACA in 1963, the scientists developed cefazolin in 1967 and reported their results at meetings such as the Japan Society of Chemotherapy and the International Society for

⁴²⁶ Yakugyō Keizai Kenkyūjo, *Yakuji Nenkan* [Pharmaceutical Annual] (Osaka: Nihon Yakugyō Shimbunsha, 1961), 187.

⁴²⁷ Minoru Nishida, Tadao Matsubara, Takeo Murakawa, Yasuhiro Mine, Yoshiko Yokota, Sachiko Goto, and Shogo Kuwahara, "Cefazolin, a New Semisynthetic Cephalosporin Antibiotic II. In vitro and In vivo Antimicrobial Activity," *Journal of Antibiotics* 23, no. 3 (1970): 137-148. See also Fujisawa Pharmaceutical Co., *Fujisawa Yakuhin 80-nenshi* [Fujisawa Pharmaceutical, a 80 Year History] (Osaka: Fujisawa Pharmaceutical Co., 1976), 342.

⁴²⁸ Fujisawa Pharmaceutical Co., *Fujisawa Yakuhin 100-nenshi* [Fujisawa Pharmaceutical, a 100 Year History] (Osaka: Fujisawa Pharmaceutical Co., 1995), 165.

Chemotherapy.⁴²⁹ Fujisawa's development of cefazolin was testament to the rising calibre of antibiotic research by Japanese firms. While it was true that Fujisawa's cephalosporin drug had taken much longer to develop than those of Eli Lilly or Glaxo, not all eight firms who obtained licenses from NRDC had been successful. Fujisawa – along with Glaxo and Lilly – was one of three firms who were ultimately able to develop a viable therapeutic.

Fujisawa's decade-long investment of over 150 million yen was, at the time, unprecedented for a Japanese firm. But the firm's entrepreneurial venture began to pay off. Following its launch in 1971, cefazolin was eventually marketed in more than 100 countries in Europe, North America and Asia. Thanks to cefazolin, antibiotic sales at Fujisawa grew from 29% to more than 40% of total sales in five years after launch – or from 32.5 billion yen in 1971 to 64.6 billion yen in 1976.⁴³⁰

Cefazolin was a product of Fujisawa's entrepreneurial foresight, whose managers undertook high-risk investments in hopes of capturing market opportunities from substantial product innovations. This was a time when Japanese firms invested little in R&D. The firm's fortunes were also the product of Fujisawa's strengths in antibiotic science and durable research alliances with both foreign and Japanese institutes.

⁴²⁹ Fujisawa Pharmaceutical Co. *Fujisawa Yakuhin 80-nenshi* [Fujisawa Pharmaceutical, a 80 Year History] (Osaka: Fujisawa Pharmaceutical Co., 1976), 342. Cefazolin was valued for its wide bacterial spectrum toward gram positive and negative bacteria. It was also stable and well absorbed in the body, without causing bodily dysfunction or allergic reactions. It was also found to be effective to various bacterial strains that had become resistant to penicillin. See Minoru Nishida, Tadao Matsubara, Takeo Murakawa, Yasuhiro Mine, Yoshiko Yokota, Sachiko Goto, and Shogo Kuwahara, "Cefazolin, a New Semisynthetic Cephalosporin Antibiotic II. In vitro and In vivo Antimicrobial Activity," *Journal of Antibiotics* 23, no. 3 (1970): 137-148.

⁴³⁰ In nominal terms, Fujisawa's antibiotic sales grew from 11.6 billion yen to 41.4 billion yen between 1960 and 1970. Fujisawa Pharmaceutical Co., *Yūka Shōken Hōkokusho* [Annual Securities Report] (Tokyo: Ōkurashō Insatsukyoku, 1972): 10; Fujisawa Pharmaceutical Co., *Yūka Shōken Hōkokusho* [Annual Securities Report] (Tokyo: Ōkurashō Insatsukyoku, 1977): 9.

Cefazolin's sales also benefited much from domestic conditions highly favourable to antibiotic sales. In any event, Fujisawa's success in cefazolin spearheaded an era in which Japanese pharmaceutical firms would invest heavily in antibiotic R&D.⁴³¹

Still, for many firms, Japanese government policies did not offer an attractive environment for innovation. Products of domestic origin often competed against products that were discovered overseas, licensed-in, or reverse engineered. By the time Fujisawa had launched cefazolin, for example, Eli Lilly and Glaxo's cephalosporin drugs, cefalothin and cefaloridine, respectively, were already marketed in Japan. Eli Lilly, the first to develop cefalothin from cephalosporin C in 1962, provided an import/sale license to Shionogi in 1966, while Glaxo, who had developed cefaloridine in 1964 exported its drug to Shin Nihon Jitsugyo and distributed by Torii Yakuhin as in 1965.⁴³² As the first cephalosporin drugs, Shionogi's Keflin and Torii's Ceporan showed strong sales in the domestic market. Many Japanese firms were long content to pursue import substitution policies as it proved profitable, and the domestic market remained dominated by antibiotics discovered outside of Japan. Between 1961 and 1975, only 14 of the 43 antibiotics (33%) introduced into the Japanese market were of Japanese origin.⁴³³ Only a third of the antibiotic market was comprised of domestic agents.

⁴³¹ See Robert Neimeth, "Japan's Pharmaceutical Industry Postwar Evolution," 160.

⁴³²Yakuji Nippōsha "Cefamedine," in *Saikin no Shinyaku* [New Drugs in Japan] (Tokyo: Yakuji Nippōsha, 1971), 66; Yakuji Nippōsha, "Cefaloridin," in *Saikin no Shinyaku* [New Drugs in Japan] (Tokyo: Yakuji Nippōsha, 1966), 51-53; and Yakuji Nippōsha, "Cefalotin," in *Saikin no Shinyaku* [New Drugs in Japan] (Tokyo: Yakuji Nippōsha, 1967), 45-46.

⁴³³ Aizawa, Minoru, and United Nations Industrial Development Organization, *Review of the Development of Antibiotic Industry in Selected Countries: Technical Report: Antibiotic Industry in Japan, History and Development*, 74. While these figures are slightly lower than those compiled by Yagisawa in 2002, they are useful in providing insight on the composition of Japan-origin drugs in the Japanese market.

Table 4. Antibiotics of Japanese Origin Marketed in Japan, 1961-1975⁴³⁴

Antibiotic	Company	Year
Chromomycin A3	Takeda	1961
Bleomycin	Nihon Kayaku	1968
Aminodexy-KM	Meiji Seika	1969
Josamycin	Yamanouchi	1969
Enramycin	Takeda	1969
Cefazolin	Fujisawa	1971
Ribostamycin	Meiji Seika	1972
Sulbenicillin	Takeda	1973
Midekamycin	Meiji Seika	1973
Dibekacin	Meiji Seika	1973
Maridomycin	Takeda	1975
Enviomycin	Toyo Jozo	1975

Still, Japanese firms improved their capacity to discover, develop and launch innovative antibiotics over the 1960s and 1970s. While government policies did help non-innovating firms survive, it did seem to offer sufficient incentive for some firms to pursue innovative discoveries in antibiotics.

⁴³⁴ Ibid.

3.3.3 1973: a year of welfare for the people – and for antibiotics makers

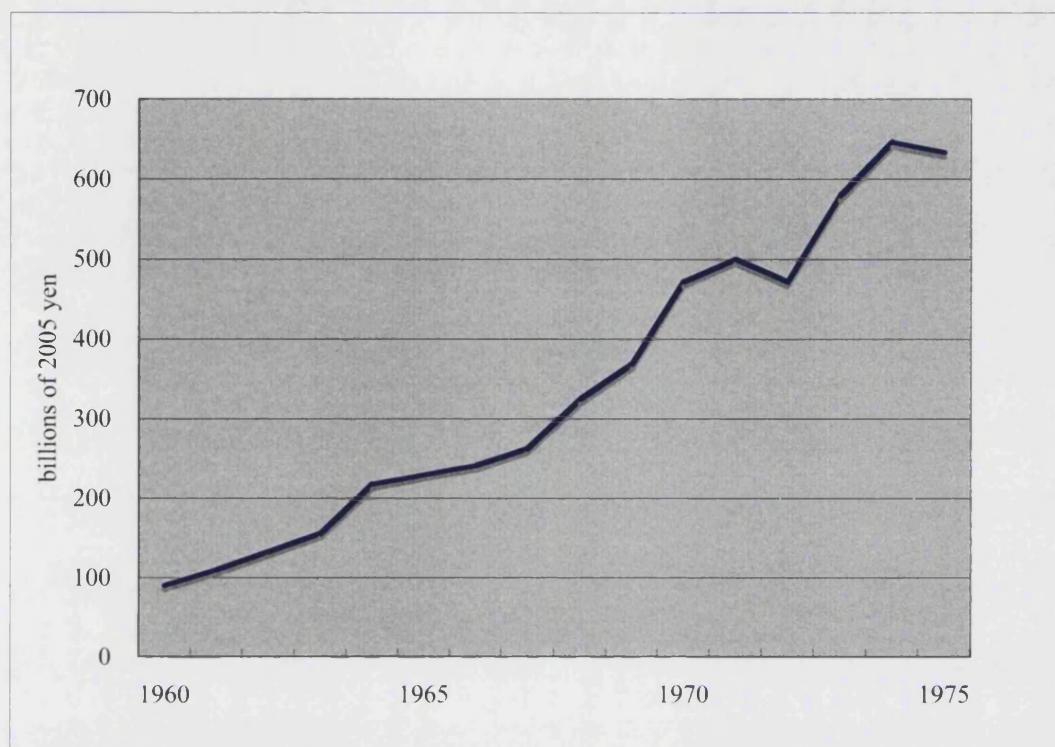


Figure 13. Value of Antibiotic Production, 1960-1975⁴³⁵

Between 1961 and 1975, the antibiotics sector expanded rapidly in terms of production, trade, and new drug discoveries.⁴³⁶ The high rate of growth in the antibiotics market coincided with the launch of a universal health insurance system in 1961 and an era of high-speed economic growth. As the above graph indicates, production levels rose 5.8 fold between 1961 and 1975 from approximately 109.5 billion yen to 633.1 billion yen.⁴³⁷ Growth in the antibiotics sector was particularly pronounced, as the size of the overall pharmaceutical market grew only 2.9 fold during the same period.

The 1973 reforms appeared particularly instrumental in raising production levels. As

⁴³⁵ Ministry of Health and Welfare, *Yakuji Kogyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Yakugyo Keizai Kenkyūjo, 1953-1967); Ministry of Health and Welfare, *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Yakugyō Keizai Kenkyūjo, 1968-2000).

⁴³⁶ Ibid. As historical data for sales are not available, production values have been used as a measure of market size.

⁴³⁷ In nominal terms, production levels rose from 22.0 billion yen to 363.4 billion yen. Ibid.

mentioned in the overview chapter, the government introduced several welfare measures in 1973 that increased its level of sponsorship of prescription pharmaceuticals. The government expanded coverage for family dependants, capped the cost of high cost treatments, and introduced free health care for the elderly.⁴³⁸ In response, growth rates jumped with 19% year-on-year growth in 1973 and 10% year-on-year growth in 1974. In fact, production growth in the five years after 1973 averaged 65 billion yen per year compared to 51 billion yen per year in the previous 5 years. Japan's rapid economic growth, too, had propelled the rise of the antibiotics sector, as more patients could afford antibiotic treatments. Supported by policy measures and economic conditions, the Japanese antibiotics sector experienced phenomenal growth in the 1960s and 1970s.⁴³⁹

3.3.4 Opening up

While strong restrictions to FDI had remained in place since 1950, Japan agreed to phase in capital liberalisation following its accession to the OECD and IMF in 1964. As well, by the mid 1970s, Japan's antibiotics sector had largely caught up with the West, and leading antibiotics makers were seeking to capture gains from abroad. While the pharmaceutical industry was not fully deregulated until 1975, the government gave approval for up to 50% investments from 1967.⁴⁴⁰ For foreign firms, the product standards introduced in 1967 still posed a significant barrier to entry.

⁴³⁸ Ministry of Health and Welfare, *Kōsei Hakusho* [White Paper on Health and Welfare] (Tokyo, Ōkurashō Insatsukyoku, Ministry of Finance, 1974).

⁴³⁹ *Ibid.*

⁴⁴⁰ Yakugyō Jihōsha, *Nihon no Iyakuin Sangyō* [The Japanese Pharmaceutical Industry] (Tokyo: Yakugyō Jihōsha, 1973), 160-161; Kōseishō 50-nenshi Henshū Inkaï [Editorial Committee for the 50 Year History of the Ministry of Health and Welfare], "Jiyūka to Kokusaika no Shinten [Progress in Capital Liberalisation and Internationalisation]," in *Kōseishō 50-nenshi* [A 50 Year History of the Ministry of Health and Welfare] (Tokyo: Kōsei Mondai Kenkyūkai, 1988), 1624-1626.

Moreover, foreign firms had yet to establish a marketing presence in Japan. But the reforms brought a fresh wave of foreign investment in Japan's pharmaceutical industry.

As the Japanese market opened up, antibiotic trade also grew, and trade values soared 8.3 fold from 10.7 billion yen to 88.0 billion yen between 1960 and 1975.⁴⁴¹ The growth of antibiotic imports was particularly remarkable, as it responded to strong demand conditions in the domestic market, and grew 14.7 fold from a mere 5.28 billion yen to 77.7 billion yen between 1960 and 1975. The average growth of imports in other therapeutic sectors, by comparison, was 6.9 fold – large, but less than half the figure for antibiotics. But the growth of antibiotic exports was much slower, as it grew only 1.9 fold from 5.38 billion yen to 10.3 billion yen. This was because many Japanese products were not approved in other markets, and because Japanese firms had yet to establish distribution networks overseas.⁴⁴² In fact, the ratio of imports to exports increased 4.4 fold in the antibiotics sector, compared to 3.6 fold among all therapeutic sectors.

As with most OECD countries, Japan relied on the United States for most of its pharmaceutical imports. In 1975, for example, 46.3 billion yen of antibiotic imports came from the United States, followed by 16.5 billion yen from Singapore and 10.8

⁴⁴¹ In nominal terms, trade values increased from 2.0 billion yen in 1960 to 50.5 billion yen in 1975. Ministry of International Trade and Industry, *Tsūshō Hakusho* [White Paper on Trade] (Tokyo: Ōkurashō Insatsukyoku, 1958-1973); Ministry of International Trade and Industry, *Tsūshō Hakusho* [White Paper on Trade] (Tokyo: Gyōsei, 1974-2000).

⁴⁴² In nominal terms, between 1960 and 1975, antibiotic imports grew from 1.0 billion yen to 44.6 billion yen while antibiotic exports grew from 1.0 billion yen to 5.9 billion yen. *Ibid.*

billion yen from the United Kingdom.⁴⁴³ While trade figures did grow, the massive trade deficit – both in antibiotics and in other therapeutic sectors – questioned whether Japanese drugs were of comparable quality to those in other developed countries.

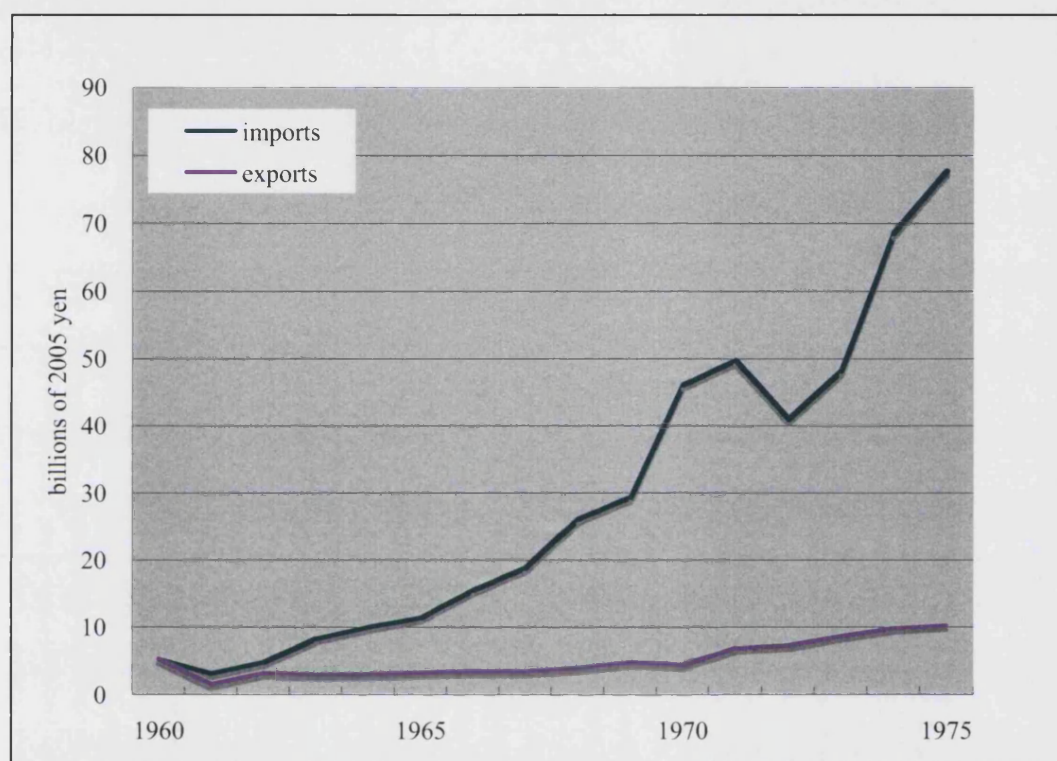


Figure 14. Value of Antibiotic Trade, 1960-1975⁴⁴⁴

Transitions in the export destinations of antibiotics did suggest that the quality of Japan origin antibiotics was improving. In 1961, for example, the leading export destinations for Japanese antibiotics were East Asian neighbours such as Okinawa and Taiwan, followed by exports destined for Germany and other European countries.⁴⁴⁵ But by the mid 1970s, the majority of antibiotic exports were destined for more

⁴⁴³ In nominal terms, antibiotic imports in 1975 from the United States, Singapore, and the United Kingdom were 26.6 billion yen, 9.5 billion yen, and 6.2 billion yen, respectively. Yakugyō Keizai Kenkyūjo, *Yakugyō Keizai Nenkan* [Pharmaceutical Economics Annual] Tokyo: Yakuji Nippōsha, 1979), 167.

⁴⁴⁴ Ministry of International Trade and Industry, *Tsūshō Hakusho* [White Paper on Trade] (Tokyo: Ōkurashō Insatsukyoku, 1958-1973); Ministry of International Trade and Industry, *Tsūshō Hakusho* [White Paper on Trade] (Tokyo: Gyōsei, 1974-2000).

⁴⁴⁵ Between 1945 and 1972, Okinawa was ruled by the United States.

developed countries; in 1975, for example, antibiotic exports were destined for South Korea, West Germany, Belgium, and the United States, in descending order.⁴⁴⁶ Japan's antibiotic trade grew rapidly over the 1960s, and as the quality of Japan origin antibiotics improved, the country's export destinations shifted from the developing to the developed world.

3.3.5 Summary of the period between 1961 to 1975

The experience of the antibiotics sector illustrates the factors that influenced the industry as a whole. There were several reasons for the strong performance of Japan's antibiotics sector in this period. All of these reasons lay in government policies that were highly favourable to the industry. The strongest stimulus was the introduction of universal health care in 1961. Universal health care spurred demand for antibiotics as the government covered most of the costs of patients' prescription drugs. This made it much easier for firms to sell drugs.

Japanese antibiotics makers also benefited from the practice permitted among Japanese physicians to both prescribe and dispense medicines. This practice created strong incentives among physicians to prescribe the newest and most expensive antibiotics, which tended to have the greatest price differentials. Given the government's modest criteria for drug approval, the antibiotics sector flourished. Both firms and physicians were incentivised to expand the domestic market for financial

⁴⁴⁶ Yakugyō Keizai Kenkyūjo, *Yakugyō Keizai Nenkan* [Pharmaceutical Economics Annual] Tokyo: Yakuji Nippōsha, 1979), 168.

gain.⁴⁴⁷ While many antibiotics would not have been approved elsewhere, Japanese firms could prosper in an environment that remained heavily protected. Foreign direct investment was restricted until 1975. In addition, Japan's distinct drug standards provided additional protection from foreign competition.

Perhaps because the government subsidised the cost of prescription drugs, Japanese patients were price insensitive, and purchased unnecessary antibiotics. Indeed, the over consumption of antibiotics became an oft-debated topic during the 1970s and 1980s. But other factors also accounted for this over consumption. Some scholars have attributed patient deference to physicians to Japan's Confucian heritage of respect for authority, while others have noted the lack of professional information available to patients.⁴⁴⁸ Prescribing antibiotics also allowed physicians to preserve their reputation with patients who often expected a prescription drug upon a visit to the doctor.⁴⁴⁹

While many Japanese pharmaceutical firms established corporate research laboratories over the 1960s, most research laboratories specialised in reverse engineering Western products rather than in pursuing product innovations. The government's drug pricing policy, whereby the government set the prices for prescription drugs, effectively capped the potential profits that could be made from drug discoveries. But the prices of antibiotics were relatively higher than in other therapeutic sectors. This encouraged some drug companies to invest in antibiotic R&D

⁴⁴⁷ Michael Reich, "Why the Japanese Don't Export More Pharmaceuticals: Health Policy as Industrial Policy," 135.

⁴⁴⁸ Eric Feldman, "Medical Ethics the Japanese Way," *The Hastings Center Report* 15, no.5 (1985): 21-24. It is, however, difficult to assess the degree to which a more hierarchical relationship might have mattered. See William E. Steslicke, "Doctors, Patients, and Government in Modern Japan," *Asian Survey* 12, no.11 (1972): 913-931.

⁴⁴⁹ P. Reed Maurer, interview by author, Tokyo, Japan, 11 July 2007.

– some of whom were able to develop internationally competitive antibiotics.

3.4 The maturation of the market and transition to product innovation, 1975-1990

The Japanese have proved themselves master soil searchers. In the last decade, many of the cephalosporins have come from Japan. Antibiotics are important there because it is the biggest user, per capita, of the wonder drugs, ahead even of the United States.

N.R. Kleinfeld, "Intense Battle for Antibiotics,"
The New York Times, 13 June 1983.

In keeping with the momentum from the previous decade, the antibiotics sector continued to expand in the 1970s. After 1975, government measures to liberalise foreign capital and strengthen intellectual property rights protection supported the growth of a number of Japanese pharmaceutical firms who had acquired the financial, scientific and technological capacity to assume higher risks and pursue more substantial innovations. Firms from other industries seeking new business opportunities entered the pharmaceutical sector during this period, as did foreign firms that had previously been alienated from the Japanese market.

While the government's decision to contain health care costs through biennial price reduction dealt a swift and intense blow to production levels after 1981, it also helped the transition from volume to value-based production. Facing rising competition and falling profits in the home market, Japanese firms also expanded their operations abroad. While Japan's expertise in antibiotic science and research networks was certainly important in sustaining the growth of Japan's antibiotic sector, the timely

implementation of government policies ultimately dictated its fortunes between 1975 and 1990.

3.4.1 Modernising the market: capital liberalisation and product patents

The legislation to liberalise foreign direct investment and to introduce product patents in 1975 and 1976, respectively, was a major milestone in Japan's pharmaceutical industry. The new legislation signalled a turning point: Japanese firms could no longer reverse engineer existing drugs and launch a new drug under a different process. They would also have to compete with an increasing number of foreign firms that were now in Japan to stay.

3.4.2 Cutting excess demand

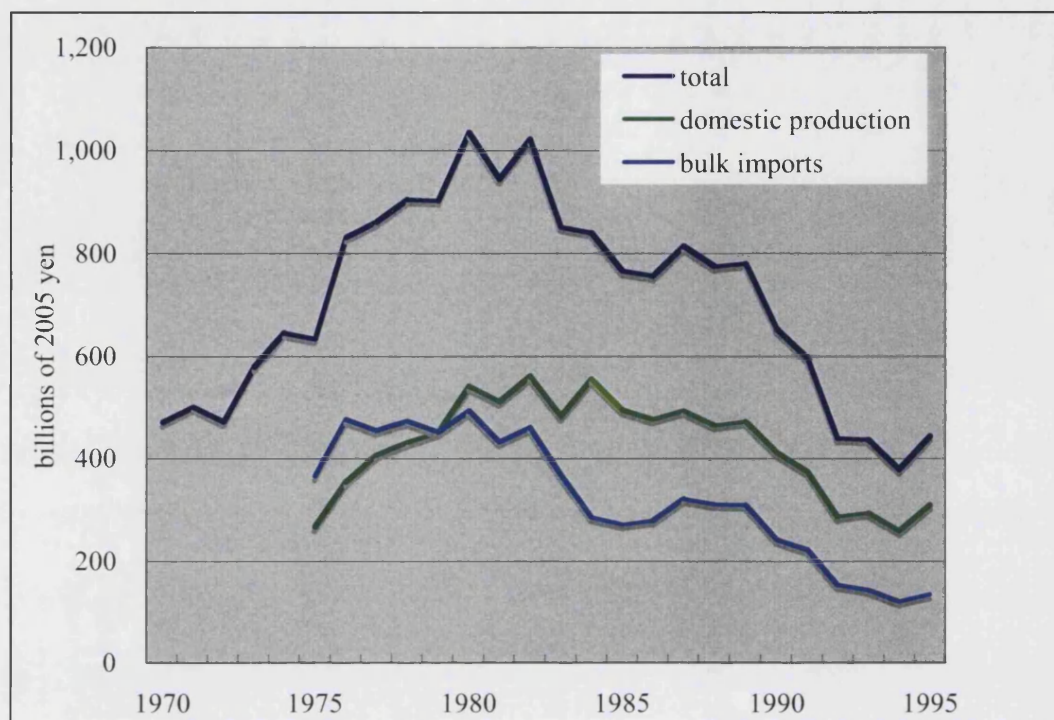


Figure 15. Value of Antibiotic Production, 1975-1995⁴⁵⁰

Following from the previous decade, antibiotic production continued to grow rapidly after 1975. Between 1975 and 1980, production levels grew from 633.1 billion yen to 1.03 trillion yen.⁴⁵¹ But from 1981, the government began to reduce the prices of prescription drugs on a biennial basis over the course of the patent protection period. This radical measure, which aimed to contain the country's escalating health care costs, began with a dramatic 18.6% reduction in 1981. While drug prices fell 5.8% between 1976 and 1981, they dropped 46.1% between 1981 and 1986.⁴⁵² The antibiotics sector was particularly hard hit, as the government began to impose steeper reductions on older drugs with less innovative value.⁴⁵³ Combined with the reforms to end free

⁴⁵⁰ Ministry of Health and Welfare, *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Yakugyō Keizai Kenkyūjo, 1968-2000).

⁴⁵¹ In nominal terms, the production level of antibiotics increased from 363.4 billion to 814.3 billion yen. Ibid.

⁴⁵² Jihō, *Iryō Iyakuhin Gyōkai no Ippan Chishiki* [General Information on the Health care and Pharmaceutical Industries] (Tokyo: Jihō, 2005): 60.

⁴⁵³ Yakugyō Jihōsha, *Yakuji Handobukku* [Pharmaceutical Affairs Handbook] (Tokyo: Yakugyō Jihōsha, 1968-1999).

healthcare for the elderly in 1983, antibiotics production peaked in 1982 and began to contract over the decade. In 1990, antibiotics production stood at 652.8 billion yen, a 47% fall from its peak, and only a 3% increase compared to 1975.⁴⁵⁴

Despite this decline, however, the size of Japan's antibiotics market was unparalleled in the global market. Japanese antibiotics makers produced drugs worth well over 600 billion yen throughout the decade – at times reaching 1 trillion yen.⁴⁵⁵ In 1988, for example, the Japanese market antibiotics market was valued at \$4.8 billion, compared to \$3.4 billion in the United States and \$360 million in the United Kingdom. This translated into a per capita consumption of \$39.1 in Japan, compared to \$13.8 in the United States and \$6.4 in the United Kingdom.⁴⁵⁶ Japanese firms also became more self-sufficient, as production from bulk imports declined from 336.3 billion yen in 1975 to 240.8 billion yen in 1990.⁴⁵⁷

While antibiotic R&D involved less cost or risk compared to other therapeutic sectors, the biennial price reductions still deterred Japanese firms from pursuing breakthrough discoveries. Not only did Japanese firms see a substantial decrease in profits from existing drugs, they had less to reinvest in R&D compared to their American or British

⁴⁵⁴ In nominal terms, antibiotic production stood at 624.1 billion yen in 1990. Ministry of Health and Welfare, *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Yakugyō Keizai Kenkyūjo, 1968-2000).

⁴⁵⁵ *Ibid.*

⁴⁵⁶ M. Itō, "Nichi-bei-ō ni okeru Kōkinyaku no Rinshōhyōkahō [A Clinical Evaluation of Antibacterial Agents in the United States, Europe and Japan]," *Saishin Igaku* 44, no.12 (1989): 2461. Per capita consumption calculated based on demographic data available at Organisation for Economic, Co-operation, and Development, *OECD Health Data 2008: Statistics and Indicators for 30 Countries* (Paris: Organisation for Economic Co-operation and Development, 2008) in SourceOECD, <http://www.sourceoecd.org>.

⁴⁵⁷ In nominal terms, antibiotic production from bulk imports changed from 210.2 billion yen to 230.2 billion yen. Ministry of Health and Welfare, *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Yakugyō Keizai Kenkyūjo, 1968-2000).

rivals. This had a particularly negative impact in undermining the capacity of Japanese firms to compete in the global market at a time when other drug regimes penalised imitation and provided substantial rewards for innovation. But there were also more positive outcomes. The price reductions were actually useful in nudging firms away from the over-production of antibiotics toward newer categories of drugs that were less subject to heavy reductions. It also helped end an era of volume-based expansion, as the minimal pharmaceutical price differentials lowered physician demand for antibiotics. In fact, it also encouraged the more innovative firms to pursue more favourable market opportunities abroad.

3.4.3 An increasing emphasis on R&D

Quinolones

The intensification and internationalisation of R&D was well observed in the firms that developed quinolone antibiotics. With the many antibiotic programmes launched after the discovery of cefazolin in the 1970s, Japanese firms spearheaded the discovery of new antibiotics. One of these belonged a group of drugs called fluoroquinolones, a subset of the quinolone family of antibiotic drugs discovered in the 1960s. The discoveries were a product of previous successes in antibiotic discovery, close research collaborations with universities, and intense inter-firm competition. The decision among Japanese firms to make new investments in R&D were not only motivated by government policies, but also by limitations to therapeutic demand and the profit potential of existing therapies. With the wide spread use of antibiotics, new products were required to combat antibiotic-resistant strains. As a purely synthetic

antibacterial drug, the discovery of quinolones were particularly timely, as by the 1970s, many strains of bacteria had grown resistant to sulfa drugs – the first synthetic antibacterials discovered in the 1940s.⁴⁵⁸

The first quinolone antibiotic was introduced by the American firm Sterling Winthrop, which launched nalidixic acid in 1962. In subsequent years, as firms worldwide competed to improve on this drug, scientists discovered that the addition of a fluorine atom to the quinolone structure significantly improved the drug's properties. The new quinolone antibiotics were valued for their superior potency, absorption, distribution, and effectiveness against a wide range of bacteria – particularly with antibiotic resistant strains. While these drugs still had side effects that, for example, affected the central nervous system, fluoroquinolones made outpatient therapy possible where hospitalisation had previously been required. While some of the drug's properties remained to be improved, its strengths far outweighed its weaknesses.⁴⁵⁹

Kyorin

In Japan, Kyorin's discovery of the first fluoroquinolone antibiotic, norfloxacin, propelled the small, little-known firm into prominence as an innovative, global antibiotics firm. Kyorin's newfound profits also helped enlarge the scale of its operations, as the firm's sales of the drug recorded 27.7 billion yen two years after

⁴⁵⁸ For general information on quinolone drugs, see Peter Ball, "The Quinolones: History and Overview," in *The Quinolones*, by Vincent T. Andriole (San Diego: Academic Press, Inc., 1988), 1-33; David C. Hooper and Ethan Rubinstein, "Introduction," in *Quinolone Antimicrobial Agents* (Washington D.C., American Society for Microbiology Press, 2003) viii-ix.

⁴⁵⁹ Hisashi Takahashi, Isao Hayakawa and Takeshi Akimoto, "The History of the Development and Changes of Quinolone Antibacterial Agents," *Yakushigaku Zasshi* 38 no. 2 (2003): 161-179.

launch.⁴⁶⁰ Kyorin's discovery of norfloxacin was motivated by the profit potentials from an innovative new drug, and was enabled by the firm's R&D capacity and collaborations with university researchers.

It was somewhat surprising that Kyorin became the first to launch a new, innovative antibiotic. Founded as a manufacturer and distributor of new medicines in 1923, Kyorin was known more for its cardiovascular agents such as Behyd, Cholexamin, and Hespander that it had launched since the 1960s. As a smaller firm with limited R&D capacities, Kyorin's R&D collaborations with university researchers were particularly crucial to the drug's discovery. In step with government policies to encourage innovation, the firm established its central research laboratory in 1977.⁴⁶¹ Forming close alliances with researchers at the nearby Department of Microbiology in Gunma University's School of Medicine, Kyorin's researchers conducted experiments to develop the drug by manipulating the quinolone structure.⁴⁶²

Kyorin's development of norfloxacin reflected considerable advances in antibiotic R&D among Japanese firms. Not only had drug development evolved from the sifting of numerous soil samples, but the quality, safety and effectiveness guidelines had also become more rigorous. Laboratory tests spanned longer durations with complex tests conducted on a more types and numbers of species. Clinical tests also became more sophisticated, as double-blind tests were conducted, and greater attention was paid to

⁴⁶⁰ Calculated on the basis of official drug prices and converted into 2005yen. See "Kyōrin Seiyaku[Kyorin Pharmaceutical]," *Fain Kemikaru* 31, no. 13 (August 2002): 20.

⁴⁶¹ Kyōrin Pharmaceutical Co., "Enkaku [History]," in *Yūka Shōken Hōkokusho* [Annual Securities Report] (Tokyo: Ōkurashō Insatsukyoku, 1995), 3.

⁴⁶² This is documented in the scholarly articles published.

side effects and adverse reactions as well as therapeutic effects. Such efforts bore fruit with the discovery of norfloxacin, which had a wider antibacterial spectrum and greater potency compared to existing antibiotics.⁴⁶³

Norfloxacin was an innovative therapy that not only proved highly profitable for Kyorin, but also brought the firm global recognition that helped expand its business beyond Japan. Approved in February 1984, norfloxacin was distributed domestically by Kyorin and Torii Pharmaceutical as Baccidal.⁴⁶⁴ Shortly thereafter, norfloxacin was approved in the United States in October 1986, and marketed by Merck Sharpe and Dohme in over 20 countries as Noroxin.⁴⁶⁵ The drug brought substantial sales to Kyorin, as Noroxin sales amounted to \$41 million in 1988.⁴⁶⁶ Kyorin's transformation with the new drug was a product of government policy, entrepreneurial initiative, and close research alliances with university researchers.

Daiichi

Around the same time, a 20-member research team at Daiichi Pharmaceutical was also searching for new quinolones in collaboration with Gunma University's School of

⁴⁶³ Akira Ito, Keiji Hirai, Matsuhisa Inoue, Hiroshi Koga, Seigo Suzue, Tsutomu Irikura, and Susumu Mitsuhashi, "In Vitro Antibacterial Activity of AM-715, a New Nalidixic Acid Analog," *Antimicrobial Agents and Chemotherapy* 17, no. 2 (1980): 103-108. Earlier quinolones were largely ineffective toward gram-negative bacteria. Keiji Hirai, Akira Ito, Yasuo Abe, Seigo Shizue, Tsutomu Irikura, Matsuhisa Inoue and Susumu Mitsuhashi, "Comparative Activities of AM-715 and Pipemedic and Nalidixic Acids Against Experimentally Induced Systemic and Urinary Tract Infections," *Antimicrobial Agents and Chemotherapy* 19, no. 1 (1981): 188-189.

⁴⁶⁴ Yakuji Nippōsha, "Norfloxacin," in *Saikin no Shinyaku* [New Drugs in Japan] (Tokyo, Yakuji Nippōsha, 1985), 128-129.

⁴⁶⁵ PJB Publications, *Scrip's Antibacterial Report* (London: PJB Publications, 1990), 26. See also, "Merck Introduces Two Drugs in the U.S.," *Chemical Week*, 26 November 1986, 16.

⁴⁶⁶ Martha Glaser, "Market-share Battle Marks Cardiovasculars, Antiarthritics; 48th Annual Prescription Review," *Drug Topics* 131 (March 1987): 43; Martha Glaser, "Quinolones, Antidepressants Gained in 1988: PDS; Pharmaceutical Data Services," *Drug Topics* 133 (April 1989): 73

Medicine.⁴⁶⁷ It was not surprising that Daiichi entered the antibiotic sector with the discovery of quinolone drugs. Daiichi was Japan's leading sulfa drug maker. Both sulfa drugs and quinolones are synthetic antibacterial compounds, and Daiichi could build upon its existing expertise to develop quinolones. Moreover, in the 1970s, sulfa drug makers were pushed to seek new opportunities as demand for sulfa drugs declined. Not only were existing sulfa drugs becoming less effective toward multiple bacterial strains, demand for sulfa drugs was being replaced by better antibiotics that were more potent but had fewer side effects.

Daiichi's investment into quinolone R&D in the 1960s was motivated more by the limitations of its core product than the government's policies to encourage innovation.⁴⁶⁸ Daiichi's discovery of its quinolone drug, ofloxacin, was a product of existing expertise, research networks, and entrepreneurship. The success of Daiichi's drug was buoyed by government policy as well as the firm's size and marketing expertise.

Daiichi was a large firm with a history as one of Japan's leading pharmaceutical firms. Founded as Arsemin Shokai by six entrepreneurs in 1915, Daiichi was formed in response to the acute shortages of antisyphilitic drugs during the First World War as German imports came to a halt. Daiichi was one of several new firms that launched salvarsan during this period as Japanese scientists such as Shōzaburō Keimatsu of

⁴⁶⁷ K. Sato, Y. Matsuura, M. Inoue, T. Une, Y. Osada, H. Ogawa, S. Mitsuhashi, "In Vitro and In Vivo Activity of DL-8280, a New Oxazine Derivative," *Antimicrobial Agents and Chemotherapy* 22, no. 4 (1982): 548-553.

⁴⁶⁸ Government pressures to innovate occurred after the mid 1970s in the form of capital liberalisation and product patents.

Tokyo University succeeded in producing the drug in Japan.

Exploiting opportunities in both domestic and East Asian markets, Daiichi flourished as the leading provider of antisyphilitic remedies. By the end of World War II, Daiichi had established itself as one of the leading pharmaceutical firms and the primary producer of sulfa drugs in Japan. In the post-war period, Daiichi remained a leading provider of sulfa drugs, as well as being a producer of vitamins and cardiovascular drugs. With long history, prominent standing, and large size, Daiichi had also developed considerable marketing strengths in pharmaceuticals.⁴⁶⁹

From the 1960s, Daiichi had invested much of its R&D efforts in seeking to develop a new drug that would replace the dwindling sales of sulfa drugs. Daiichi not only spent substantial time and funds in drug development, but also sought alliances – both with university researchers and foreign pharmaceutical firms. Indeed, such collaborations were essential to the discovery of the new drug. Daiichi's ofloxacin was developed out of nalidixic acid, which was licensed-in from Winthrop in 1964, and was until the early 1980s its popular quinolone drug branded as "Wintomylon."⁴⁷⁰ The new drug was a product of 20 years of research, after thousands of derivatives were created out of Wintomylon in collaboration with researchers at Gunma University. Like norfloxacin, ofloxacin was valued for its potency, wide antibacterial spectrum, and

⁴⁶⁹ For Daiichi's history, see Daiichi Pharmaceutical Co., *Daiichi Seiyaku 70-nen no Ayumi* [Daiichi Pharmaceutical, a 70 Year History] (Tokyo: Daiichi Pharmaceuticals Co., 1986); Daiichi Pharmaceutical Co., *Daiichi Seiyaku 80-nenshi* [Daiichi Pharmaceutical, a 80 Year History] (Tokyo: Daiichi Pharmaceutical Co., 1998); or Daiichi Pharmaceutical Co., *Daiichi Seiyaku 90-nenshi* [Daiichi Pharmaceutical, a 90 Year History] (Tokyo: Daiichi Pharmaceutical Co., 2007).

⁴⁷⁰ Daiichi Pharmaceutical Co., *Daiichi Seiyaku 70-nen no Ayumi* [Daiichi Pharmaceutical, a 70 Year History], 35, 77; Daiichi Pharmaceutical Co., *Daiichi Seiyaku 80-nenshi* [Daiichi Pharmaceutical, a 80 Year History], 242.

effectiveness toward bacteria that had developed antibacterial resistance. As at Kyorin, Daiichi's development of ofloxacin reflected the advances in drug R&D of the times in step with greater demands placed on standards during this time. Records of clinical tests, for example, reported much larger sample sizes and higher degrees of effectiveness.⁴⁷¹

Much like Kyorin's norfloxacin, Daiichi's launch of ofloxacin as Taravid in 1985 fuelled the growth of the firm and spurred its internationalisation.⁴⁷² Indeed, a decade after its launch, antibiotics sales at Daiichi grew almost three fold from 23.3 billion yen to 69.2 billion yen, and the firm's reliance on antibiotics more than doubled from 15% to 30%. Largely a domestic firm until the mid 1980s, exports grew from 8.12 billion yen in 1985 to 15.4 billion yen in 1990.⁴⁷³

While Daiichi discovered norfloxacin a year after Kyorin, Daiichi's superior marketing strategies, larger size and previous alliances with foreign firms helped Daiichi's drug achieve much greater success in the domestic and global market. Daiichi licensed ofloxacin to numerous foreign firms, such as to Hoechst (Germany), Johnson & Johnson (United States), Sigma Dow, Glaxo Italy (Italy) in 1983 and to Roussel-Uclaf (France) in 1984. While, ofloxacin was marketed by Hoechst as Taravid in all Europe excluding France and Germany, the Middle East, Africa and

⁴⁷¹ Trials for ofloxacin were carried out on 4,785 subjects, including 8 double-blind tests, and revealed that the substance was effective in 3,701 subjects, or 77.3%, of the cases. Side effects were found in 4.1% of the cases.

⁴⁷² Yakuji Nippōsha, "Ofloxacin," in *Saikin no Shinyaku* [New Drugs in Japan] (Tokyo, Yakuji Nippōsha, 1986), 125-126.

⁴⁷³ In nominal terms, Daiichi's antibiotic sales grew from 21.1 billion yen to 70.4 billion yen. Exports grew from 7.3 billion yen to 11.2 billion yen. Daiichi Pharmaceutical Co., *Daiichi Seiyaku 80-nenshi* [Daiichi Pharmaceutical, a 80 Year History], 399; Daiichi Pharmaceutical Co., *Yūka Shōken Hōkokusho* [Annual Securities Report] (Tokyo: Ōkurashō Insatsukyoku, 1986), 10, 13; Daiichi Pharmaceutical Co., *Yūka Shōken Hōkokusho* [Annual Securities Report] (Tokyo: Ōkurashō Insatsukyoku, 1991), 19; Daiichi Pharmaceutical Co., *Yūka Shōken Hōkokusho* [Annual Securities Report] (Tokyo: Ōkurashō Insatsukyoku, 1996), 24.

some parts of Asia, the drug was marketed by Johnson & Johnson as Floxacin in North and South America, as well as the Pacific region.⁴⁷⁴ Eventually reaching more than 120 countries, ofloxacin's worldwide sales neared \$500 million in 1990.⁴⁷⁵ Daiichi's greater success relative to Kyorin embodied some of the changes in the pharmaceutical industry more generally, where marketing was becoming as important as R&D in securing sales.⁴⁷⁶

It was true that Daiichi was not able to capture the gains of firms with a direct marketing presence abroad. But the firm gained substantially from its overseas sales. Ofloxacin's discovery was a product of Daiichi's prior strengths in synthetic antibacterials and initiative to seek new market opportunities. Its strong sales performance was a product of the high domestic demand secured by government policy and Daiichi's distribution strengths in both domestic and global markets. The experiences of the Japanese firms that pioneered the development of new quinolone drugs shows the importance of entrepreneurship, research collaborations, and government policy to their success.

There were other antibiotics firms – aside from quinolone drug makers – that invested in R&D and expanded overseas. This included Sumitomo Pharmaceutical, which launched the antibiotic, meropenem.⁴⁷⁷ Sumitomo's meropenem belonged to the

⁴⁷⁴ "Ofloxacin/Levofloxacin," *Gekkan Mix* [Monthly Medical Information Express](December 1996): 55-56

⁴⁷⁵ In 2005 values, this was nearly \$750 million. Daiichi Pharmaceutical Co., *Daiichi Seiyaku 70-nen no Ayumi* [Daiichi Pharmaceutical, a 70 Year History], 277; John Elmsey, "Flourine Helps the Medicine Go Down" *The Independent*, 18 March 1991, 17.

⁴⁷⁶ See Matthew Lynn, *The Billion-Dollar Battle: Merck v Glaxo* (London: Mandarin, 1992).

⁴⁷⁷ Yakuji Nippōsha, "Meropenem," in *Saikin no Shinyaku* [New Drugs in Japan] (Tokyo, Yakuji Nippōsha, 1996), 103-109.

carbapenem family of antibiotics, and was developed by altering the chemical structure of Merck's imipenem, which had been launched in 1985. Compared to imipenem, Sumitomo's new antibiotic had a wider effective range, fewer side effects, and was easier to use. Research collaborations were essential to the drug's development, especially with the increasing rigour involved in antibiotic R&D.⁴⁷⁸ Test results reflected higher criteria in the drug approval process and the internationalisation of the research process.

As an innovative therapy, Sumitomo's drug quickly gained global recognition. In fact, meropenem was first launched in Italy in 1994 before it was launched in Japan as Meropen in 1995. Sumitomo licensed meropenem to ICI to develop the drug for most major markets outside of Japan. After FDA approval in June 1996, meropenem was launched in September by Zeneca Pharmaceuticals as Merrem in the United States.⁴⁷⁹ With sales of 13.3 billion yen in 2000, or 10.8% of total sales, meropenem proved a blockbuster discovery. For Sumitomo, meropenem not only allowed it to gain footage in the domestic market, but also helped its internationalization.⁴⁸⁰

Led by successes like these, Japan's antibiotics sector experienced its height of antibiotics discovery during this period. Indeed, Japan discovered more than 40% of

⁴⁷⁸ Saburō Fukai, ed., *Konnichi no Shinyaku: Kindai Iyakuhin no Hensen* [New Drugs Today: Changes in Modern Pharmaceuticals] (Tokyo: Yakuji Jihōsha, 1995), 878. See also, Yutaka Takeuchi, Yoshiaki Takebayashi, Makoto Sunagawa, Yutaka Isobe, Yukari Hamazume, Akura Uemura, and Tetsuo Noguchi, "The Stability of a Novel Carbapenem Antibiotic, Meropenem (SM-7338), in a Solid State Formulation for Injection," *Chemical & Pharmaceutical Bulletin* 41, no.11 (1993): 1998-2002.

⁴⁷⁹ FDA/Center for Drug Evaluation and Research, "Label and Approval History," Drugs@FDA, FDA Approved Drug Products, http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist (accessed 8 May 2008).

⁴⁸⁰ In nominal terms, meropenem reached 13.6 billion yen in sales. Jenny Wilson, *Antibacterial Products and Markets, Scrip Reports* (Richmond: PJB Publications, 1997), 78.

its antibiotics in the decade after 1975.⁴⁸¹ But innovation was often incremental, and dependent on pre-existing discoveries of certain bacterial strains, and global recognition of these drugs was varied.⁴⁸² Yet international recognition of Japan-origin drugs did increase. As the figures in parentheses in table 4 show, the increase in the proportion of Japan-origin antibiotics recognised globally after 1975 reflects the shift from volume to value-based growth.

Table 5. Antibiotic Discoveries Originating from Japan, 1946 - 1995⁴⁸³

Number of Products Discovered					Total
1946-1955	1956-1965	1966-1975	1976-1985	1986-1995	
11	12	23	40	13	99
(4=36.4%)	(4=33.3%)	(5=21.7%)	(18=45%)	(7=53.8%)	(38=38.4%)

Note: Figures in parentheses represent the number of Japanese discoveries that were licensed abroad.

From a global perspective, too, the number of antibiotics discovered by Japanese firms at this time was not insignificant. A study of new drugs discovered worldwide between 1969 and 1980 revealed that a total of 113 antibiotics were discovered during this period. Of these, 22.5 substances, or almost 20 percent, originated from Japan, while 37 (or 33%) were discovered in the United States, 11.5 (or 10%) in Italy and 9.5 (or 8%) in the United Kingdom.⁴⁸⁴ It was true that the innovative value among these

⁴⁸¹ The degree of international competitiveness (according to rates of overseas licensing) has varied according to types of antibiotics. The number of Japan-origin antibiotics has been highest in β lactam antibiotics at 39 substances, or 39% of all discoveries. The volume of discovery has not necessarily correspond to the degree of competitiveness, either. While macrolides comprise 11.6% of antibiotic discoveries, they comprise 8.6% of overseas licensings. While quinolones comprise 15% of discoveries, they comprise 20% of licensings.

⁴⁸² Joichi Kumazawa and Morimasa Yagisawa, "The History of Antibiotics: The Japanese Story," 127; Morimasa Yagisawa, unpublished document, "Antibiotics, Chemotherapeutics and Other Microbial Products Originated from Japan," sent to author.

⁴⁸³ Ibid.

⁴⁸⁴ Ibid.

substances likely varied, and that Japanese antibiotics may have been more incremental than breakthrough discoveries. But the figures provide insight into the fruition of Japanese efforts in antibiotic research during this time.

3.4.4 Expanding abroad

The liberalisation of foreign capital in 1975 prompted many Japanese firms to seek opportunities abroad, as they faced limited growth potential at home. In addition to foreign rivals, Japanese firms were also facing competition from a growing number of new firms specializing in chemicals, textiles to food companies that had entered the pharmaceutical sectors. These firms, facing saturated markets in their respective sectors, were eager to pursue new opportunities in a high technology sector that held greater potential for high returns and long-term growth. The introduction of product patents in 1976 encouraged Japanese firms to intensify their R&D efforts to develop innovative drugs. Japanese firms expanded their overseas ventures as government policies shifted from protection to liberalisation, imitation to innovation, domestic to export-oriented growth.

There were several other measures that facilitated export growth during this period. Japan was pressured by the United States to open its market to foreign drugs.⁴⁸⁵ Japanese firms responded to increased competition in their home market by expanding abroad. Shorter drug examination times and quarterly drug approvals also made it easier for Japanese firms to bring new drugs to the market. Moreover, the government

⁴⁸⁵ United States Department of Commerce, International Trade Administration, Market Access and Compliance, "MOSS Agreement on Medical Equipment and Pharmaceuticals."

improved Japanese drug standards such as GLP (Good Laboratory Practice), GCP (Good Clinical Practice), and GMP (Good Manufacturing Practice) over the decade.⁴⁸⁶

While most of these quality guidelines were legally enacted after 1990, Japanese firms upgraded their drug development processes in anticipation of their legislation, and made their products more competitive in the global market. These policies helped Japanese firms raise R&D capacities, and achieve export growth abroad.

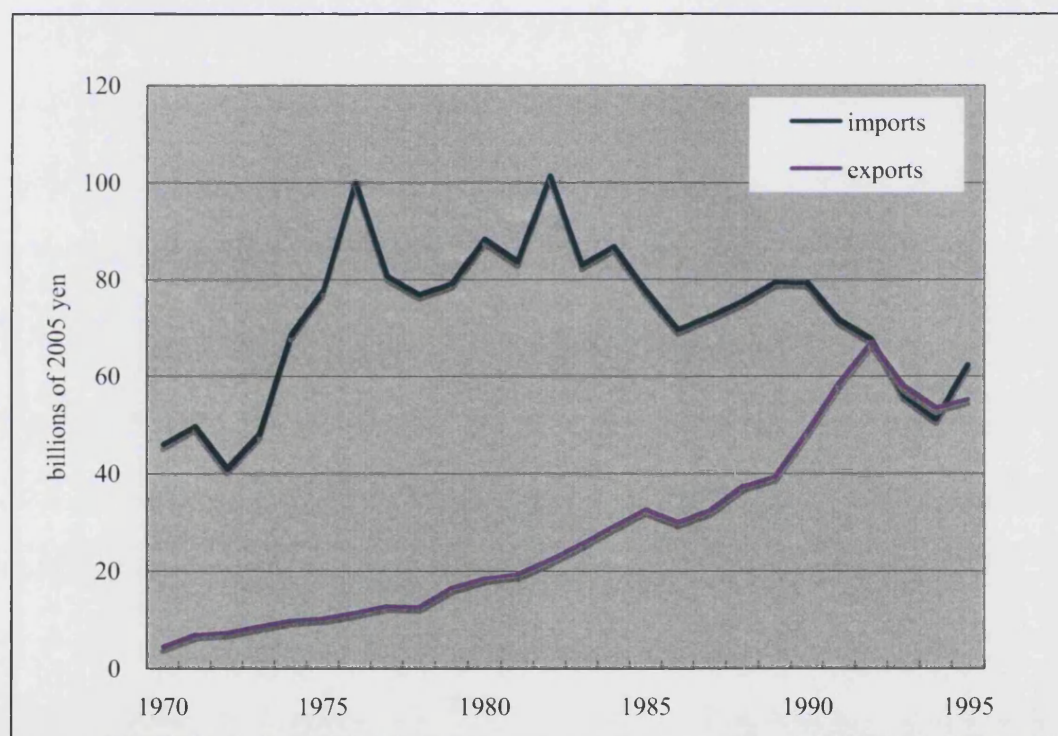


Figure 16. Value of Antibiotic Trade, 1970-1995⁴⁸⁷

Antibiotic exports continued to grow after 1975. Between 1975 and 1990, antibiotic trade grew 50% from 88.0 billion yen to 128.0 billion yen.⁴⁸⁸ Antibiotic imports, as with production, appeared to be heavily influenced by government reforms. The

⁴⁸⁶ GLP GCP and GMP are quality standards for the laboratory, for clinical trials, and for manufacturing, respectively. Yakugyō Jihōsha, *Yakuji Handobukku*. [Pharmaceutical Affairs Handbook] (Tokyo: Yakugyō Jihōsha, 1968-1999).

⁴⁸⁷ Ministry of International Trade and Industry, *Tsūshō Hakusho* [White Paper on Trade] (Tokyo: Ōkurashō Insatsukyoku, 1958-1973); Ministry of International Trade and Industry, *Tsūshō Hakusho* [White Paper on Trade] (Tokyo: Gyōsei, 1974-2000).

⁴⁸⁸ In nominal terms, antibiotic trade grew from 50.5 billion yen in 1975 to 122.4 billion yen in 1990. Ibid.

decline of imports after 1981, for example, corresponds to the government's introduction of biennial price reductions that reduced both physician demand for antibiotics as well as firm incentives to produce antibiotics. The growth of exports, in the mean time, appeared to reflect the rising competitiveness of Japanese antibiotics, as government policies to introduce product patents or liberalise foreign capital incentivised Japanese firms to adopt a more R&D intensive orientation. Antibiotic imports rose only slightly from 77.7 billion yen in 1975 to 79.3 billion yen in 1990 while exports more than quadrupled from 10.3 billion yen to 48.7 billion yen.⁴⁸⁹ While import growth was somewhat stunted by the regular price cuts, export growth reflected the rising capacity of Japanese firms to launch globally competitive antibiotics.

While production levels began to contract in the early 1980s, the Japanese antibiotics sector experienced solid growth in international trade and R&D between 1975 and 1990. The growth in trade was largely due to the government's steps to lift the protective barriers that secured profits for Japanese firms and opened up the market. This was done first through the liberalisation of capital controls, and later through the harmonisation of Japan's pharmaceutical regulations with those in foreign countries. While these measures made it easier for foreign drugs to penetrate the Japanese market, it also made it easier for Japanese drugs to be access overseas markets.

The strong performance of the antibiotic sector was also fuelled by advances in

⁴⁸⁹ In nominal terms, between 1975 and 1990, antibiotic imports increased from 44.6 billion yen to 75.8 billion yen while antibiotic exports increased from 5.9 billion yen to 46.5 billion yen. Ibid.

antibiotic R&D. With advances in science and technology, and health and industrial policies to promote-volume based production, discoveries of semisynthetic and synthetic antibiotics were made during this period.⁴⁹⁰ As more became known of the therapeutic benefits and disadvantages of antibiotics – as well as outcomes of their use over the long-term and in specific populations – better antibiotics were developed.⁴⁹¹ To counter resistant bacterial strains there was also a continuous need to modify and develop new products.⁴⁹²

The introduction of product patents and capital liberalisation had suggested a shift, both that Japanese industry would be incentivised to develop novel drugs that could compete against non-Japanese products, and that Japanese industry was prepared to do so. Antibiotic R&D under the process patent regime centred on the development of new methods of production or new types of formulations to the extent it did not infringe upon patent law. But given the lower threshold for innovation that merited government recognition of NCEs, many Japanese firms pursued incremental product innovations after the introduction of the product patent law. The Japanese antibiotics market grew mostly through the proliferation of similar products, rather than the discovery of original drugs.⁴⁹³ Still, Japanese strengths in drug development evolved

⁴⁹⁰ Most of these were semisynthetic β lactam, aminoglycoside, and macrolide antibiotics or synthetic quinolone antibiotics. In addition, research evolved in new therapeutic applications of microbial metabolites. These included the immunomodulators ubemimex discovered in 1975 by Nippon Kayaku, gusperimus discovered in 1985 by Nippon Kayaku, and tacrolimus discovered in 1986 by Astellas – as well as the anticholesterol agent pravastatin discovered in 1983 by Sankyo. Tacrolimus and pravastatin, two of the four substances discovered during this period, were distributed overseas.

⁴⁹¹ Specific patient populations refer to patient groups whose response to a given drug may differ from an average healthy adult. Such groups include children, pregnant women, the elderly, and patients undergoing other types of treatment. Between 1949 and 1982, the concentration of streptomycin required in a given dose increased from 37.5% to 89.8%.

⁴⁹² See for example, Harold C Neu, “The Crisis in Antibiotic Resistance,” *Science* 257, no. 5073 (1992): 1064-1073; and John Travis, “Reviving the Antibiotic Miracle?” *Science* 264, no. 5157 (1994): 360-362.

⁴⁹³ See for example, Yano Research Institute, *Iyaku Sangyō Nenkan* [Pharmaceutical Industry Annual], (Tokyo: Yano Research Institute, 1985), 2-12.

in step with advances in safety, quality and efficacy standards and were recognised internationally. By the mid 1980s, antibiotics developed in Japan and licensed to American companies accounted for about 20 percent of the \$5 billion US antibiotics market.⁴⁹⁴

3.4.5 Summary of the period between 1975 to 1990

In this period, Japanese antibiotics makers faced increasing challenges and pressures to innovate. These pressures included foreign penetration of the Japanese market, the introduction of a new patent regime, the government's policy to contain drug prices.

3.5 1990 onwards

By the 1990s, the Japanese antibiotics sector had matured as a strong, domestically oriented industry. But the antibiotics market continued to evolve over the 1990s. Facing increasing competition in a saturated home market, many firms diversified out of antibiotics while other firms stepped up efforts to strengthen their overseas presence. These antibiotics makers intensified their R&D efforts to develop globally competitive products. The antibiotics market contracted during this period, as firms suspended sales of imitative antibiotics and innovative antibiotics makers began to concentrate on developing their overseas operations.

3.5.1 A shrinking domestic market

With regular price reductions, rising co-payment levels, and the re-evaluation of

⁴⁹⁴ The US antibiotics market at the time would have been approximately \$9 billion in 2005 values. Eric Schmitt, "What's Hot in Imported Products; Antibiotics Made Jointly," *The New York Times*, 30 November 1986.

existing prescription drugs since the 1980s, the Japanese antibiotics market contracted rapidly in the 1990s.⁴⁹⁵ These measures had been implemented in an attempt to resolve severe fiscal problems arising from the country's anachronistic health care system, which was struggling to cope with an ageing population, rising costs, and growing patient consciousness over health care.⁴⁹⁶ As the government's policies provided symptomatic relief to its finances, it also reduced the size of the antibiotics market.

The biennial price reductions, combined with the lower launch prices of antibiotics, placed an enormous dent in physician prescribing incentives. Artificial demand fell as pharmaceutical price differentials became minimal. In fact, the percentage of prescription drugs dispensed by physicians fell from 87.2% in 1990 to 49.5% in 2005.⁴⁹⁷ The government's decision to raise co-payment levels from the late 1990s also lowered patient demand for antibiotics. Many firms no longer viewed antibiotics as a profitable business, physician demand for antibiotics fell, and an increasing number of better-informed patients were more wary of purchasing unnecessary antibiotics.⁴⁹⁸

In addition, fewer antibiotics came onto the market.⁴⁹⁹ Part of this was due to low

⁴⁹⁵ Ministry of Health and Welfare, *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Yakugyō Keizai Kenkyūjo, 1968-2000).

⁴⁹⁶ See Naoki Ikegami and John Creighton Campbell, "Health Care Reform in Japan: The Virtues of Muddling Through," *Health Affairs* 18 (May/June 1999): 56-75.

⁴⁹⁷ Japan Pharmaceutical Association, *Iyakuhin Bungyō Shinchoku Jōkyō* [Progress on the Separation on the Prescribing and Dispensing of Medicines], Japan Pharmaceutical Association, <http://www.nichiyaku.or.jp/contents/bungyo/default.html> (accessed 20 April 2008).

⁴⁹⁸ The biennial price reductions on reducing demand has been widely discussed. See for example, Hidenao Takahashi, "Iyakuhin no Juyō no Kakaku Danryokusei no Suikei [The Price Elasticity of Demand in Pharmaceuticals: An Examination of the Biennial Price Reductions]," *Hitotsubashi University COE Working Paper* 12 (August 2005): 16

⁴⁹⁹ Yakugyō Jihōsha, *Yakuji Handobukku* [Pharmaceutical Affairs Handbook] (Tokyo: Yakugyō Jihōsha, 1968-1999); Jihō,

levels of discovery during this period. Indeed, manufacturing and import approvals for new antibiotics tapered off after the 1990s.⁵⁰⁰ The number of antibiotics approved for manufacture or import averaged 1.9 per year in the 1990s compared to 4.9 per year in the 1980s. With the continual need to develop new drugs for antibiotic resistant infections, firms invested in new, advanced methods of drug discovery such as genomic science, high throughput screening, rapid DNA sequencing, combinatorial chemistry, and cell based assays to launch innovative antibiotics.⁵⁰¹ Daiichi Pharmaceutical, for example, had a collaborative agreement with the US firm Pharmacopoeia to use combinatorial chemistry and high throughput screening for new drug discovery.⁵⁰² Yet in Japan, as elsewhere, fewer new antibiotics were discovered in the 1990s compared to previous decades.⁵⁰³

Moreover, the antibiotics market became smaller as the few antibiotics that were discovered encountered longer drug approval times. Politically, exposure of the HIV blood scandal in the 1980s slowed the drug approval process and discouraged many firms from investing in antibiotics. For many firms, investment in antibiotics became less attractive, as longer assessment times raised the cost of drug development for a relatively low priced drug. As well, the drug scandal had produced better-informed patients reluctant to spend on unnecessary antibiotics. The drug scandals also

Yakuji Handobukku [Pharmaceutical Affairs Handbook] (Tokyo: Jihō, 2000-2007).

⁵⁰⁰ Ibid.

⁵⁰¹ J. R. Broach and J. Thorer, "High-throughput Screening for Drug Discovery," 14-16; Jürgen Drews, "Drug Discovery: A Historical Perspective," *Science* 287, no. 5460 (17 March 2000): 1962.

⁵⁰² Pharmacopoeia Drug Discovery, Inc. *Annual Report 2006* (Cranbury, NJ: Pharmacopoeia Drug Discovery, Inc., 2007), 2.

⁵⁰³ Joichi Kumazawa and Morimasa Yagisawa, "The History of Antibiotics: The Japanese Story," 126; Morimasa Yagisawa "Biseibutsu Taisha Sanbutsu Tansaku Kenkyū no Dōkō [Trends in Exploratory Research of Microbial Metabolite Part 2; 20 Years after Antibiotics]," *Baiosaiensu to Indasutori* 58, no. 2 (2000): 92. The difficulty of drug discovery despite advances in phenomenal advances in drug discovery technologies has been widely discussed. See for example, Gerry Higgs, "Molecular Genetics: the Emperor's Clothes of Drug Discovery?" *Drug Discovery Today*, 9 (September 2004): 727-729.

contributed to the contraction of the antibiotics sector in the 1990s.

The decline in actual therapeutic demand, too, reduced size of the antibiotics market. By the 1990s, with improvements in health care and public health, demand for antibiotics had become minimal. Mortality and morbidity rates for infectious diseases stood at remarkably low levels compared to half a century earlier. While it was true that the incidence of infectious disease in Japan tended to be higher than countries such as the United States, United Kingdom, or Germany, the incidences and deaths of infectious diseases such as diphtheria, typhoid fever or dysentery were negligible and declining.⁵⁰⁴

⁵⁰⁴ In 1999, tuberculosis still affected 43.8 thousand and killed 3,000 in Japan, but these figures were about 10% and 2% of 1945 figures, respectively. See Ministry of Health and Welfare, "Patients and Deaths of Infectious Diseases and Food Poisoning (1876-1999)," <http://www.stat.go.jp/data/chouki/02.htm> (accessed 6 May 2008); and World Health Organisation. Global TB database, accessed 1 November 2007. http://www.who.int/tb/country/global_tb_database/en/index.html.

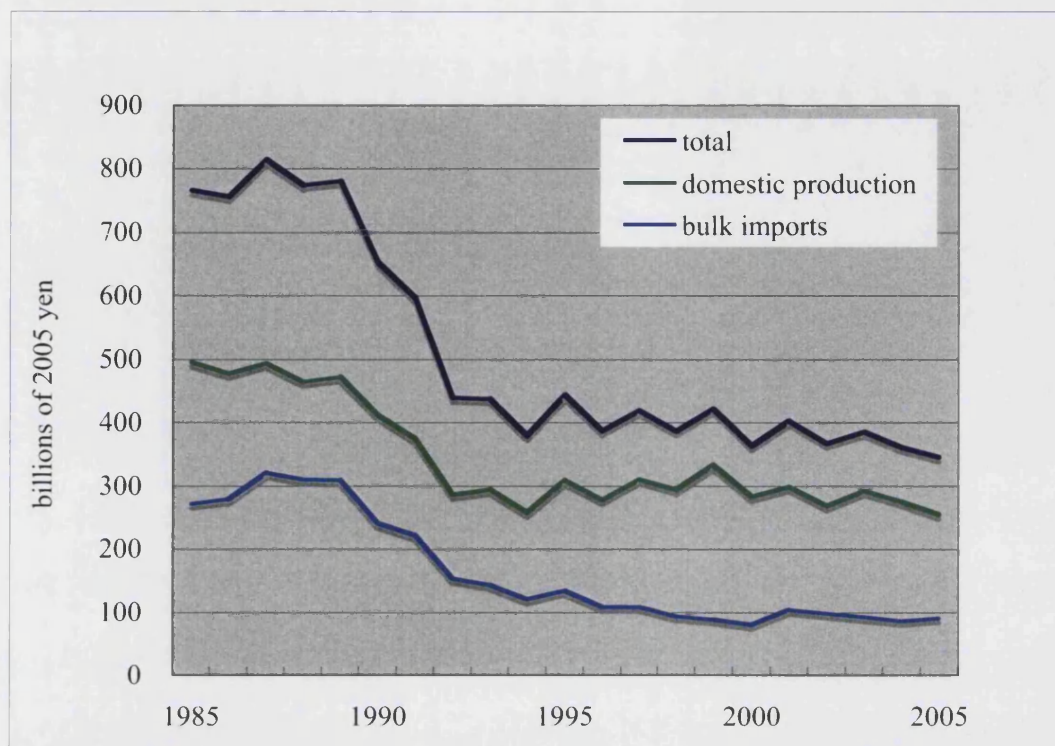


Figure 17. Value of Antibiotic Production, 1985-2005⁵⁰⁵

With the government's cost containment measures, few new discoveries, and limited therapeutic demand, antibiotic production levels contracted then stabilised in the 1990s. Indeed, for the first time since the 1940s, antibiotics production fell to almost half the level a decade earlier. While antibiotic production levels averaged 858 billion yen during the 1980s, for example, these figures almost halved to an average of 456 billion yen during the 1990s, thereafter steadying near 400 billion yen.⁵⁰⁶ In the end, few firms found it attractive to invest in what were now relatively low priced drugs that were reduced every two years – particularly given the rising cost of drug development and declining physician dispensing rates. Facing saturated markets at home, many firms began to suspend their sales of antibiotics or seek new opportunities

⁵⁰⁵ *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Yakugyō Keizai Kenkyūjo, 1968-2000); Ministry of Health, Labour and Welfare, *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Jihō, 2001-2006).

⁵⁰⁶ *Ibid.* *Yakuji Jihōsha, Yakuji Handobukku* [Pharmaceutical Affairs Handbook] (Tokyo: Yakugyō Jihōsha, 1968-1999).

abroad.⁵⁰⁷

3.5.2 Stepping up efforts at globalisation

As in most sectors of the Japanese economy, the bursting of the bubble in 1990 prompted a reorientation and modernisation of industry. As mentioned in the overview chapter, the major change in Japan's pharmaceutical industry was the harmonisation of regulatory standards with Europe and the United States. It was a significant milestone that not only opened doors to foreign competition, but also made it easier for Japanese drug makers to access overseas markets. Reforms to the distribution system in the early 1990s also improved transparency in the market and prompted greater competition in the domestic market. The enforcement of quality standards such as GCP and GPMP in 1990 and 1993, respectively, also improved the quality of Japanese drugs. In the late 1990s, the government discarded another longstanding protectionist policy that obliged foreign firms to establish production facilities in Japan to operate the country. As well, the drug approval process was simplified and made more transparent.⁵⁰⁸ These reforms made the Japanese market become much more comparable to the advanced markets of the United States and Europe.

While the biennial price reductions dented innovative incentives, the government's new policies to harmonise regulations and encourage rigorous innovation encouraged Japanese firms to develop globally competitive products. While antibiotic discoveries

⁵⁰⁷ See for example, "Japan's Medicine Men Take Aim," *The Economist*, 2 March 1991, 69.

⁵⁰⁸ Yakugyō Jihōsha, *Yakuji Handobukku* [Pharmaceutical Affairs Handbook] (Tokyo: Yakugyō Jihōsha, 1968-1999); Yakuji Nippōsha, *The Japanese Pharmaceutical Industry in the New Millennium* (Tokyo: Yakuji Nippōsha, 2001). See also, Ralph Paprzycki, "The Impact of Foreign Direct Investment in Japan: Case Studies of the Automobile, Finance, and Health Care Industries," *Hi-Stat Discussion Paper Series* 141 (February 2006): 26-31.

were not numerous, new antibiotics such as quinolones were launched by Daiichi, Dainippon, and Toyama Kagaku, while several cephalosporin drugs were launched by Shionogi, Takeda, and Fujisawa.⁵⁰⁹ The major dilemma for Japanese antibiotics makers was not so much to strengthen their R&D capacities but to develop the capacity to commercialise their discoveries abroad. Japanese antibiotics firms were latecomers to the global market. While they had previously gained profits from licensing agreements, they failed to reap the gains from a direct marketing presence abroad.

Trade figures demonstrate that Japan's antibiotic sector was gaining the capacity to compete in the global market in the 1990s. Over the decade, antibiotic exports rose from 48.7 billion yen to 57.3 billion yen while imports declined slightly from 79.3 billion yen to 57.3 billion yen. In 2000, import and export figures were roughly comparable, as Japanese firms imported 58.3 billion yen as it exported 57.3 billion yen.⁵¹⁰ Following the burst of Japan's economic bubble in the 1980s, antibiotic trade did decline in the early 1990s. Japan's imports of antibiotics originated from Britain, Germany, and Switzerland while its exports were destined for China, Thailand and Italy.⁵¹¹

⁵⁰⁹ Saburō Fukai, ed., *Konnichi no Shinyaku: Kindai Iyakuhin no Hensen* [New Drugs Today: Changes in Modern Pharmaceuticals] (Tokyo: Yakuji Jihōsha, 1995) 928-941, 854-894.

⁵¹⁰ In nominal terms, between 1990 and 2000, antibiotic exports rose from 46.6 billion yen to 59.0 billion yen while antibiotic imports declined from 75.8 billion yen to 59.9 billion yen. Ministry of International Trade and Industry, *Tsūshō Hakusho* [White Paper on Trade] (Tokyo: Gyōsei, 1974-2000); Ministry of Economy Trade and Industry, *Bōeki Dōkō Dētabēsu* [Database on Trends in Trade], http://www.meti.go.jp/policy/trade_policy/trade_db/html/01.html (accessed 12 May 2008).

⁵¹¹ Ministry of Health and Welfare, *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Yakugyō Keizai Kenkyūjo, 1968-2000).

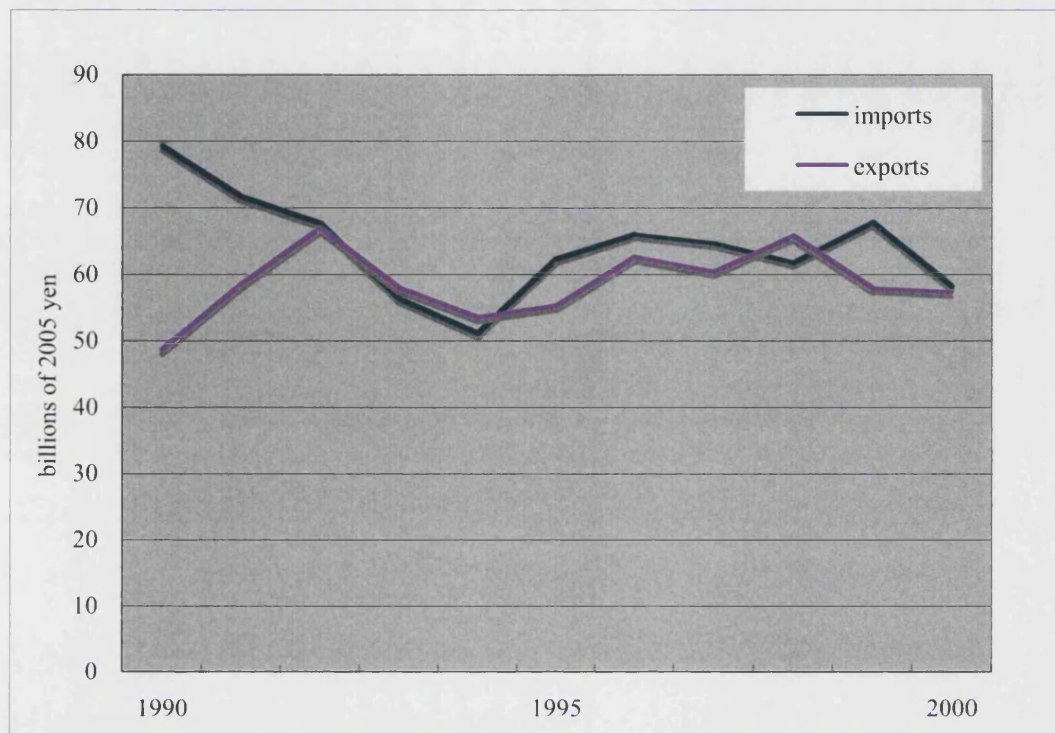


Figure 18. Value of Antibiotic Trade, 1990-2000⁵¹²

But this data needs to be interpreted with caution, as they do not fully capture Japan's performance in antibiotics. For example, the export destinations of Japanese antibiotics have mostly been to the developing world rather than to the developed world.⁵¹³ Import figures also do not include the rise in the number of overseas products directly distributed by foreign firms. Import figures may also be lower due to downward price pressures in the domestic market. Japanese drug prices have been roughly comparable with other countries, but the biennial price reductions have led to a more rapid decline in prices over the patent protection period.⁵¹⁴ At the same time, export figures also do not capture the availability of Japanese antibiotics abroad, as most firms licensed out their technologies rather than directly distributing their

⁵¹² Ministry of International Trade and Industry, *Tsūshō Hakusho* [White Paper on Trade] (Tokyo: Gyōsei, 1974-2000).

⁵¹³ Ministry of Health and Welfare, *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Yakugyō Keizai Kenkyūjo, 1968-2000).

⁵¹⁴ See Nigel Thompson, *International Price Comparison: Japan* (Tokyo: Japan Pharmaceutical Manufacturers Association Long Term Vision Research Council, 1999).

products abroad.⁵¹⁵ Antibiotics makers struggled to expand in the midst of increasing competition with lower cost, quality antibiotics from the developing world – and from high barriers to entry in most markets. Historical data on antibiotic trade, technology trade, and NCE discoveries well demonstrate the strengths of Japan’s antibiotics sector, as do qualitative data from academic and popular press.⁵¹⁶

To a certain extent, the strengths of Japan’s antibiotics sector were observed in the absence of foreign firms in the Japanese market. By the new millennia, large multinational firms such as GlaxoSmithKline, Abbott, Bayer and Roche topped global antibiotics rankings and dominated most antibiotics markets in world, ranging from United States, the United Kingdom and Germany.⁵¹⁷ But these firms were largely absent in Japan. Instead, domestic firms such as Shionogi, Fujisawa, and Daiichi dominated the Japanese market.⁵¹⁸

This was partly because the Japanese market still posed barriers to entry. Antibiotics were a mature sector comprised of many substitutable, high quality drugs that were marketed by numerous firms with extensive distributional networks. Japan was not an attractive market for most foreign firms, as local partnerships were essential for

⁵¹⁵ See for example, “Global Drug Market: 30 Years of Growth,” *Pharma Marketletter*, January 4, 1993; Peter Martin, “Weak Link in the Chain: Distribution Difficulties have meant that Japan’s Successes in the West’s Car and Consumer Electronics Markets have not been Equalled in Other Industries,” *Financial Times*, 6 March 1997.

⁵¹⁶ For trade statistics, see Ministry of International Trade and Industry, *Tsūshō Hakusho* [White Paper on Trade] (Tokyo: Gyōsei, 1974-2000) and Ministry of Health and Welfare, *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Yakugyō Keizai Kenkyūjo, 1968-2000). Management and Coordination Agency, Statistics Bureau & Statistics Centre, *Kagaku Gijutsu Kenkyū Chōsa Hōkoku* [Report on the Survey of Research and Development] (Tokyo: Management and Coordination Agency, 1985-2000). Various writers have documented Japan’s strong performance in antibiotics. See for example, Michael Reich, “Why the Japanese Don’t Export More Pharmaceuticals: Health Policy as Industrial Policy,” 136; Eric Schmitt, “What’s Hot in Imported Products; Antibiotics Made Jointly,” *The New York Times*, 30 November 1986.

⁵¹⁷ Datamonitor, “Global – Antibacterial Drugs,” *Industry Profile* (London: Datamonitor, 2002), 8.

⁵¹⁸ Datamonitor, “Japan – Antibacterial Drugs,” *Industry Profile* (London: Datamonitor, 2002), 9. Most Japanese firms relied upon domestic sales for a significant portion of total revenue.

distribution, just as the reverse was true for Japanese firms. But the absence of foreign firms was also reflective of the fact that Japanese firms were competitive. Indeed, during the mid 1990s, four of the top 15 global antibiotics firms were Japanese, while six were American.⁵¹⁹ While the strengths of these firms were better known to the domestic – rather than global – market, the government's earlier policies had succeeded in establishing a strong Japanese antibiotics industry.

3.5.3 Summary of the period between 1990 to 2005

The value of antibiotics produced declined substantially over the 1990s. It did so for several reasons. Antibiotics were a now a mature drug with relatively low prices. Rather than invest in developing antibiotics, many firms opted to invest in launching more profitable types of drugs. In addition, the 1992 reforms to Japan's distribution system eliminated the artificially high demand for antibiotics, and lowered production levels. Moreover, in the 1990s, the government began to harmonise Japan's pharmaceutical regulations with American and European regulations. As drugs approved in foreign countries were recognised in Japan, domestic firms faced greater competition from foreign firms in their home market. Antibiotics of minimal innovative value were no longer able to compete in the Japanese market. In addition, as drugs approved in Japan were recognised in the United States and Europe, more Japanese firms began to channel their efforts on expanding abroad.

⁵¹⁹ Jenny Wilson, *Antibacterial Products and Markets, Scrip Reports* (Richmond: PJB Publications, 1997), 137.

3.6 Analysis of the antibiotics chapter

This section considers several possible explanations as to why the Japanese antibiotics sector flourished in comparison with the rest of the industry. One hypothesis is that Japan's strong foundations in science supported the development of a strong antibiotics sector. The historical strengths of Japan's medical research, in particular, have been cited by scholars such as James Bartholomew.⁵²⁰ Contributions to the international scientific community made by Meiji era scientists such as Sahachirō Hata, Shibasaburō Kitasato, and Hideyo Noguchi, who led scientific research both inside and outside of Japan attest not only to the calibre of scientists in Japanese universities, but also to the academic infrastructure that supported scientific research since the Meiji period.

Some scholars have argued that while the Japanese have been very competitive in the applied sciences, the country's comparative weakness in the basic sciences may have undermined the development of a stronger pharmaceutical industry.⁵²¹ The Meiji era achievements of Japanese academic science, particularly in bacteriology, would suggest that this is untrue.⁵²² But even if the claims made by these scholars held some validity, Japan's relative strengths in applied science in fact, would not have hampered the discovery or development of antibiotics, which are based more on the linear,

⁵²⁰ See James R. Bartholomew, *The Formation of Science in Japan* (New Haven: Yale University Press, 1989).

⁵²¹ See for example, Eleanor Westney, "Country Patterns in R&D Organization: The United States and Japan," in *Country Competitiveness: Technology and the Organizing of Work*, by Bruce Kogut (Oxford: Oxford University Press, 1993), 36-53; David T. Methé and Joan D. Pinner-Hahn, "Globalization of Pharmaceutical Research and Development in Japanese Companies: Organizational Learning and the Parent-Subsidiary Relationship," in *Japanese Multinationals Abroad: Individual and Organizational Learning*, by Schon Beechler and Allan Bird (New York: Oxford University Press, 1999), 191-210.

⁵²² See for example, Christian Oberlaender, "The Rise of Western 'Scientific Medicine' in Japan: Bacteriology and Beriberi," in *Building a Modern Japan: Science, Technology and Medicine in the Meiji Era and Beyond*, ed. Morris Low (New York: Palgrave Macmillan, 2005), 11-36.

incremental, and evolutionary learning rather than breakthrough discoveries. While Japan's historical foundations in science demonstrate how the country provided a favourable environment for antibiotic development, it does not fully explain why Japanese firms were actually able to develop a strong antibiotic sector.

A more plausible explanation for the strength of Japan's antibiotics sector stems from industrial structure. Japan's pharmaceutical industry was dominated by many small firms compared to the pharmaceutical industries of other countries. While Japanese pharmaceutical firms were smaller than their foreign counterparts, antibiotic R&D required fewer resources compared to other types of drugs, such as anticancer drugs. As Japanese firms opted to invest in antibiotic R&D, they were able to develop a strong antibiotics sector.

With a large number of firms engaged in antibiotic production, Japan's antibiotics sector was also intensely competitive. Moreover, the barriers to entry were relatively low, and food, beverages, and textiles firms were able to enter the industry. In order to survive intense competition, Japanese firms developed antibiotics with better quality, safety and efficacy profiles. While the competitive domestic environment may have contributed to the strong performance of Japan's antibiotics sector, it does not ultimately account for its strengths. The United States, for example, developed a world-class antibiotics sector in a market dominated by a few large firms. Industrial structure alone does not provide a sufficient reason for the strengths of Japan's antibiotics sector.

The close research links formed between Japanese academia and the pharmaceutical industry also help explain why the antibiotics sector became internationally competitive. During the Second World War, for example, government, academic, and industry scientists collaborated in their attempts to commercialise penicillin. These collaborative links were often based on long standing personal connections developed during university, and persisted well into the post-war era. The government supported antibiotic research since the immediate post-war period, and these connections were invaluable in helping translating the fruits of academic research into leading commercial discoveries such as kanamycin, josamycin, or oxalyplatin in later years. Japanese academics were not restricted from collaborating with firms in the formative years of Japan's antibiotics sector.

While restrictions on formal collaborations with industry were put in place after the student protests of the late 1960s, this rule had a limited impact on the formation of the antibiotics sector. In addition, the restrictions were lifted in 1998.⁵²³ Louis Galambos and Jane Eliot Sewell have argued that networks of collaboration were essential to the building of a competitive pharmaceutical industry in the United States.⁵²⁴ The same was true in Japan. But smaller firms without links to academia such as Kyorin and Toyama Chemical were also able to build a strong foothold in the Japanese antibiotics

⁵²³ See Takehiko Hashimoto, "The Hesitant Relationship Reconsidered: University-Industry Cooperation in Post-war Japan," in *Industrializing Knowledge: University-Industry Linkages in Japan and the United States*, eds. Lewis M. Branscomb, Fumio Kodama, and Richard L. Florida (Cambridge: MIT Press, 1999), 234-251; and Robert Kneller, "The Beginning of University Entrepreneurship in Japan: TLOs and Bioventures Lead the Way," *Journal of Technology Transfer* 32 (2007): 435-456.

⁵²⁴ Louis Galambos and Jane Eliot Sewell, *Networks of Innovation: Vaccine Development at Merck, Sharp & Dohme, and Mulford, 1895-1995*.

market. The strength of Japan's antibiotics sector cannot sufficiently explained by the existence of collaborative networks.

Another explanation for the development of a strong antibiotics sector in Japan relates to the strong demand for antibiotics created under the country's medical system. Japanese physicians both prescribed and dispensed drugs. Under Japan's fee for service system, Japanese physicians were compensated more generously for prescribing rather than consultation services. Physicians were particularly incentivised to prescribe drugs that could be easily administered to a wide patient population, and had a greater difference between wholesale and retail prices. Japan's antibiotics sector grew, as both physicians and patients were insensitive to actual drug prices under the universal health care system. After all, the government reimbursed physicians for drug sales and subsidised patients for drug expenses.

Finally, it was the effectiveness of government policy that helped develop a strong, globally competitive antibiotics sector. Until the 1970s, Japan's government concentrated on enabling Japanese firms to acquire foreign technologies. As Japanese firms caught up with Western firms, the government gradually opened the market.

The most important turning point occurred when the government liberalised capital controls in 1975 and introduced product patents in 1976. The shift from a process patent regime to a product patent regime encouraged Japanese pharmaceutical firms to pursue product innovations. To compete against foreign firms, Japanese firms began to

strengthen their R&D capacities and launch more competitive products.

The government's introduction of product and quality standards since the 1970s also helped improve the quality, safety and efficacy of Japanese pharmaceutical products, But it is worthwhile noting that country-specific standards also protected firms from foreign competition, and eased Japan's transition to a more R&D intensive and global industry. This was because foreign firms found it overly costly and risky to adapt their products for the Japanese market. Government policies helped nurture Japan's pharmaceutical industry within a heavily protected environment.

The harmonisation of Japanese pharmaceutical regulations with Europe and the United States in the 1990s further pressed Japanese firms to invest in substantial innovations to survive the rising competition from foreign firms. The Japanese government changed its policies toward the antibiotics sector in a timely fashion, encouraging Japanese firms to pursue breakthrough innovations after Japan had caught up with the West. The timely implementation of these policies was key to the strong performance of Japan's antibiotics sector.

Government intervention was more effective in developing the antibiotics sector than in other pharmaceutical sectors because of certain features specific to antibiotics. Antibiotics are a hospital and clinic based therapy that can be prescribed for a wide variety of infections. As a remedy for an acute ailment, its cost burden was relatively low, yet its effects were quickly observable, and patient demand was high.

Other features of antibiotics facilitated Japan's entry into global markets. Antibiotics are medicines that are used for a short period of time for a wide range of infectious ailments, and have few side effects. Patients and physicians can evaluate the safety and efficacy of antibiotics within a short period of time. These features are particularly important when translating drugs into overseas markets. Obtaining approval in foreign drug regimes is difficult for drugs that require long-term administration or have heavy side effects – such as cancer drugs. Japanese firms have been much more successful in exporting or licensing antibiotics because their safety and efficacy are relatively easy to establish for drug authorities.

In addition to its industrial policies, the government's health policies also helped strengthen Japan's antibiotics sector. In introducing universal health care in 1961, the government guaranteed demand for prescription pharmaceuticals and supported the growth of Japan's pharmaceutical industry. The government further expanded this market by reducing co-payment levels and introducing free health care for the elderly. By setting high prices on antibiotics, the government also provided strong incentives for firms to launch antibiotics, while the greater price differentials in high-priced drugs incentivised physicians to prescribe more antibiotics. As a drug prescribed to a wide population, these government policies were particularly helpful in expanding the size of Japan's antibiotics market.

The Japanese antibiotics sector was built upon a long history of expertise in

fermentation technology, strong academic science, and informal networks between government, industry and academia. By a stroke of luck, antibiotics proved relatively easy to discover, produce, and export in a developing economy. Helped by the Occupation regime and the government's developmental health and industrial policies, Japanese antibiotics makers were able to capitalise on their potential.

4 Anticancer drug chapter

In the early 1980s, many Western observers speculated that the Japanese pharmaceutical industry might become a global leader. In fact, *The Economist* reported in 1983 that Japan rivalled America as a place of discovery for new drugs, and that Western pharmaceutical companies were increasingly turning to Japan. In particular, it emphasised the strengths of the Japanese antibiotics sector, and the potentials of the anticancer drug sector.⁵²⁵ *The Economist* was suggesting that Japanese pharmaceutical firms were about to penetrate overseas markets and achieve successes similar to those of Toyota and Sony in the automobile and electronics sectors. Other Western publications in the 1980s discussed the potential threat posed by Japanese firms who might – with their traditional strengths in fermentation technology – be better positioned to take advantage of new advances in biotechnology to develop innovative therapies, including anticancer drugs.⁵²⁶

To date, Japanese pharmaceutical firms have largely failed to live up to these predictions. The weakness of Japan's pharmaceutical industry is especially visible in the realm of anticancer drugs. Japan has had a massive trade deficit in anticancer drugs; most anticancer drugs in the country are either imports or foreign-discovered drugs produced under license.⁵²⁷ It is true that Japanese pharmaceutical firms have launched several anticancer drugs that have been used in other countries. But the

⁵²⁵ "Japanese Drug Companies Pull Ahead in the Race to Innovate," *The Economist*, 24 September 1983, 93.

⁵²⁶ U.S. Congress, Office of Technology Assessment, *Commercial Biotechnology: An International Assessment* (Washington, DC: U.S. Government Printing Office, 1984); Geoffrey M. Holdridge, ed., "JTEC/WTEC Annual Report and Program Summary, 1993/1994" (Baltimore: Japan Technology Evaluation Center, 1994).

⁵²⁷ Yakugyo Jihōsha, *Yakuji Handobukku* [Pharmaceutical Affairs Handbook] (Tokyo: Yakugyo Jihōsha, 1968-1999); Jihō, *Yakuji Handobukku* [Pharmaceutical Affairs Handbook] (Tokyo: Jihō, 2000-2007).

successes have been few and far between, and contradict the general trend depicted in the trade data. In addition, the more successful Japanese drug companies that have developed global drugs, such as Takeda, have expanded abroad by transferring their R&D, production, and marketing operations overseas. These firms have sought to benefit from overseas environments more favourable to pharmaceutical innovation. The experience of firms such as Takeda suggests at why Japan's anticancer drug sector as a whole has underperformed.

The previous chapter demonstrated why Japan's antibiotics sector flourished. In contrast, this chapter surveys the development of the anticancer drug sector in Japan and considers why it failed to live up to the optimistic predictions made by foreign observers in the 1980s. It concludes by providing several possible explanations for the failure of Japan to develop a globally competitive anticancer drug sector.

The chapter follows the development of the anticancer drug sector across four phases of development. The first phase refers to the historical foundations of anticancer drug development before the Second World War. In the next phase during the 1950s and 1960s – which coincided with the golden age of antibiotic discovery – Japanese firms launched anticancer antibiotics and pursued the small-scale production of foreign anticancer drugs under license. Between 1975 and 1990, there was a volume-based expansion of drugs for the domestic market. During this phase, anticancer drugs of limited efficacy flourished in a market protected by universal health insurance, unique product standards, a distinct medical system – and links between government, industry

and academia. The Japanese pharmaceutical industry, in fact, lost more than a decade in developing a globally competitive anticancer drug sector, as it misdirected investments into developing largely ineffective drugs rather than breakthrough drugs.

After the early 1990s, regulatory reforms opened the market to foreign firms and drugs, and the government improved incentives for firms to adopt a more research-intensive orientation. But with more favourable regimes for innovation abroad, leading Japanese firms began to move some of their core R&D operations abroad. While the more outward oriented Japanese firms became stronger, launched blockbuster drugs, and expanded their global reach, the more domestic oriented firms began to suffer as they faced stiff competition from foreign firms in the domestic market.

4.1 On anticancer drugs

Anticancer drugs refer to a substance, other than food, that is used to prevent, diagnose, treat, or relieve symptoms of cancer, a disease in which abnormal cells divide without control and migrate from the original site to other parts of the body.⁵²⁸ Cancer treatments, which aim to remove or control the cancer, range from surgery, radiation, chemotherapy, immunotherapy, hormone therapy, and bone marrow transplantation.⁵²⁹

The range, effectiveness, and purpose of anticancer drugs have evolved in step with medical advances in cancer therapy. In practice, the specific drugs used differ according to a range of factors – such as the afflicted body region, type, and stage of

⁵²⁸ National Cancer Institute, "Dictionary of Cancer Terms," National Cancer Institute, <http://www.cancer.gov/dictionary/> (20 March 2007).

⁵²⁹ Jacqueline L. Longe, Deirdre S. Blanchfield, eds., *Gale Encyclopedia of Medicine*. (Farmington Hills, : Gale Group, 2001), 635-636.

cancer. Anticancer drugs are classified into several categories according to their chemical origins and functional attributes. These include alkylating agents, antimetabolites, plant alkaloids, antitumour antibiotics, hormonal therapies, and others.

As in other therapeutic sectors, the product attributes of anticancer drugs shape its market dynamics. Compared to older drugs such as antibiotics, anticancer drugs – as a newer drug – share the attributes of more recent therapies for neurological disorders or autoimmune diseases. For example, the safety and effectiveness profile of newer drugs are often unknown and continue to be improved. Such features reflect the status of medical research, as scientists are only beginning to understand the complex interactions between the genetic and environmental factors that govern the progression of diseases grouped as cancer. While drug profiles are continuously modified, newer drugs such as anticancer drugs tend to exhibit serious side effects such as hair loss, nausea, or death.⁵³⁰ To balance the effectiveness of anticancer drugs against the high levels of toxicity, the amount and type of drug prescribed is adjusted according to the patient. While some drugs can be taken orally, most anticancer drugs require more invasive, hospital based methods of administration.

A single anticancer drug is generally used as part of a therapy with other anticancer drugs for a particular type and stage of cancer over a prolonged period of time, and generally produces severe side effects. This is unlike antibiotics, where a given drug is

⁵³⁰ This is because most anticancer drugs available today cannot distinguish between benign and malign cells. See Jacqueline L. Longe, Deirdre S. Blanchfield, eds., *Gale Encyclopedia of Medicine*, 634-635.

effective toward a wide range of infectious diseases for a short period without risk of significant side effects. Given the small number of applicable conditions, anticancer drugs are produced on a more limited scale compared to other therapeutic sectors, such as antibiotics. As treatment for a life threatening disease, however, therapeutic demand for anticancer drugs tends to be strong and price insensitive. Anticancer drugs also tend to be highly profitable, with significant first mover advantages. This is because in Japan, initial drug prices for anticancer drugs are high do not fall as quickly as in other therapeutic sectors. In addition, few substitutes are available. Moreover, switching costs are high due to the long-term and individualised nature of cancer therapy, where changing to another therapy carries additional therapeutic risk.

Therefore, whereas the antibiotics market is characterised by intense price competition, the anticancer drug market is characterised largely by non-price competition. In the anticancer drug market, sales are determined by a drug's therapeutic quality and the marketing efforts of medical representatives. Despite the incomplete nature of anticancer drugs as a product, the life-saving prospects of a scarce yet risky remedy with few substitutes have created a price inelastic market where information is highly valued.⁵³¹

4.2 Predawn, before 1945

Before 1945, there was no anticancer drug sector in Japan. This was because, in Japan

⁵³¹ See Hisao Endō, Maturō Oka, Masaki Ozawa, Yoshiaki Kamoya, and Nobuo Tanaka, "Iryōyō Iyakuhiin Shijō ni Okeru Kyōsō Keitai [Forms of Competition in the Ethical Pharmaceutical Market]," in *Iyakuhiin Sangyō Soshikiron* [On the Organisation of the Pharmaceutical Industry], ed. Tsurihiko Nanbu (Tokyo: University of Tokyo Press, 2002), 49-74.

or elsewhere, there were no anticancer drugs available before World War II. But Japanese scientists were actively engaged in cancer research well before the Second World War. Japanese government officials, entrepreneurs, and academic scientists worked together to pursue cancer research – including research on cancer therapies.

As James Bartholomew has noted, the First World War prompted Japan to strengthen its capacities in scientific research.⁵³² Japanese efforts in cancer research, in fact had merited the formation of national research institutes such as the Japan Foundation for Cancer Research (*Gankenkyūkai*) in 1908 and the Japanese Cancer Association (*Ganakkai*) in 1935.⁵³³ Japan was among the first countries to establish national cancer research institutes. While Britain's Imperial Cancer Research Fund was established in 1902, the American National Cancer Institute in 1937, and the German Cancer Research Center (*Deutsches Krebs Forschungs Zentrum*) was established in 1964.⁵³⁴

Despite these early developments, however, Japanese cancer research remained relatively small, unorganised, and lacked coordination between fundamental and applied research. It seemed to lack the government guidance that supported industrial research in countries such as the United States, Britain, and Germany. This poorly integrated approach to research often lacked the momentum to translate academic

⁵³² James R. Bartholomew, *The Formation of Science of Japan*, 199-237.

⁵³³ Japan Cancer Association, "Ganakkai no Rekishi [The History of the Japan Cancer Association]," Japan Cancer Association. <http://www.jca.gr.jp/b01.html> (accessed 1 December 2007).

⁵³⁴ National Cancer Institute, "The National Cancer Institute Act, 1937-2007: Celebrating 70 Years of Excellence in Cancer Research," The National Cancer Institute Act, <http://www.cancer.gov/aboutnci/ncia> (accessed 1 December 2007); Cancer Research UK, "Our History," <http://info.cancerresearchuk.org/cancerandresearch/historyandachievements/ourhistory/> (accessed 1 December 2007); German Cancer Research Center, "History," <http://www.dkfz.de/en/dkfz/geschichte.html>, (accessed 1 December 2007).

research into a final product. After 1945, cancer research in the United States was backed by the American government, who helped coordinate, and organise large scale, interdisciplinary, and results-oriented industrial research at the National Cancer Institute.⁵³⁵ By World War II, Germany and the United States had managed to integrate academic science in pharmaceuticals with industrial research, whereas academic pharmaceutical research in Japan remained detached from the industrial laboratory well after World War II.⁵³⁶

Japan was unable to develop a strong anticancer drug sector despite its strong foundation in academic science. Japan was neither able to capitalise on the fruits of its early research nor the networks of collaboration formed between government, industry, and academia. It is true that, at a time when the disease was less common, there was less demand for anticancer drugs. In addition, most of Japan's small pharmaceutical firms were wholesalers or licensed producers of foreign-discovered drugs who lacked the capital or equipment necessary to develop anticancer drugs. Research institutes, such as Riken, were established to promote university-industry collaboration in scientific research in the early 20th century. But there remained a relative disconnect between university scientists who pursued research for purely academic purposes and industrial scientists who pursued research for commercial ends.⁵³⁷ What appears lacking was a government commitment to industrial R&D that would coordinate these

⁵³⁵ Robert F. Bud, "Strategy in American Cancer Research After World War II: A Case Study" *Social Studies of Science* 8 (November 1978): 425-459.

⁵³⁶ Jonathan Liebenau, "Industrial R&D in Pharmaceutical Firms in the Early Twentieth Century," *Business History* 26, no.3 (1984): 229-346.

⁵³⁷ See for example, Bowen C. Dees, "Japanese Science and Technology Before 1945," in *The Allied Occupation and Japan's Economic Miracle: Building the Foundations of Japanese Science and Technology, 1945-52* (Richmond: Japan Library, 1997): 1-11.

differences and help translate the fruits of academic research into commercial products.

4.3 Beginnings, from 1945 to 1975

Japan's anticancer drug sector emerged during the 1950s when the first chemotherapy drugs began to be sold in Japan. As elsewhere, the only cancer treatments available prior to this time were surgery and radiation. Despite its later weakness, Japan's anticancer drug sector was relatively successful in its early years. Japanese firms launched improved versions of foreign discovered drugs and developed original anticancer drugs that were distributed worldwide and continue to be used today. In a heavily protected environment, Japanese firms were able to launch domestic versions of foreign-discovered drugs with relative ease. Japanese firms were also able to discover several anticancer drugs that were basically a type of antibiotic effective toward cancer. For Japanese firms operating in a still developing economy, the low cost, labour intensive, and serendipitous method of developing these drugs suited their comparative advantage.

Yet in terms of size, Japan's anticancer drug sector remained small and undeveloped until the early 1970s. As figure 19 shows, anticancer drug production rose dramatically after the mid 1970s. This was because the therapeutic demand for anticancer drugs was less than for other types of therapies, such as antibiotics. As well, the anticancer drugs developed during this time had limited efficacy despite their heavy side effects. While the introduction of national health insurance in 1961 and

launches of several new anticancer drugs such as mitomycin, bleomycin, and fluorouracil. Although production levels increased over the 1960s, they did not prompt a significant expansion of the anticancer drug market.

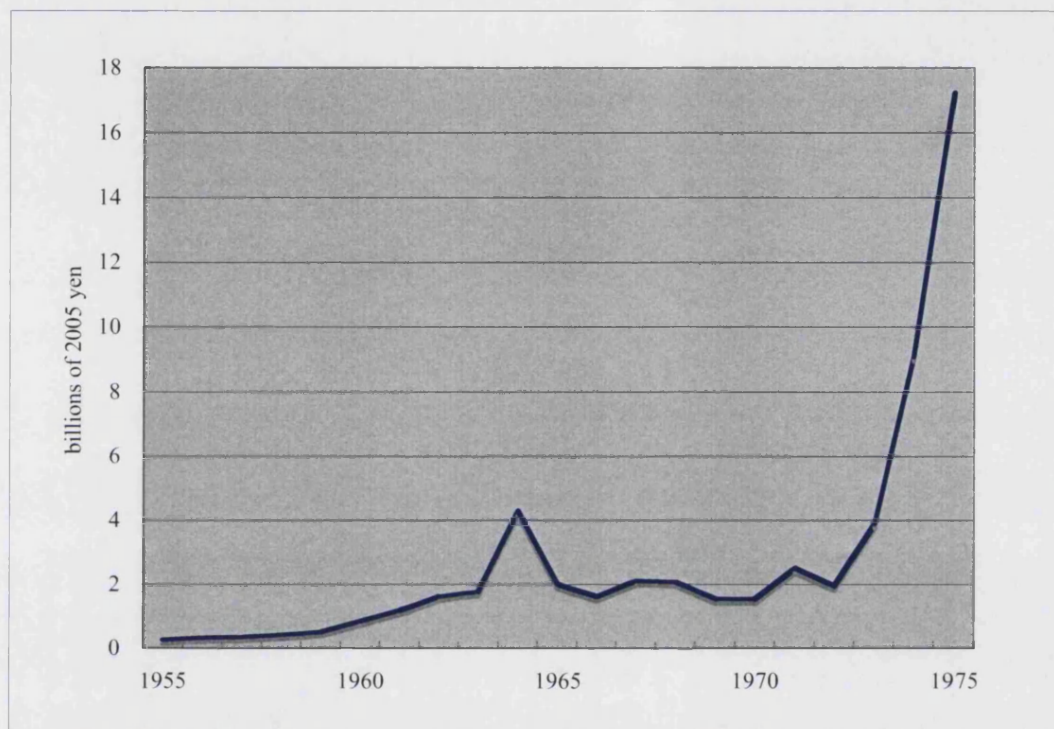


Figure 19. Value of Anticancer Drug Production, 1955-1975⁵³⁸

Yoshitomi

The launch of one of Japan's first anticancer drugs, Nitromin, originated out of academia. During World War II, US scientists had found the chemical weapon, nitrogen mustard, to be effective in fighting cancer.⁵³⁹ Soon after the war, Morizō Ishidate and Tomizō Yoshida, two leading cancer scientists based at the University of

⁵³⁸ Ministry of Health and Welfare, *Yakuji Kogyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Yakugyo Keizai Kenkyūjo, 1953-1967); Ministry of Health and Welfare, *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Yakugyo Keizai Kenkyūjo, 1968-2000). When the Japanese government began to collect statistics on anticancer drugs in the mid 1950s, these figures were aggregated into the category of antitumour drugs. As the vast majority of antitumour drugs are comprised of anticancer drugs, this thesis has used antitumour drugs as a proxy for anticancer drugs over the post war period.

⁵³⁹ L.S. Goodman, M.M. Wintrobe, W. Dameshek, M.J. Goodman, A. Gilman and M.T. McLennan, "Nitrogen Mustard Therapy. Use of methyl-bis(beta-chloroethyl)amine hydrochloride and tris(beta-chloroethyl)amine hydrochloride for Hodgkin's disease, Lymphosarcoma, Leukemia, and Certain Allied and Miscellaneous Disorders," *Journal of the American Medical Association* 105 (1946): 475-476; C.P. Rhoads, "Nitrogen Mustards in the Treatment of Neoplastic Disease: Official Statement" *Journal of the American Medical Association* 131 (1946): 656-658.

Tokyo and Tohoku University, respectively, succeeded in reducing its toxicity to a tenth.⁵⁴⁰ The scientists then collaborated with Yoshitomi Pharmaceutical Industries to commercialise the drug, whereby the scientists guided the firm through the screening and manufacturing process.⁵⁴¹

Yoshitomi was then a small pharmaceutical firm that had been established in 1940 as a joint venture between Takeda Pharmaceuticals – Japan’s leading pharmaceutical firm – and Mitsubishi Chemicals. Yoshitomi developed quickly after the war, and by 1950, employed over 1,000 workers and produced 2.3% of the nation’s pharmaceuticals. From its inception, Yoshitomi had particularly strong ties with Takeda, which distributed most of its products. In 1949, for example, sales to Takeda comprised 76% of the firm’s total sales, followed by the Ministry of Health and public hospitals, at 13% and 4%, respectively.⁵⁴²

Despite its success in developing a new anticancer drug, launching Nitromin in 1952 did not lead to substantial sales for Yoshitomi.⁵⁴³ While Nitromin marked a milestone as one of the first anticancer drugs developed in Japan, demand for the drug remained limited – due mostly to limited therapeutic demand and the drug’s heavy side effects.

⁵⁴⁰ T. Yoshida, H. Sato, and M. Ishidate, “Yoshida Nikushu ni yoru Akusei Shuyō Kagakuryōhō no Jikkenteki Kenkyū 1 [Experimental Studies on Chemotherapy of Malignant Growth Employing Yoshida Sarcoma 1,” *Gann* 41 (1950): 93-96; M. Ishidate, K. Kobayashi, Y. Sakurai, H. Sato, and T. Yoshida, “Experimental Studies on Chemotherapy of Malignant Growth Employing Yoshida Sarcoma Animals (II). The Effect of N-oxide derivatives of Nitrogen Mustard,” *Proceedings of the Japan Academy* 27 (1951): 493-498.

⁵⁴¹ Yoshitomi Pharmaceutical Co., *Yoshitomi Seiyaku 50-nen no Ayumi* [A 50 Year History of Yoshitomi Pharmaceutical Co.] Tokyo: Yoshitomi Pharmaceutical Co., 1990): 55-57; Shinpei Miyata, “Tomizo Yoshida: Yoshida Carcinoma and the Beginning of a New Era (Yoshida Tomizō: Shinjidai o Hiraita Yoshida Nikushu),” *Gekkan Gan* 33 (September 2002): 42-45.

⁵⁴² Yoshitomi Pharmaceutical Industries, Ltd., *Yūka Shōken Hōkokusho* [Annual Securities Report] (Tokyo: Ōkurashō Insatsukyoku, 1949).

⁵⁴³ Yakuji Nippōsha, “Nitromin,” in *Saikin no Shinyaku* [New Drugs in Japan] (Tokyo: Yakuji Nippōsha, 1952), 118. Approved at 1,000 yen per 5 ampoules, Nitromin was manufactured by Yoshitomi and distributed through Takeda.

In fact, Nitromin accounted for only 0.5% of Yoshitomi's total sales in 1960.⁵⁴⁴ Despite the ability of academic scientists to develop and launch drugs in collaboration with private firms, the cancer market grew slowly.

Kyowa Hakko

The first anticancer drug of Japanese origin to be distributed worldwide was mitomycin by Kyowa Hakko Co. Like many of the firms that developed anticancer drugs in Japan, Kyowa Hakko's area of expertise was not in pharmaceuticals. In fact, Kyowa Hakko's predecessor was a government-funded manufacturer of methanol and acetone established in 1933.⁵⁴⁵ Drawing on its expertise in fermentation and chemical synthesis, Kyowa Hakko was established in 1949 as a producer of raw material alcohol, pharmaceuticals, chemicals, and fertilisers. As with many non-traditional pharmaceutical firms during this period, Kyowa Hakko gained its strengths through the production and sale of the leading antibiotics: penicillin and streptomycin. By 1960, Kyowa Hakko had developed into a fairly large firm, which was capitalised at 12.9 billion yen and employed over 2,700 workers.⁵⁴⁶

In 1955, the firm gained approval to sell five anticancer substances (eight drugs). Kyowa Hakko had formed alliances with universities such as the Kitasato Research Institute or foreign firms such as Roche to market new anticancer drugs.⁵⁴⁷ In terms of

⁵⁴⁴ Yoshitomi Pharmaceutical Industries, Ltd., *Yūka Shōken Hōkokusho* [Annual Securities Report] (Tokyo: Ōkurashō Insatsukyoku, 1961).

⁵⁴⁵ Methanol is an alcohol used as a raw material in many industrial and chemical processes. Acetone is a widely used solvent.

⁵⁴⁶ In 2005 values, this would be approximately 66.8 billion yen. Kyowa Hakko Kyogyo Co., *Yūka Shōken Hōkokusho* [Annual Securities Report] (Tokyo: Ōkurashō Insatsukyoku, 1960).

⁵⁴⁷ Yakuji Nippōsha, "Mitomycin," in *Saikin no Shinyaku* [New Drugs in Japan] (Tokyo: Yakuji Nippōsha, 1960), 15-18; Shigetoshi Wakaki, "Tōsha ni okeru Seiganzai no Kenkyū to Kaihatsu no Genjō" [The Status of Anticancer Drug R&D at Our

its own R&D, Kyowa Hakko concentrated on the development and improvement of anticancer antibiotics such as mitomycin.⁵⁴⁸

Kyowa Hakko's development of mitomycin was, in fact, motivated by university researchers who had contacted the firm to jointly develop its discovery. In 1955, Tōju Hata's laboratory at the Kitasato Institute for Infectious Diseases asked Kyowa Hakko to produce a large volume of samples for laboratory use.⁵⁴⁹ Japan's first antitumour antibiotic, carzinophilin, had actually been discovered by Hata in 1954 and developed by Kyowa Hakko, but its success was short lived because of its instability and toxicity.⁵⁵⁰ Similar to many antibiotics of its time, mitomycin had been isolated from a soil sample. Preclinical tests had shown mitomycin to be effective in the destruction of both microbes and malignant tumour cells.⁵⁵¹ By forming an alliance with Kyowa Hakko, the Kitasato Institute hoped to capitalise on the firm's expertise in fermentation. This collaboration resulted in the isolation of several types of mitomycin. Among these, mitomycin C, identified by Shigetoshi Wakaki of Kyowa Hakko, was found to be most effective and was developed into a potential therapy.⁵⁵²

Company],” *Kagakukōgyō* (April 1976): 96-98.

⁵⁴⁸ Anticancer antibiotics are, like antibiotics, a substance produced by bacteria that is used to treat cancer. See for example, National Cancer Institute, “Dictionary of Cancer Terms: Antitumor Antibiotic” National Cancer Institute, http://www.cancer.gov/templates/db_alpha.aspx?CdrID=44488 (accessed 26 May 2008). Biological modifiers are substances that alter the interaction between the body's immune system and cancer cells, in order to boost, direct or restore the body's ability to fight the disease. See, National Cancer Institute, “Biological Therapies for Cancer: Questions and Answers,” National Cancer Institute, <http://www.cancer.gov/cancertopics/factsheet/Therapy/biological#q3> (accessed 26 May 2008).

⁵⁴⁹ Kyowa Hakko Kyogyo Co., *Bara wa Bara: Kyōwa Hakkō 35-nenshi* [A Rose is a Rose: A 35 year History of Kyowa Hakko] (Tokyo: Kyowa Hakko Kyogyo Co., 1984), 70.

⁵⁵⁰ Toju Hata, Fumiwaka Koga, Yoshitomo Sano, Kokichi Kanamori, Akihiro Matsumae, Ryoza Sugawara, Tadashi Hoshi, Tatsuo Shima, Shinya Ito, and Setsuo Tomizawa, “Carzinophilin, New Tumor Inhibitory Substance Produced by Streptomyces,” *Journal of Antibiotics* 7 (August 1954): 107-112.

⁵⁵¹ Toju Hata, Yoshimoto Sano, Ryoza Sugawara, Akihiro Matsumae, Kokichi Kanamori, Tatsuo Shima, Tadashi Hoshi, “Mitomycin, a New Antibiotic from Streptomyces. I,” *Journal of Antibiotics, Series A* 9 (July 1956): 141-146; Ryoza Sugawara and Toju Hata, “Mitomycin C, a New Antibiotic from Streptomyces II,” *Journal of Antibiotics, Series A* 9 (July 1956): 147.

⁵⁵² S. Wakaki, H. Marumo, K. Tomioka, “Isolation of New Fractions of Antitumour Mitomycins,” *Antibiotics and Chemotherapy* 8, no. 8 (1958): 228-240.

The drug's success was not only a product of government funding for academic research in antibiotics, but also of collaborations between academic and company scientists both within and beyond Japan.⁵⁵³ Research on mitomycin was also conducted abroad, and favourable research results by prominent scientists such as Kanematsu Sugiura of the Memorial Sloan-Kettering Institute for Cancer Research in the United States proved particularly effective in gaining international recognition for the drug.⁵⁵⁴

But while the Japanese government approved mitomycin C in 1959, differences in drug approval standards according to country and time meant that the drug was not available in some major markets for a considerable time. The United States, for example, initially rejected mitomycin as a potential cure for cancer due to “major toxic reactions but seldom objective improvement.”⁵⁵⁵ The FDA did, however, grant approval in 1974, and mitomycin was distributed by Bristol-Myers Squibb.⁵⁵⁶ By the mid 1980s, mitomycin was available in more than 60 countries.⁵⁵⁷

While mitomycin became one of Kyowa Hakko's core products, its sales records demonstrated why Japanese firms had weak incentives to invest heavily in drug R&D.

⁵⁵³ As mentioned in the previous chapter, the government had supported academic research in antibiotics from the late 1940s. This funding was useful in the search for other therapeutic uses of substances produced by bacteria, including the treatment of cancer.

⁵⁵⁴ Thomas W. Ennis, “Dr. Kanematsu Sugiura, 89, Dies; A Pioneer in Cancer Chemotherapy; Research Dates to 1912,” *The New York Times*, 23 October 1979. Since the end of World War II, the Japanese American scientist Kanematsu Sugiura had liaised with Japanese scientists for collaborations in cancer research. See also, John Hillaby, “Cancer Increase is not Clear-Cut; World Congress in London Attributes Some of It to Regular Check-Ups,” *The New York Times*, 9 July 1958; William L. Laurence, “Science in Review: Reports of Progress in Fight on Cancer Hold Out Hope of Cutting Death Toll,” *The New York Times*, 13 July 1958.

⁵⁵⁵ “Cancer Drug Rejected; U.S. Says Japanese Antibiotic has Significant Side-effects,” *The New York Times*, 22 January 1959.

⁵⁵⁶ U.S. Food and Drug Administration, Center for Drug Evaluation and Research, “FDA Oncology Tools Approval Summary for Mitomycin C,” U.S. Food and Drug Administration, <http://www.accessdata.fda.gov/scripts/cder/onctools/summary.cfm?ID=273> (accessed 10 November 2007).

⁵⁵⁷ Kyowa Hakko Kyogyo Co., *Bara wa Bara: Kyowa Hakko 35-nenshi* [A Rose is a Rose: A 35 Year History of Kyowa Hakko], 70.

Japan's process patent regime meant that the fruits of R&D could easily be shared by a rival firm. While Kyowa Hakko's application for mitomycin C, for example, was approved in September and launched in October 1959, Sankyo was able to launch mitomycin in the same month. As well, although mitomycin was one of Kyowa Hakko's key products, with an yearly production level of 839,000 yen by 1965, this was still less than a fifth of the firm's production values for streptomycin – a drug it produced under license.⁵⁵⁸ With little reward, many firms could not justify the heavy investments necessary for innovation.

With its success in mitomycin, Kyowa Hakko was able to carve out a prominent position in the anticancer drug sector – initially through anticancer antibiotics. After all, the government offered funding for antibiotic research, set relatively high prices for both antibiotics and anticancer drugs, and provided rewards for incremental innovations. Kyowa Hakko invested heavily in its human resources, and concentrated its investments on drugs that utilised the firm's expertise in fermentation technology to strengthen R&D capacity.⁵⁵⁹ Kyowa Hakko also formed alliances with academic and industry research laboratories both inside and outside of Japan to compensate for, as well as build upon, limited technological expertise.⁵⁶⁰ In addition to importing technologies, the company had also sent its key researchers to study at leading cancer research centres in the United States from the mid 1960s onwards. These efforts

⁵⁵⁸ In nominal terms, Kyowa Hakko's yearly production level was approximately 214,000 yen. Kyowa Hakko Kogyo Co., *Yūka Shōken Hōkokusho* [Annual Securities Report] (Tokyo: Ōkurashō Insatsukyoku, 1965), 8, 16; Kyowa Hakko Kogyo Co., *Yūka Shōken Hōkokusho* [Annual Securities Report] (Tokyo: Ōkurashō Insatsukyoku, 1966), 20.

⁵⁵⁹ Benzaburō Katō, "Innen no Dōri ni Rikkyaku Shita Jigyō Keiei [Business Management Based on the Philosophy of Fate]," in *Gendai Toppu Keiei no Jigyō Tetsugaku* [Business Philosophies among Today's Leading Managers], ed. Nihon Jitsugyō Shuppansha (Tokyo: Nihon Jitsugyō Shuppansha, 1969). Benzaburō Katō became the president of Kyowa Hakko in 1949 and its chairman in 1969.

⁵⁶⁰ *Ibid.*

helped Kyowa Hakko to learn of cutting-edge research and strengthen its research capacities.⁵⁶¹

Nippon Kayaku

As its name “Kayaku (explosives),” might suggest, Nippon Kayaku was a firm with core interests outside of pharmaceuticals. The firm was established in 1916 to produce explosives for the construction sector as German imports became unavailable during World War I. Building upon its core competencies, the firm diversified into chemical dyes and pharmaceuticals in the interwar period. By 1950, Nippon Kayaku had established itself as the ninth leading pharmaceutical firm in Japan in terms of production, with particular strengths in aspirin and penicillin (in which it was second and fifth in the Japanese market, respectively).⁵⁶² In the late 1960s, the launch of a new anticancer drug, bleomycin, helped strengthen the firm’s pharmaceutical business. Nippon Kayaku’s pharmaceutical sales stood at 19.4 billion yen, or 19.5% of the firm’s total sales five years after bleomycin’s launch.⁵⁶³ A decade later, the firm’s pharmaceuticals sales reached 24.0 billion yen, or 22.3% of total sales.⁵⁶⁴

Nippon Kayaku’s entry into the anticancer drug sector was motivated by the firm’s contacts with university researchers. One of the firm’s scientists, Tomohisa Takita,

⁵⁶¹ Shigetoshi Wakaki, “Tōsha ni Okeru Seiganzai no Kenkyū to Kaihatsu no Genjō [The Status of Anticancer Drug R&D at our Company],” 96-98.

⁵⁶² Nippon Kayaku Co., *Yūka Shōken Hōkokusho* [Annual Securities Report] (Tokyo: Ōkurashō Insatsukyoku, 1950), 1; Nippon Kayaku Co., *Yūka Shōken Hōkokusho* [Annual Securities Report] (Tokyo: Ōkurashō Insatsukyoku, 1951), 19. The market positions of Japanese firms are based on production, as sales values are not readily available.

⁵⁶³ In nominal terms, Nippon Kayaku’s pharmaceutical sales five years after launch stood at 9.3 billion yen. Nippon Kayaku Co., *Yūka Shōken Hōkokusho* [Annual Securities Report] (Tokyo: Ōkurashō Insatsukyoku, 1974), 20.

⁵⁶⁴ In nominal terms, Nippon Kayaku’s pharmaceutical sales a decade after launch reached 17.8 billion yen. Nippon Kayaku Co., *Yūka Shōken Hōkokusho* [Annual Securities Report] (Tokyo: Ōkurashō Insatsukyoku, 1979), 22.

worked at Hamao Umezawa's laboratory at the Institute of Microbial Chemistry.⁵⁶⁵

As observed in the antibiotics chapter, Umezawa was a leading authority in microbiology who had been involved in the development of antibiotics such as penicillin, streptomycin, and kanamycin in Japan. In 1962, Umezawa discovered the anticancer antibiotic, bleomycin, out of a soil sample from Fukuoka prefecture, and asked Nippon Kayaku for assistance in its development.⁵⁶⁶ Solid collaboration between academic and industrial scientists was essential to the development of bleomycin. Clinical trials of bleomycin were conducted with the assistance of Tokuji Ichikawa, then the Director of First Tokyo National Hospital.⁵⁶⁷

As a globally competitive anticancer drug, bleomycin's launch in 1969 not only bolstered sales of Nippon Kayaku's pharmaceutical division, but also solidified the firm's position in the anticancer drug market. Bleomycin was recognised globally, with overseas approval in Denmark, Norway, France and Taiwan before its approval in the United States in July 1973.⁵⁶⁸ Nippon Kayaku's ambitions to enter overseas markets also led to the upgrading of production standards. In the early 1970s, the Federal Drug Administration (FDA) imposed the adoption of modern manufacturing standards for exports to the United States. In hopes of gaining FDA approval, Nippon

⁵⁶⁵ Nippon Kayaku Co., *Nippon Kayaku no Ayumi: Kono 10-nen o Chūshin ni Shite* [The History of Nihon Kayaku: With Special Attention to the Past 10 years] (Tokyo: Nippon Kayaku Co., 1976), 93; Tokuji Ichikawa, "Bureomaishin no Shōkai [An Introduction to Bleomycin]," *Gan no Rinshō* 14 (1967): 149.

⁵⁶⁶ Hamao Umezawa, Kenji Maeda, Tomio Takeuchi, and Yoshiro Okami, "New Antibiotics, Bleomycin A and B," *Journal of Antibiotics, Series A* 19 (September 1966): 200-209; Hamao Umezawa, "Kōseibusshitsu o Motomete (3): Michi no Ryōiki Gan e no Chōsen [Searching for Antibiotics (3): Challenging Cancer]," *Shokun* 12, no. 3 (1980): 230-244. The discovery of bleomycin followed upon the failure of phleomycin, a substance that proved too unstable and toxic for commercialisation.

⁵⁶⁷ Yakuji Nippōsha, "Bleomycin," in *Saikin no Shinyaku* [New Drugs in Japan] (Tokyo: Yakuji Nippōsha, 1969), 51-55. See also, Institute of Microbial Chemistry, *Institute of Microbial Chemistry: 1962-1977* (Tokyo: Center for Academic Publications, 1977), 18-21.

⁵⁶⁸ Nippon Kayaku Co., *Nippon Kayaku no Ayumi: Kono 10-nen o Chūshin ni Shite* [The History of Nihon Kayaku: With Special Attention to the Past 10 years], 94. Partly because of its lower toxicity levels, bleomycin proved more successful compared to mitomycin C. See also, U.S. Food and Drug Administration, Center for Drug Evaluation and Research, "FDA Oncology Tools Approval Summary for Bleomycin," U.S. Food and Drug Administration, <http://www.accessdata.fda.gov/scripts/cder/onctools/summary.cfm?ID=208> nnk (accessed 10 November 2007).

Kayaku modernised its standards.⁵⁶⁹ The launch of an innovative drug strengthened the firm's operations.

Table 6. Anticancer Antibiotics Discovered in Japan⁵⁷⁰

Anthracyclines (2)	Aclarubicin (1975) Pirarubicin (1979)
Bleomycin Group (2)	*Bleomycin (1965) Peplomycin (1974)
Miscellaneous (5)	*Sarkomycin (1953) Crazinophilin (1954) *Mitomycin C (1955) Chromomycin A ₃ (1956) *Zinostatin (1965, previously Neocarzinostatin)

Note: Nine substances. * indicates those that have also been used outside of Japan.

In the 1950s and 1960s, Japanese discoveries in anticancer drugs were primarily in anticancer antibiotics, which were effectively bacterial substances that could be used to treat tumours instead of bacteria. Japanese firms took advantage of the lower R&D costs for developing anticancer antibiotics during this time. In addition, the government supported antibiotic research through research funding and by promoting technology imports in a protective environment that recognised process patents. Support for antibiotic research indirectly supported the discovery, development, and launch of anticancer antibiotics. Long standing connections formed between academia and industry also helped scientists build upon the synergies of academia and industry to develop commercially viable therapies.

⁵⁶⁹ Nippon Kayaku Co., *Nippon Kayaku no Ayumi: Kono 10 nen o Chūshin ni Shite* [The History of Nihon Kayaku: With Special Attention to the Past 10 years], 95.

⁵⁷⁰ Compiled from Joichi Kumazawa and Morimasa Yagisawa, "The History of Antibiotics: The Japanese Story," 125-133; Morimasa Yagisawa, unpublished document, "Antibiotics, Chemotherapeutics and Other Microbial Products Originated from Japan," sent to author.

But while Japan's expertise in antibiotic development could help create anticancer antibiotics, it seemed less able to develop some other types of anticancer drugs that were being developed in the West. Overseas, the anticancer drug sector saw the development of drugs such as methotrexate and 5 fluorouracil (5-FU) and actinomycin in the 1950s, and the vinca alkaloids vincristine and vinblastine in the 1960s.⁵⁷¹ In Japan, firms such as Meiji Seika and Takeda launched the anticancer antibiotics sarkomycin and chromomycin, respectively, while Japan Lederle introduced methotrexate.⁵⁷² The development of more advanced chemotherapy drugs developed in the West required much higher levels of R&D and human capital than Japan could invest. The fact that the Japan origin drugs during this time were in anticancer antibiotics, and that Japan's greatest contributions in the anticancer drug sector have been in this field, also suggests at some of the causes for Japan's subsequent weakness in this sector.

⁵⁷¹ Yano Research Institute, *Iyaku Sangyō Nenkan* [Pharmaceutical Industry Annual], (Tokyo: Yano Research Institute, 1985), 17-19.

⁵⁷² Yakugyō Keizai Kenkyūjo, *Yakugyō Keizai Nenkan* [Pharmaceutical Economics Annual] (Tokyo: Yakuji Nippōsha, 1967), 182-173.

4.3.1 Transitions in therapeutic demand

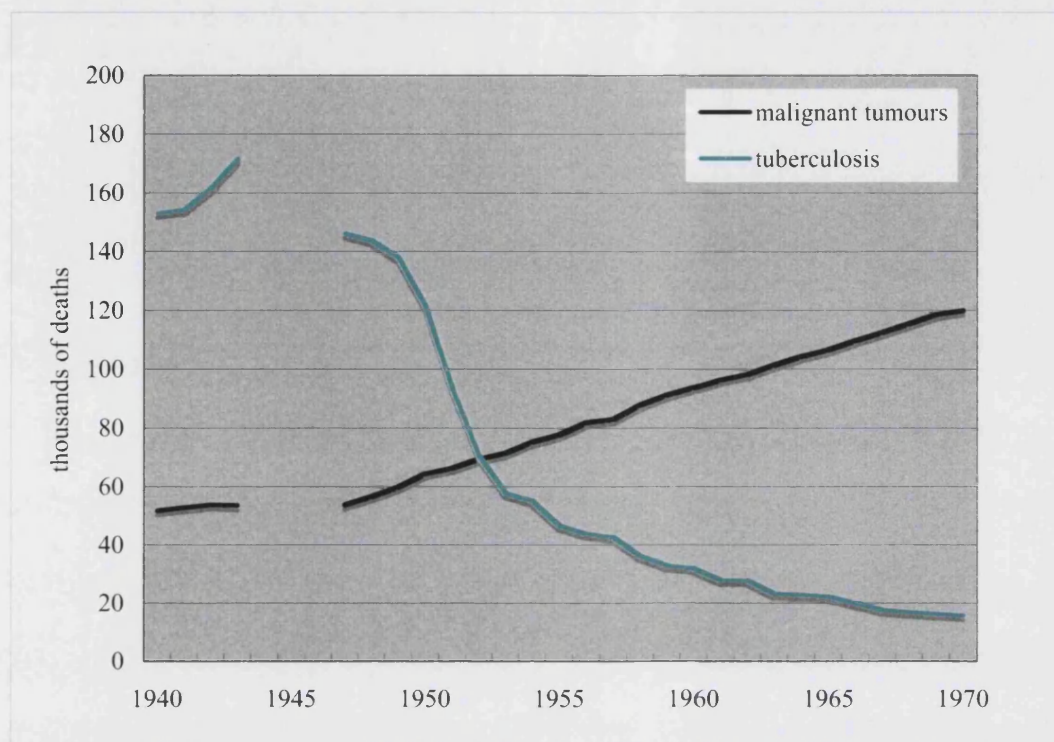


Figure 20. Deaths from Tuberculosis and Malignant Tumours⁵⁷³

Part of the reason that the anticancer drug market remained undeveloped over the 1950s and 1960s, stemmed from the smaller therapeutic demand for anticancer drugs in Japan compared to drugs such as antibiotics. As indicated in figure 22, cancer deaths rose gradually after the Second World War. But it was not until the mid 1950s that figures for cancer overtook those for tuberculosis, which was only one type of infectious disease. On the other hand, cancer deaths in the United States and Britain, for example, had overtaken deaths from infectious disease much earlier.⁵⁷⁴ Moreover, while deaths from cancer became more common than deaths from infectious diseases

⁵⁷³ Ministry of Health, Labour and Welfare, "Deaths by Leading Cause of Death, Population and Households," <http://www.stat.go.jp/english/data/chouki/02.htm> (accessed 1 December 2007).

⁵⁷⁴ See for example, "Death rate, by cause: 1900–1998." Table Ab929–951 in *Historical Statistics of the United States, Earliest Times to the Present: Millennial Edition*, eds. Susan B. Carter, Scott Sigmund Gartner, Michael R. Haines, Alan L. Olmstead, Richard Sutch, and Gavin Wright (New York: Cambridge University Press, 2006), <http://hsus.cambridge.org/HSUSWeb/index.do>; John Charlton and Mike Murphy, "'Trends in Causes of Mortality: 1841–1994 – An Overview,'" in *The Health of Adult Britain*, eds. John Charlton and Mike Murphy (London: Stationery Office, 1997), 30–57.

in Japan, the number of cancer patients remained significantly lower than the numbers with infectious diseases such as tuberculosis well into the 1970s.⁵⁷⁵

To a certain extent, the undeveloped status of Japan's anticancer drug sector during the 1950s and 1960s might be explained by the lack of government guidance during this period. At a time when the therapeutic demand for anticancer drugs remained low but antibiotics remained high, it was much more active in supporting antibiotic research. While the Ministry of Health and Welfare and the Ministry of Education did launch cancer research subsidies from 1963, these did not immediately translate into substantial drug launches.⁵⁷⁶ But by 1970, much more attention was paid to the development of anticancer drugs as the death toll from cancer had more than doubled since the immediate post-war years.

While therapeutic demand for anticancer drugs remained relatively low compared to the more developed countries, university scientists were actively engaged in cancer research, and were able to translate these discoveries into commercial products by collaborating with Japanese firms, often based on long standing personal connections. The government's funding for antibiotic research indirectly supported the development of anticancer antibiotics, as Japanese firms commercialised research that originated in universities. Japan could also build upon its prior experience in antibiotics. Japanese industrial policy may have helped firms import technologies in a

⁵⁷⁵ Ministry of Health and Welfare, *Kanja Chōsa* [Patient Survey] (Tokyo: Ministry of Health and Welfare, 1953-1985).

⁵⁷⁶ National Cancer Center, "Cancer Statistics in Japan, 2007," http://ganjoho.ncc.go.jp/public/statistics/backnumber/2007_en.html (accessed 1 December 2007).

protected environment, and Japanese health policy may have supported physician demand for anticancer drugs, but these factors did not have a direct impact on the anticancer drug sector in the 1950s and 1960s.

4.3.2 Beyond anticancer antibiotics

The lack of government policies such as product patents to incentivise the development of anticancer drugs, however, came to adversely impact the development of Japan's anticancer drug sector in later years. By the late 1970s, Japan had discovered the last of its anticancer antibiotics. Development of the next generation of anticancer drugs required scientists with more highly specialised knowledge of cancers and anticancer drugs, and firms able to undertake much larger R&D investments.

The limited reward for undertaking significant risk in the Japanese pharmaceutical market disincentivised many firms from developing other types of anticancer drugs. In addition, the smaller, non-traditional pharmaceutical firms that had pioneered the emergence of Japan's anticancer drug sector lacked the expertise and funds to discover, develop, and distribute highly sophisticated anticancer drugs. During the discovery of anticancer antibiotics, the absence of a coherent government policy to develop anticancer drugs did not hurt short-term performance. But after the discoveries of the last anticancer antibiotics, the lack of a more research-intensive research orientation undermined long-term prospects for a competitive anticancer drug sector.

4.3.3 Summary of period between 1950 and 1975

Despite the small size of Japan's anticancer drug market, however, Japanese firms were able to launch globally competitive anticancer drugs. Japan's emergence in this field might be explained by the same reasons for the strengths of its antibiotics sector. After all, the development of these drugs involved the same scientists, universities, and firms involved in the development of antibiotics.⁵⁷⁷ The anticancer antibiotics launched by the Japanese were essentially antibiotics effective against tumours rather than bacteria. As a drug whose discovery was based on labour intensive, empirical methods to cultivate effective bacterial strains, anticancer antibiotics was suited to an developing economy as it did not require high levels of R&D investment or human capital. Similar to antibiotics, anticancer antibiotics were discovered out of serendipity, screening thousands of soil samples to locate bacteria that produced substances that would harm the growth of tumours – and could be done by scientists from a range of disciplines. It was relatively easy for Japanese scientists to learn, adapt, and build upon these techniques and develop strengths in anticancer antibiotics.

Although government policies did encourage the development of anticancer antibiotics via incremental innovation, state interventions did not have a vital impact on the development of the early anticancer drug sector. The anticancer drugs of the 1950s and 1960s originated in the academic laboratory and were transformed into commercial products through collaborations between academia and industry. Thus,

⁵⁷⁷ Institute of Microbial Chemistry, *Institute of Microbial Chemistry: 1962-1977* (Tokyo: Center for Academic Publications, 1977); See also, Hamao Umezawa, "Seiganzai wa Dokomade Kitaka [The Status of Anticancer Drugs]," *Kagaku Asahi* (September 1982): 50-54.

while government policy did not explicitly guide the anticancer drug sector, it did support its growth.

Firms such as Kyowa Hakko and Nippon Kayaku often entered the anticancer drug sector by chance, prompted not out of research at their own laboratories, but through alliances formed with academic laboratories engaged in anticancer drug research. For firms with access to academic knowledge for potential therapies during the 1950s and 1960s, entry barriers in the anticancer drug sector were fairly low. Few firms had entered the market, truly effective medicines had yet to be developed, and demand remained lower than other therapeutic sectors. With the launch of globally competitive drugs, Kyowa Hakko and Nippon Kayaku were able to carve out a strategic position in a niche market, as non-traditional pharmaceutical firms that had diversified into pharmaceutical sector. While anticancer drugs were not highly profitable at this time, new entrants did gain first mover advantages by establishing alliances with foreign pharmaceutical firms and forming distribution networks that proved beneficial in the long term.

While some firms developed new anticancer drugs and others obtained approval to sell imports of new anticancer drugs, Japan's anticancer drug market remained small during the 1950s and 1960s. Not only were the therapeutic effectiveness of the few drugs available counterbalanced by their toxic effects, the more recent drugs developed abroad had yet to be approved in Japan.⁵⁷⁸ The belated approval of

⁵⁷⁸ Yakugyō Keizai Kenkyūjo, *Yakugyō Keizai Nenkan* [Pharmaceutical Economics Annual] (Tokyo: Yakuji Nippōsha, 1967),

anticancer drugs in Japan stemmed from the lack of demand for more invasive therapies, and the lack of cancer specialists to examine or use such drugs in Japan. Still, Japan's anticancer drug sector during the 1950s and 1960s emerged with strong beginnings. It was able to launch globally competitive anticancer drugs that remain in use to date.

4.4 A period of volume-based growth, 1975-1990

Between 1975 and 1989, the Japanese anticancer drug sector saw an unprecedented expansion of the domestic market unparalleled elsewhere in the world. By the 1980s, more anticancer drugs were being sold in Japan than in any other country, including the United States.⁵⁷⁹ In 1985, the US anticancer drug market was only 40% of the size of Japan's anticancer drug market.⁵⁸⁰ But Japan's anticancer drug market was dominated by drugs that could not gain approval in other pharmaceutical markets. Japan's leading anticancer drugs did not meet the more rigorous efficacy criteria established by foreign drug regulators in the United States, the United Kingdom, or Germany. In retrospect, the drug approval process in Japan appeared political and unscientific. Japan's anticancer drug sector experienced extraordinary expansion during this period with drugs of limited therapeutic value.

From the late 1970s to the late 1980s, two drugs, Krestin and Picibanil, dominated Japan's anticancer market. A third drug, SSM (Specific Substance Maruyama), was

172-173; National Cancer Institute, "Developmental Therapeutics Program, FDA Approved Drugs," National Cancer Institute. <http://dtp.nci.nih.gov/timeline/flash/FDA.htm> (accessed 10 November 2007).

⁵⁷⁹ Masanori Fukushima, "The Overdose of Drugs in Japan," *Nature* 342 (December 1989): 850-851; Yano Research Institute, *Iyaku Sangyō Nenkan* [Pharmaceutical Industry Annual] (Tokyo: Yano Research Institute, 1985).

⁵⁸⁰ "The Pharmaceutical Market," *Nikkei Business*, 9 December 1985, 10.

not officially approved, but was also used widely. It is now recognised, however, that the two drugs had limited therapeutic value, and they are in very limited circulation today.⁵⁸¹ This section examines the experience of the firms that launched these popular anticancer drugs to identify why the Japanese anticancer drug remained weak in global perspective despite domestic success. None of these drugs were approved in other advanced markets because the evidence regarding efficacy did not meet drug standards in these countries. Even while Japan was producing more anticancer drugs than the United States, cancer survival rates in Japan tended to be lower.⁵⁸² The experience of these firms suggests that the weakness of Japan's anticancer drug sector – as well as its volume based expansion – was largely a product of limited R&D incentives, lack of transparency in the drug approval process, and the distinct medical practices of the times.

4.4.1 The formation of a distinctly domestic anticancer drug market

The phenomenal expansion of Japan's anticancer drug production began soon after the launch of Krestin and Picibanil in 1975 and 1976, respectively. The two drugs belonged to a new category of anticancer drugs that had very few side effects and were therefore relatively easy to prescribe. Production levels of anticancer drugs, which were 17.2 billion yen in 1975, had jumped more than 50% to 51.6 billion yen in 1976. By 1980, production values had reached 136.4 billion yen, nearly 88 times the values a

⁵⁸¹ Jihō, *Yakuji Handobukku* [Pharmaceutical Affairs Handbook] (Tokyo: Jihō, 2000-2007).

⁵⁸² See Masanori Fukushima, "The Overdose of Drugs in Japan," 850-851; and Suketami Tominaga, Kunio Aoki, Isaburo Fujimoto, Minoru Kurihara, eds., *Cancer Mortality and Morbidity Statistics: Japan and the World -1994* (Tokyo: Japan Scientific Societies Press, 1994).

decade earlier.⁵⁸³ In fact, between 1975 and 1989, Chugai's Picibanil and Kureha and Sankyo's Krestin accumulated over 1 trillion yen in sales.⁵⁸⁴

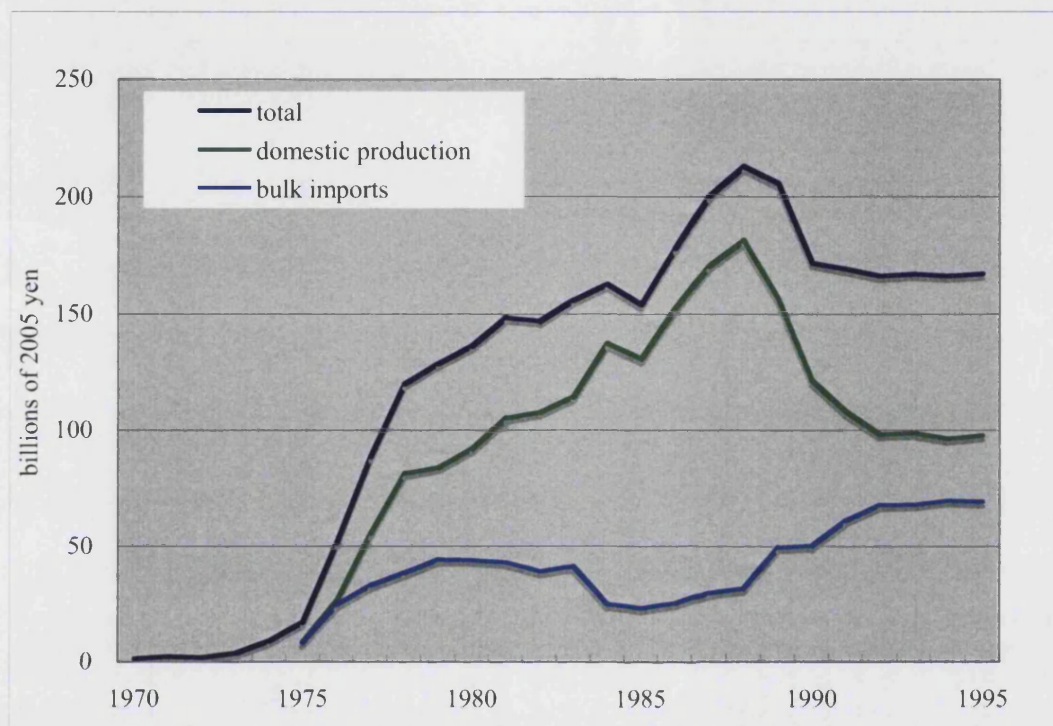


Figure 21. Value of Anticancer Drug Production, 1970-1995⁵⁸⁵

The Japanese anticancer drug market was intensely domestic, in terms of both the nationality of the firms and the origin of drugs that dominated the sector. Drug sales came almost solely from the domestic market, as the Japan-origin drugs were not approved in Europe or North America. In fact, as figure 23 indicates, even the amount of drugs produced from bulk imports declined during this period. But this volume based expansion ended as abruptly as it had begun. After the government

⁵⁸³ In nominal terms, anticancer drug production jumped from 9.9 billion yen in 1975 to 32.4 billion yen in 1976. By 1980, production levels reached 107.4 billion yen. Ministry of Health and Welfare, *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Yakugyō Keizai Kenkyūjo, 1968-2000).

⁵⁸⁴ This has been documented widely. See for example, "Kōganzaï de I-chō en no Iryōhi ga Muda, Nihon Byōinkai ga Kenkai [Japan Hospital Association Estimates Waste of 1 Trillion Yen from Two Cancer Drugs," *Asahi Shimbun*, 29 December 1989.

⁵⁸⁵ Ministry of Health and Welfare, *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Yakugyō Keizai Kenkyūjo, 1968-2000).

reduced the effective range of Picibanil and Krestin in 1989, production levels peaked conspicuously at 205.7 billion in 1989 before slipping suddenly and steeply into decline.⁵⁸⁶

Interestingly, the extraordinary expansion in Japan's anticancer drug market during this period appeared to be little related to actual therapeutic needs. It was true that cancer mortality rose steadily. Between 1970 and 1980, the number of deaths from cancer increased from 119,977 to 161,764, and cancer became the leading cause of death in 1981.⁵⁸⁷ But in contrast to the 1.3 fold increase in the number of cancer deaths, however, there was an 88-fold jump in drug production during the same period – from 1.55 billion yen to 136.4 billion yen.⁵⁸⁸ Moreover, morbidity rates suggest that the number of cancer patients remained relatively low compared to other types of diseases – which did not see a similar increase in production.⁵⁸⁹ While it is true that neither mortality nor morbidity rates are directly indicative of demand – as only a portion of the deceased or ill would have been treated by chemotherapy – they do provide an approximation of therapeutic demand. To this extent, therapeutic demand had little to do with the massive expansion of Japan's anticancer drug market.

4.4.2 Anticancer drugs in Japan during the 1970s and 1980s

While cancer therapy had made significant advances since the development of

⁵⁸⁶ In nominal terms, anticancer drug production reached 190.9 billion yen in 1989. Ibid.

⁵⁸⁷ Ministry of Health, Labour and Welfare, Deaths by Leading Cause of Death, Population and Households.” <http://www.stat.go.jp/english/data/chouki/02.htm> (accessed 1 December 2007).

⁵⁸⁸ In nominal terms, anticancer drug production increased from 517 million yen in 1970 to 107.4 billion yen in 1980. Ministry of Health and Welfare, *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Yakugyō Keizai Kenkyūjo, 1968-2000).

⁵⁸⁹ Yano Research Institute, *Iyaku Sangyō Nenkan* [Pharmaceutical Industry Annual] (Tokyo: Yano Research Institute, 1985), 13.

nitrogen mustard in the 1940s, increases in government spending and higher demand for anticancer drugs in the 1970s had yet to result in a viable cure for cancers. Anticancer drugs at this time – in Japan and worldwide – did not cure the disease. At best, they contained metastases. Despite heavy side effects, most anticancer drugs tended only to extend life by a few months.⁵⁹⁰

In the 1970s, Japanese firms began to develop and launch a new type of anticancer drug. Cancer immunotherapy drugs were developed in response to advances in immunology and the limitations of existing cancer therapies such as surgery, chemotherapy, and radiation therapy. Rather than attacking the tumour directly, immunotherapy aimed to boost the immune system to destroy or control cancer – providing an alternative or a complement to existing cancer therapies. Cancer immunotherapy aimed to extend the life expectancy of cancer patients through the control of and coexistence with cancer. These drugs were approved for a wide range of cancers, in various stages and locations of the body. While scientific advances produced new medicines with improved efficacy, cancer immunotherapy continued to offer remedies with significantly less side effects compared to radiation or chemotherapy, and gave hope to patients for whom surgery was not an option.⁵⁹¹

In the 1970s and 1980s, the Japanese anticancer drug market was dominated by cancer immunotherapy drugs – a phenomenon not observed among Western counterparts.

⁵⁹⁰ Yano Research Institute, *Iyaku Sangyō Nenkan* [Pharmaceutical Industry Annual] (Tokyo: Yano Research Institute, 1980), 8, 58.

⁵⁹¹ Jacqueline L. Longe, Deirdre S. Blanchfield, eds., *Gale Encyclopedia of Medicine*, 636. See also, “Japanese Drug Companies Pull Ahead in the Race to Innovate,” *The Economist*, 24 September 1983, 93.

Chugai's Picibanil, Kureha and Sankyo's Krestin, and Zeria's SSM were the first cancer immunotherapy drugs to become widely available. The discovery and development of these drugs bore a striking resemblance to the labour intensive and serendipitous research on naturally occurring substances – which was similar to antibiotic R&D and conducive to a developing economy. While the discovery of Picibanil was based on earlier scientific efforts involving a bacteriological approach to cancer therapy, Krestin was based on traditional medicine, and SSM was based on clinical observations in medical practice. The discovery of cancer immunotherapy drugs may not have been influenced by government incentives, but their success was very much a product of a regime that rewarded incremental innovations; where informal links between government, industry and academia facilitated drug approval; and where the practice of oncology had yet to develop. These were also plausible explanations for the weakness of Japan's anticancer drug sector.

Chugai

Chugai Pharmaceutical's new anticancer drug, Picibanil, changed the fortunes of the mid-ranking pharmaceutical firm in the early 1970s, transforming it into one of Japan's largest and well-known pharmaceutical firms by the early 1980s.⁵⁹² In fact, soon after launch, Picibanil sales saved the finances of the heavily indebted firm.⁵⁹³ Chugai's success with the drug was a product of a regime that rewarded incremental innovations and featured a non-transparent drug approval system.

⁵⁹² Carla Rapoport, "Chugai – a Portfolio of Pills," *Financial Times*, 22 September 1983.

⁵⁹³ Chugai Pharmaceutical Co., *Yūka Shōken Hōkokusho* [Annual Securities Report] (Tokyo: Ōkurashō Insatsukyoku, 1977), 10.

It was somewhat surprising that Chugai not only launched a new anticancer drug, but also that it would become a blockbuster drug that both changed the firm's fortunes and altered the dynamics of the anticancer drug sector. After all, Chugai sold no anticancer drugs before 1975. The firm was founded by Jūzo Ueno in 1925 as an import distributor of drugs from the Germany pharmaceutical firm, Gehe & Co.⁵⁹⁴ Unlike many of its rivals which had grown through the sales of antibiotics in the post war period, Chugai developed expertise in substances such as disinfectants and anthelmintics. In 1960, for example, over half of Chugai's sales came from disinfectants, followed by tonics and chemotherapeutics.⁵⁹⁵ A decade later, the firm derived a third of its sales from disinfectants, followed by a much smaller segment of central nervous system drugs and anthelmintics.⁵⁹⁶ Chugai was a newcomer to the anticancer drug sector.

Chugai's first anticancer drug emerged out of its contacts with academia. Since 1954, Hajime Okamoto at Kanazawa University had sought to identify the scientific mechanism behind the old knowledge that erysipelas, a type of bacterial skin infection, could at times control or destroy cancer. This bacteriological approach to cancer therapy had been studied by scientists and physicians, and involved administering a combination of dead bacteria to patients. In the 19th century, for example, William Coley of the New York Cancer Hospital argued that the bacteria produced a substance

⁵⁹⁴ See Chugai Pharmaceutical Co. *Chūgai Seiyaku 75-nen no Ayumi* [A 75 year History of Chugai Pharmaceutical] (Tokyo: Chugai Pharmaceutical Co., 2000).

⁵⁹⁵ Chugai Pharmaceutical Co., *Yūka Shōken Hōkokusho* [Annual Securities Report] (Tokyo: Ōkurashō Insatsukyoku, 1961), 12.

⁵⁹⁶ Chugai Pharmaceutical Co., *Yūka Shōken Hōkokusho* [Annual Securities Report] (Tokyo: Ōkurashō Insatsukyoku, 1971), 12.

that could prevent tumour growth.⁵⁹⁷ Okamoto attempted to identify and dilute the relevant strain of bacteria to develop the effective substance into a drug.⁵⁹⁸ Chugai co-developed Picibanil in collaboration with university scientists. Picibanil's commercialisation was evidence of active cancer research in universities and strong links between government and with private enterprise to develop potential therapies.

Despite its phenomenal popularity in Japan, Picibanil was a distinctly domestic drug that was not distributed outside Japan. Launched in October 1975 as the first officially recognised cancer immunotherapy drug in the world, the drug was popular for its applicability to a wide range of cancers and remarkably minor side effects compared to existing cancer therapies.⁵⁹⁹ During the 1980s, in fact, Picibanil sales ranged from 10% to 15% of the anticancer drug market, and generated approximately 25 billion yen in annual revenues.⁶⁰⁰ Such strong sales enabled Chugai to recover from the struggling sales of its leading product, the health tonic Guronsan. But the drug did not meet approval criteria in Europe or the United States, and remained a domestic drug. Indeed, Japanese critics also began to question whether approval standards had been particularly ambiguous or lenient, as strong sales were not matched by clinical results.⁶⁰¹ After the MHW's reappraisal in December 1989 banned Picibanil from

⁵⁹⁷ William Bradley Coley, *The Treatment of Malignant Tumors by Repeated Inoculations of Erysipelas: With a Report of Ten Original Cases* (Philadelphia: Lea Brothers & Co., 1893).

⁵⁹⁸ Jane E. Brody, "Japanese Study Use of Toxins in Cancer Treatment," *The New York Times*, 24 January 1968; Hajime Okamoto, Susumu Shoin, Mikio Minami, Saburo Koshimura and Ryusaku Shimizu, "Experimental Anticancer Studies part XXX. Factors Influencing the Streptolysin S-forming Ability of Streptococci Having Anticancer Activity," *Japanese Journal of Experimental Medicine* 36 (1966): 161–174; Hajime Okamoto, Mikio Minami, Susumu Shoin, Saburo Koshimura and Ryusaku Shimizu, "Experimental Anticancer studies part XXXI. On the Streptococcal Preparation Having Potent Anticancer Activity," *Japanese Journal of Experimental Medicine* 36 (1966): 175–186; Hajime Okamoto, Susumu Shoin, Saburo Koshimura, and Ryusaku Shimizu, "Studies on the Anticancer and Streptolysin S-Forming Abilities of Hemolytic Streptococci," *Japanese Journal of Microbiology*, 11, no. 4 (1967): 323–326.

⁵⁹⁹ Examples of such side effects were fever, aches, and lack of appetite, rather than death. See Yakuji Nippōsha, "Picibanil," in *Saikin no Shinyaku* [New Drugs in Japan] (Tokyo: Yakuji Nippōsha, 1976), 67–73.

⁶⁰⁰ Yakugyō Jihōsha, *Yakuji Handobukku* [Pharmaceutical Affairs Handbook] (Tokyo: Yakugyō Jihōsha, 1968–1999).

⁶⁰¹ See for example, "Nihon no Kusuri, Kuresuchin [Krestin, a Japanese Drug]," *Nikkei Business*, 9 December 1985, 9–11.

being prescribed as the main drug in an anticancer regimen, Chugai's anticancer drug sales plunged from 25.3 billion yen in 1989 to 8.5 billion yen in 1990.⁶⁰² As will be discussed later, Picibanil's fortunes were a product of Japan's drug approval system.

Kureha Kagaku and Sankyo

Much like Picibanil, the launch of Krestin, changed the fortunes of both the firm that discovered and developed the drug, Kureha Chemical Industry Co., and the firm that distributed the drug, Sankyo Co. During its peak in 1984, Krestin captured 31.1% of the anticancer drug market.⁶⁰³ In fact, combined with Taiho's Ftorafur and Chugai's Picibanil the top three anticancer drugs comprised approximately half of the anticancer drug market during the mid 1980s.⁶⁰⁴ Yet none of these drugs were approved in the advanced Western markets. It was somewhat peculiar that so few drugs were used to treat cancer in Japan, given that cancer is comprised of over 100 types of complex diseases.⁶⁰⁵

Like Picibanil, it was somewhat surprising not only that Kureha would discover a new anticancer drug, but also that it would become a blockbuster drug that changed both the firm's fortunes and the dynamics of the anticancer drug sector. Before launching Krestin, Kureha was a medium size chemical company with no dealings in pharmaceuticals, let alone anticancer drugs. The firm was established in 1944, when it

⁶⁰² In nominal terms, Chugai's sales fell from 23.5 billion yen in 1989 to 8.2 billion yen in 1990. Chugai Pharmaceutical Co., *Yūka Shōken Hōkokusho* [Annual Securities Report] (Tokyo: Ōkurashō Insatsukyoku 1991), 19.

⁶⁰³ Yano Research Institute, *Iyaku Sangyō Nenkan* [Pharmaceutical Industry Annual] (Tokyo: Yano Research Institute, 1985), 537.

⁶⁰⁴ Yakugyō Jihōsha, *Yakuji Handobukku* [Pharmaceutical Affairs Handbook] (Tokyo: Yakugyō Jihōsha, 1968-1999).

⁶⁰⁵ National Cancer Institute, "What is Cancer?" National Cancer Institute, <http://www.cancer.gov/cancertopics/what-is-cancer> (accessed 10 July 2008).

became independent from the textile maker Kureha Boseki. Kureha was a mid ranking chemical firm capitalised at 8 billion yen, specialising in plastics, agrochemicals and other industrial chemicals. The company was known for its popular cling film “Kurerappu,” which was launched in 1960. Kureha was not only a newcomer to anticancer drugs, but also to pharmaceuticals.⁶⁰⁶

Kureha’s entry into the anticancer drugs was accidental. In 1965, Chikao Yoshikumi, a Kureha researcher began to investigate the possible antitumour properties of Kawaratake mushrooms, based on rumours in his hometown that an elderly patient had been cured of stomach cancer by taking the traditional remedy.⁶⁰⁷ The head of research at Kureha indulged Yoshikumi’s request to investigate the substance, and allowed him to pursue research outside of normal working hours.⁶⁰⁸ Kureha’s engagement in anticancer drugs was not prompted by any government policy or academic connections.

The drug’s development, however, was a product of collaboration with academic scientists, government officials, and other firms. In 1968, Kureha formed an academic alliance with the Kyoto Institute of Technology to identify the effective agent.⁶⁰⁹ After polysaccharide K was identified and isolated in 1971, Kureha established an internal research group and consulted researchers at the Japan Foundation for Cancer Research

⁶⁰⁶ In 2005 values, Kureha’s capitalisation in 1975 was 13.7 billion yen. Kureha Chemical Industry Co., *Yūka Shōken Hōkokusho* [Annual Securities Report] (Tokyo: Ōkurashō Insatsukyoku, 1976), 1, 10.

⁶⁰⁷ Kawaratake mushrooms are found in Japan’s mountainous regions and have been used in Chinese traditional medicine as a medicinal mushroom, which are harvested, dried, ground and reconstituted as tea to boost the immune system.

⁶⁰⁸ Kureha Chemical Industry Co., *Kureha Kagaku 50-nenshi* [A 50 Year History of Kureha Chemical Industry] (Tokyo, Kureha Chemical Industry Co., 1995), 419.

⁶⁰⁹ *Ibid.*, 420.

and the University of Tokyo for further advice. The clinical trials were performed by researchers from these two organisations, and Kureha received guidance from government officials in the drug application process.⁶¹⁰ As a new entrant, the firm's collaborations with government and academia were essential to drug development.

To substitute for lack of experience in pharmaceutical distribution, Kureha's alliances with more established firms were important. For Kureha, Sankyo was an optimal choice as a marketing partner. Sankyo was one of the largest Japanese pharmaceutical firms with a reputation for its strengths in marketing. The firm had been founded in 1899 by the Meiji entrepreneur Matasaku Shiobara who established Sankyo Shoten as an import distributor of Tadiastase, a stomach medicine discovered by the Japanese-American scientist Jōkichi Takamine.⁶¹¹ The company grew quickly in the pre-war era and rivalled Takeda as one of Japan's leading pharmaceutical firms by the Second World War.⁶¹² In the post war period, Sankyo built its operations through the import-distribution and licensed manufacture of new medicines from firms in the United States and Europe.⁶¹³ Sankyo's historical marketing strengths were indispensable to Krestin's success.

Krestin experienced unparalleled success, but remained a domestic drug. After its launch in October 1976, Krestin sales rose from approximately 15 billion yen in 1977

⁶¹⁰ Yakuji Nippōsha, "Krestin," in *Saikin no Shinyaku* [New Drugs in Japan] (Tokyo: Yakuji Nippōsha, 1978), 96-101.

⁶¹¹ The firm became the Japanese agent for Parke Davis in 1902 and began to manufacture drugs in 1905. It launched vitamins in 1911. See Sankyo Co., *Sankyo 60-nenshi* [Sankyo, a 60 year History] (Tokyo: Sankyo Co., 1960).

⁶¹² Sankyo Co., *Sankyo 90-nenshi* [Sankyo, a 90 year History] (Tokyo: Sankyo Co., 1990).

⁶¹³ Particularly prominent was the manufacture of chloromycetin licensed in from Parke Davis in 1951. A year prior to the launch of PSK in 1975, Sankyo derived most of its sales from nervous system drugs, followed by vitamins and antibiotics.

to a peak in 1984 with 31.1% of the Japanese anticancer drug market at approximately 52 billion yen.⁶¹⁴ In fact, in 1987, it was the top selling drug in Japan and 12th worldwide.⁶¹⁵ As Kureha's corporate history notes, "There was no product in our 50 year history that grew so rapidly and strongly as Krestin."⁶¹⁶

The drug's success was a product of Japan's drug approval and pricing system. Krestin was popular for its wide range of approved indications, limited side effects, and ease of administration. But its therapeutic effects were not matched by its extraordinary sales performance.⁶¹⁷ Anticancer drugs, after all, commanded high prices. Critics began to voice scepticism over drug approval standards, particularly as it was revealed, for example, that much of the research had been published in non-refereed company-sponsored journals, and that efficacy had been measured in terms of tumour size rather than survival.⁶¹⁸ After the MHW's reappraisal in December 1989 reduced Krestin's indications, Sankyo's anticancer drug sales plunged from 34.7 billion yen in the fiscal year ending March 1990 to 13.5 billion yen in the fiscal year ending March 1991.⁶¹⁹

⁶¹⁴ In nominal terms, sales of Krestin grew from approximately 10 billion to 32.5 billion yen. Market share is based on production values. Toshihiko Suguro, "Kureha Kagaku Kōgyō: Daikokubashira 'Kuresuchin' Gekigen no Kiki [Kureha Chemical Industry: Sales of Core Product 'Krestin' may Plummet]," *Shūkan Tōyō Keizai*, 12 May 1990, 139-140. Yano Research Institute, *Iyaku Sangyō Nenkan* [Pharmaceutical Industry Annual] (Tokyo: Yano Research Institute, 1985), 537.

⁶¹⁵ Peter Marsh, "Pharmaceuticals 6; Optimistic But Still Some Way to Go," *Financial Times*, 1 October 1987.

⁶¹⁶ Kureha Chemical Industry Co., *Kureha Kagaku 50-nenshi* [A 50 Year History of Kureha Chemical Industry], 424.

⁶¹⁷ Yano Research Institute, "Kōryoku ga Yowai kara Tsukawareru, Kuresuchin, Pishibaniru [Krestin and Picibanil Used because of Minimal Effects]," *Iyaku Sangyō Nenkan* (Tokyo: Yano Research Institute, 1985): 15-18; "Mukō no Rakuin, Kōganzai Kuresuchin no Unmei [Fate of Krestin, a Drug Labelled Ineffective]," *Shūkan Shinchō* (15 August 1991), 164-165; Yakuji Nippōsha, "Krestin," in *Saikin no Shinyaku* [New Drugs in Japan] (Tokyo: Yakuji Nippōsha, 1978), 96-101.

⁶¹⁸ "Kōganzai 1-chō en no Kiyasume-ryō [1 Trillion Yen Anticancer Drug for Ease of Mind]" *Aera*, 7 June 1988, 6-11; "Soshite Ima [And Today]" *Aera*, 20 December 1988, 22. See, Isao Nakao, Tadashi Yokoyama, Ichirō Urushizaki, Akira Wakui, Hisashi Furue, Yoshiyuki Koyama, Kiyoji Kimura, Nobuya Ogawa, and Tatsuo Saitō, "Shinkō Igan ni Taisuru PSK no Rinshō Kōka [Clinical Effects of PSK in Advanced Gastric Cancer]," *Oncologia* 14 (1985): 163-170; Minoru Niimoto, Takao Hattori, Ryūichiro Tanida, Koyoshi Inokuchi, and Nobuya Ogawa, "Igan Chiyu Setsujo Shōrei ni Taisuru Maitomaishin C, Futorafūru, Kuresuchin o Mochiita Jutsugo Men'eki Kagaku Ryōhō [Postoperative Immunotherapy for Curatively Resected Gastric Cancer Patients Using Mitomycin C, Ftorafur and Krestin]," *Oncologia* 14 (1985): 171-180. *Oncologia* is a journal sponsored by Kureha.

⁶¹⁹ In nominal terms, Sankyo's sales of anticancer drugs fell from 32.5 billion yen in the fiscal year ending March 1990 to 13.0 billion yen in the fiscal year ending March 1991. Sankyo Co., *Yūka Shōken Hōkokusho* [Annual Securities Report] (Tokyo: Ōkurashō Insatsukyoku, 1991), 23. See also Toshihiko Suguro, "Kureha Kagaku Kōgyō, Daikoku Bashira Kuresuchin Gekigen

Zeria

In 1976, a small, Tokyo based pharmaceutical firm filed an application for SSM, another cancer immunotherapy drug. Unlike Picibanil and Krestin, however, SSM never gained official approval. This decision was extremely controversial and prompted intense public debate over Japan's drug approval process. Critics charged that the drug was denied approval due to the influence of competing pharmaceutical firms.⁶²⁰ SSM's rejection suggested that the success of a drug was heavily influenced by its connections in government, industry, and academia. More specifically, it implied that scientists and firms needed to develop strong connections to key individuals in government, industry and academia to facilitate a drug's success.

Like Chugai, Kureha and Sankyo, Zeria's entry into the anticancer drug sector was accidental. SSM's discovery was neither a direct product of government policy nor corporate strategy; it was a chance discovery by a physician. The drug was discovered and developed by Chisato Maruyama of the Nippon Medical School, a small private university in Tokyo. A dermatologist by training, Maruyama began to develop SSM from human tuberculosis bacilli at the end of World War II in 1944. His bacteriological approach to cancer therapy was similar to Picibanil and Coley's toxins in the 19th century. In 1956, Maruyama began to investigate whether the presence of tuberculosis or leprosy bacilli hindered cancerous growth.⁶²¹ SSM's discovery was not influenced

no Kiki [Kureha Chemical Industries' Core Product Krestin Under Threat],” *Shūkan Tōyō Keizai*, 12 May 1990, 139-140.

⁶²⁰ For example, see “Maruyama Wakuchin o Dō Kangaeruka [What to think of the Maruyama Vaccine],” *Asahi Shimbun*, 12 July 1981.

⁶²¹ The Research Institute of Vaccine Therapy for Tumors and Infectious Diseases, Nippon Medical School, “Maruyama Vaccine,” Nippon Medical School, <http://vaccine.nms.ac.jp/> (accessed 1 December 2007). Given the possible harm or side effects stemming from tuberculosis vaccines made of live or killed organisms, Maruyama decided to use his vaccine which was a derivative of the human tuberculosis bacteria.

by government or company incentives, and its development was much more ad-hoc than planned.

Despite lack of evidence from animal tests, Maruyama began to administer his patients with SSM from 1964 and opened a clinic in 1972.⁶²² In the meanwhile, scientists continued research on SSM. For example, Hiroshi Satō, a leading authority in Japanese cancer research at the Sasaki Institute found that SSM reduced pain and controlled cancerous growth for a wide range of cancers – in different types and stages – with limited side effects.⁶²³ The fact that a physician could widely administer a drug without official approval indicates that pharmaceuticals in Japan were more loosely regulated than in many developed markets.⁶²⁴

Zeria entered the anticancer drug sector upon the request of SSM's discoverer to co-develop the drug. Established in 1955, Zeria was known mostly for its dietary supplement chondroitin, and was engaged in the import distribution or manufacture of pharmaceuticals.⁶²⁵ As the building of its first central laboratory at the late date of 1983 suggests, the Tokyo-based firm was neither heavily engaged in R&D nor prescription drugs until the mid 1980s.⁶²⁶ Zeria resembled Chugai, Kureha, or Sankyo as a new entrant to the anticancer drug sector, but was a much smaller firm, with

⁶²² The Research Institute of Vaccine Therapy for Tumors and Infectious Diseases, Nippon Medical School, "Maruyama Vaccine." Maruyama established the Research Institute of Vaccine Therapy for Tumors and Infectious Diseases at the Nippon Medical School in 1972 to provide vaccine therapy for patients with tumors or infectious disease.

⁶²³ The Sasaki Institute is a non-profit cancer research institute established by the scientist Takaoka Sasaki in 1939. See Sasaki Foundation, "Sasaki Institute" <http://www.sasaki-foundation.jp/labo/eg-top.html> (accessed 1 December 2007).

⁶²⁴ "Maruyama Wakuchin Jissitsu 1-man en: Kōseisho Zeria Seishiki ni Giōi [Maruyama Vaccine Effectively Available for 10 thousand yen]," *Asahi Shimbun*, 28 November 1981, 1. Article states that the drug will be available via post to patients who pay out of pocket – almost as an over the counter drug.

⁶²⁵ Zeria Pharmaceutical Co., "Enkaku (Company History)," Zeria Pharmaceutical Co., <http://www.zeria.co.jp/comp/co01.html> (accessed 1 December 2007); Datamonitor, "Chugai Pharmaceutical Co. Ltd.," *Company Profile* (London: Datamonitor, 2007).

⁶²⁶ Zeria Pharmaceutical Co., *Yūka Shōken Hōkokusho* [Annual Securities Report] (Tokyo: Ōkurashō Insatsukyoku, 1990), 1.

limited links to individuals or organisations in government, industry or academia.

Without the size and connections of larger firms, Zeria was placed in a much more disadvantaged position compared to Chugai or Sankyo. For example, four of the 12 examiners on SSM's approval committee had direct conflicts of interests with its approval, as they were involved in the development of its rival drugs: one in Picibanil and three in Krestin.⁶²⁷ While the two leading drugs were highly profitable, SSM – with similar therapeutic claims – threatened to take sales away from Picibanil and Krestin. In 1979, Picibanil and Krestin comprised 15.8% and 33.4% of the anticancer drug market, respectively.⁶²⁸ At a time when Krestin and Picibanil charged 3,254 yen and 5,313 yen for treatment per day, respectively, Maruyama had been prescribing SSM for 125 yen per day.⁶²⁹ As a small firm with limited connections, Zeria was not in a position to attract political support for drug approval.

Zeria's lack of interest in forming such connections also failed to garner support for drug approval. Maruyama's refusal to form a partnership with Yūichi Yamamura – an Osaka University academic with strong connections in both industry and academia – for example, reportedly created a political conflict.⁶³⁰ Diet proceedings revealed, for

⁶²⁷ Yoshio Sakurai, Shigeru Tsugakoshi, and Kazuo Ōta were involved in the development of Krestin, while Hisashi Furue was involved in the development of Picibanil. See for example, Japan, House of Representatives, Labour and Welfare Committee, *Official Report of Debates*, 94th Diet, 20th Session, 30 July 1981.

⁶²⁸ Yano Research Institute, *Iyaku Sangyō Nenkan* [Pharmaceutical Industry Annual] (Tokyo: Yano Research Institute, 1980), 446.

⁶²⁹ Japan, House of Representatives, Labour and Welfare Committee, *Official Report of Debates*, 94th Diet, 20th Session, 30 July 1981; Japan, House of Councillors, Labour and Welfare Committee, *Official Report of Debates*, 95th Diet, 3rd Session, 27 October 1981. See also, Yakugyō Kenkyū-kai, *Hokenyaku Jiten* [Insured Drugs Almanac] (Tokyo: Jihō, 1969-2006) or Nihon Yakuzai-shi-kai, *Shakaihoken Yakka Kijun* [Insured Drug List] (Tokyo: Yakuji Nippōsha, 1977-2006).

⁶³⁰ Yasunari Iwai, "Maruyama Wakuchin wa Naze Ninka Sarenakatta noka [Why the Maruyama Vaccine was not Approved]," *Shūkan Shinchō*, 4 and 11 January 2001, 66-69; Yasunari Iwai, "Maruyama Wakuchin wa Naze Ninka Sarenakatta noka, [Why the Maruyama Vaccine was not Approved]," *Shūkan Shinchō*, 18 January 2001, 58-61.

example, that Yamamura and Yoshio Sakurai, who had been in charge of allocating government funds for cancer research, diverted research away from SSM. In addition, important clinical trial data supplied to the MHW allegedly “disappeared,” and the drug approval committee had revised drug approval regulations in the summer of 1980 to more rigorous standards – incorporating new criteria that had not been applied to the two earlier drugs. Much public criticism pointed to the double standards used to evaluate “efficacy,” as the committee discredited widely acclaimed clinical trial data, which used double blind tests for the first time in Japan.⁶³¹

Maruyama’s secondary status and lack of deference to custom also failed to win friends that might have otherwise facilitated the drug’s success. Maruyama was associated with a small private university without the prestige of national universities. In addition, he was a practitioner who had inadvertently stumbled upon a potentially effective therapy. As a medical practitioner, his status was viewed as secondary to those engaged solely in academic research.⁶³²

Moreover, Maruyama failed to subscribe to the conventions of the discipline. As a dermatologist, he initially published his findings in journals of dermatology rather than journals that published more cancer research – such as internal medicine, surgery or obstetrics. Maruyama also published and presented overseas prior to wider,

⁶³¹ PS-K, for example, was reportedly approved after two meetings, without requests for comparative trials or explanation of survival rates. See for example, “Maruyama Wakuchin Yūkosei 3% ika no Imi [The Meaning of Less than 3% Efficacy],” *Asahi Shimbun*, 27 December 1980, 3.

⁶³² Yasunari Iwai, “Maruyama Wakuchin wa Naze Ninka Sarenakatta noka [Why the Maruyama Vaccine was not Approved],” *Shūkan Shinchō*, 4 and 11 January 2001, 66-69; Yasunari Iwai, “Maruyama Wakuchin wa Naze Ninka Sarenakatta noka, [Why the Maruyama Vaccine was not Approved],” *Shūkan Shinchō*, 18 January 2001, 58-61.

domestic recognition of his work.⁶³³ He also published books such as “Maruyama Vaccine: Conquering Cancer (*Maruyama Wakuchin: Gan o Oitsumeru*)” before an official decision on the drug had been made.⁶³⁴ Maruyama’s flamboyant decision to name the drug after himself further alienated the more conservative parties engaged in anticancer drug development.⁶³⁵ Most poignantly, he administered the drug without official approval, whereby SSM had become a drug even before it was approved.

Ready opponents and the lack of strong supporters undermined the drug’s potential for success. This was particularly so in an environment where approval standards remained undeveloped and informal connections could facilitate a drug’s approval. Maruyama and Zeria’s failure to form these links helped to exclude SSM from direct competition with Krestin and Picibanil.

SSM’s rejection also revealed that Japan’s drug approval process was not transparent – and that its decisions were not entirely binding, either.⁶³⁶ While the approval of Krestin and Picibanil was swiftly decided in one year and two and a half years, respectively, the decision on SSM was not made for almost five years.⁶³⁷ This roused public debate and support groups, such as Patients and Families of the Maruyama

⁶³³ One of Maruyama’s first presentations on the potential effects of cancer chemotherapy with his colleague Keishiro Fujita at the 11th International Cancer Congress, Florence, Italy, October, 1974.

⁶³⁴ Maruyama Chisato, *Maruyama Wakuchin: Gan o Oitsumeru* [Maruyama Vaccine: Conquering Cancer] (Tokyo: KK Bestsellers, 1976).

⁶³⁵ A detailed history of SSM has been written in Kazuo Miwa, “Shiseiji Maruyama Wakuchin no 17-nen [A 17 Year History of Our Maruyama Vaccine],” *Bungei Shinjū*, August 1981, 208-236.

⁶³⁶ “O o Hiku Aimaisha: Fushin Maneku Yakuji Gyōsei [The Effects of Ambiguity: Pharmaceutical Administration Invites Mistrust],” *Asahi Shimbun*, 16 August 1981.

⁶³⁷ An application for SSM was made on November 1976, and was rejected in July 1981. See “Gan no Maruyama Wakuchin, Shinyaku Ninka Shinsei o Teishutsu [A New Drug Application Filed for the Maruyama Vaccine that Treats Cancer],” *Asahi Shimbun*, 30 November 1976; “Maruyama Wakuchin Kōka Nashi [Maruyama Vaccine Found Ineffective],” *Asahi Shimbun*, 11 July 1981.

Vaccine (*Maruyama Wakuchin: Kanja Kazoku no Kai*) headed by University of Tokyo law professor Shionohara Hajime, that championed the drug's approval.⁶³⁸ The government's eventual response was ambiguous. In July 1981, the Central Pharmaceutical Affairs Council refused to approve the drug, citing the lack of evidence regarding efficacy.⁶³⁹ But the panel attached a separate opinion to the main report, stating that the vaccine could not be considered "invalid," and that further research might be pursued.⁶⁴⁰

As a compromise measure, the MHW adjusted and adapted legal provisions over the years to allow for the provision of SSM without official approval, responding to patient demand but restricting supply.⁶⁴¹ Government provisions allowed Zeria to supply the drug to Nippon Medical University, albeit on a much more limited scale than an official approval would have allowed. Given the large number of patients already using the drug, the MHW permitted use of the vaccine, as part of clinical tests in drug development.⁶⁴² Since, 1981, the period of clinical testing has been extended indefinitely for over two and a half decades.⁶⁴³ As of 31 March 2002, SSM had been

⁶³⁸ "Maruyama Wakuchin Ninka Sokushin o: Shinohara Kyōjura 40-man nin Seigan Shōmei [Accelerate Approval of the Maruyama Vaccine: Professor Shinohara and Others Collect 40,000 Petitions]," *Asahi Shimbun*, 22 October 1980; "Maruyama Wakuchin Shiryō Jōhōkōkai no Men Kara Yōkyū [Request for Disclosure of Maruyama Vaccine Documents]," *Asahi Shimbun*, 12 May 1982; "Maruyama Wakuchin Sōki Ninka Yōsei [Request for Swift Approval of the Maruyama Vaccine]," *Asahi Shimbun*, 1 October 1993.

⁶³⁹ The Central Pharmaceutical Affairs Council is an advisory panel to the MHW that evaluates drugs in Japan.

⁶⁴⁰ "Maruyama Wakuchin Kōka Nashi [Maruyama Vaccine Found Ineffective]," *Asahi Shimbun*, 11 July 1981.

⁶⁴¹ "Kōseishō ga Kyōkyū Keizoku Yōsei: Maruyama Wakuchin, Seiyaku Gaisha ni [MHW Requests Pharmaceutical Firms to Continue to Supply the Maruyama Vaccine]," *Asahi Shimbun*, 11 July 1981; "Maruyama Wakuchin no Kyōkyū Enchō Sara ni 3-nen Mitomeru [3 year Extension Granted to Supply the Maruyama Vaccine]," *Asahi Shimbun*, 30 November 1984; "Maruyama Wakuchin Yūshō Chiken Sara ni 3-nen Enchō [3 year Extension Granted for For-fee Clinical Trials of the Maruyama Vaccine]," *Asahi Shimbun*, 21 November 1987; "Maruyama Wakuchin Sara ni 3-nen Enchō [3 year Extension Granted for Use of the Maruyama Vaccine]," *Asahi Shimbun*, 15 November 1990; "Maruyama Wakuchin Shiyō 4-nenkan no Enchō [4 year Extension Granted for Use of the Maruyama Vaccine]," *Asahi Shimbun*, 7 December 1993.

⁶⁴² "Chikenyaku' Irei no Atsukai; Kyōkyū Kakudai suru Maruyama Wakuchin [Unprecedented Handling as 'Trial Drug': Supplies of the Maruyama Vaccine Grow]," *Asahi Shimbun*, 2 October 1981; "Maruyama Wakuchin Hikitsuzuki Kyōkyū e [Supply of the Maruyama Vaccine to Continue]," *Asahi Shimbun* 24 November 1984. This article discusses MHW's deference to large numbers of patients already using the drug.

⁶⁴³ See The Research Institute of Vaccine Therapy for Tumors and Infectious Diseases, Nippon Medical School, "Maruyama Vaccine." See also "Maruyama Wakuchin Seibun Nōshukuyaku: Fukusayō Yokuseizai de Shōnin [Concentrated Maruyama

provided to 355,805 patients.⁶⁴⁴

While the government remained undecided about whether to approve the drug, it was still willing to adjust its laws to allow for its distribution. Patients who have wished to receive the drug have been required to appear at Nippon Medical University to receive guidance regarding its use. Nippon Medical University has coordinated all supply of the vaccine, manufactured by Zeria at a price of 9,000 yen for 20 ampules or 40 days supply. In 1991, the MHW made another concession and approved a concentrated version of the vaccine, Ancer 20, developed by Zeria Pharmaceuticals Co. However, Ancer 20 was approved as a remedy to treat the side effects of radiotherapy rather than as an anticancer drug. While access to the original drug remained uncovered by national health insurance, the new drug was approved by the MHW. Firms such as Zeria suffered from opaque standards, as they could not assess the risks involved in planning drug development.

These three popular anticancer drugs, Picibanil, Krestin and SSM were remarkably similar in their manner of discovery, therapeutic attributes, and mechanisms of action. But the three drugs experienced remarkably different levels of success in the Japanese market. With swift government approval, Chugai's Picibanil as well as Kureha and Sankyo's Krestin experienced unprecedented sales growth, contributing not only to the firms' financial health but also to spectacular growth in national production. The

Vaccine: Approved as Remedy for Side Effects],” *Asahi Shimbun*, 6 June 1991.

⁶⁴⁴ The Research Institute of Vaccine Therapy for Tumors and Infectious Diseases, Nippon Medical School, “Maruyama Vaccine.”

non-approval of Zeria's SSM, however, did not simply result in losses for the firm. The government's refusal to approve SSM, in fact, evolved into a social issue debated widely by politicians, academics, journalists and patient groups in the media and Diet proceedings. Incidentally, these discussions revealed much about the dynamics of Japan's pharmaceutical industry. They raised critical questions over: the still rudimentary level of R&D in the Japanese pharmaceutical industry; the malleability of drug regulation in comparison with overseas counterparts; and the often non-transparent and politicised process of drug approval – where outcomes could be strongly influenced by linkages between government, industry, and academia. Understanding the dynamics of Japan's anticancer drug sector at this time help illuminate the reasons for its weakness.

4.4.3 On the phenomenal growth of Japan's anticancer drug sector

The extraordinary expansion of Japan's anticancer drug market requires further explanation. It is particularly important to examine why the demand for anticancer drugs abruptly grew so rapidly, and why firms developed drugs that were not approved beyond Japan.

The impact of medical culture

Japanese medical culture had a significant impact on the expansion of Japan's anticancer drug market during the 1970s and 1980s. Different approaches to cancer therapy in Japanese medical practice help explain why many anticancer drugs of questionable efficacy were prescribed and sold in Japan. It should be noted that anticancer drugs of the time could not cure cancer patients and could only extend life

by a few months while creating severe side effects.⁶⁴⁵ Given the small benefits to be gained from an arduous therapy, many Japanese physicians preferred to prescribe anticancer drugs with minimal side effects, even if such drugs had limited efficacy. Japanese physicians' aversion to side effects may also have stemmed from the widely publicised drug tragedies that surfaced over the 1960s and 1970s.⁶⁴⁶ Effective but highly toxic anticancer drugs such as adriamycin, bleomycin, and vincristine were available for use in Japan in this time, but had lower sales in comparison their performance in Western markets.⁶⁴⁷ Japanese approaches to cancer therapy diminished the demand for the more effective but more toxic anticancer drugs that were in high demand in the American and European markets. The medical culture in Japan incentivised drug companies to develop ineffective anticancer drugs with mild side effects.

Another important factor behind the growth of Japan's anticancer drug sector during this time relates to the unwillingness of Japanese doctors to inform cancer patients of their illness. Until recently, Japanese physicians seldom informed cancer patients of their diagnosis, based on the belief that communicating such a death sentence was unwelcome.⁶⁴⁸ Doctors typically prescribed anticancer drugs with the fewest side effects so as to prevent patients from discovering that they had an almost fatal disease. As the prescriptions given to patients were not labelled, many patients remained

⁶⁴⁵ Yano Research Institute, *Iyaku Sangyō Nenkan* [Pharmaceutical Industry Annual] (Tokyo: Yano Research Institute, 1980), 8, 58.

⁶⁴⁶ Widely publicised scandals involved drugs such as thalidomide, SMON, and chloroquine.

⁶⁴⁷ Yano Research Institute, *Iyaku Sangyō Nenkan* [Pharmaceutical Industry Annual] (Tokyo: Yano Research Institute, 1985), 17-23.

⁶⁴⁸ David Swinbanks, "Japanese Doctors Keep Quiet," *Nature* 339 (June 1989): 409.

ignorant of the drugs prescribed – and their diagnosis. In Japan’s hierarchical society, few patients questioned the physician’s authority.⁶⁴⁹ While the diffusion of cancer information on the Internet has empowered patients, who have become more informed and assertive in demanding particular treatments, this technology was not available in the 1970s or 1980s. Japanese medical practice therefore played an important role in generating the final demand for safe yet largely ineffective therapies.

Japanese medical practices towards cancer generated demand for a type of anticancer drug that was very different from those in demand in the West. Japanese firms were incentivised to develop anticancer drugs that were safer, if less effective, than those found in Western markets.

R&D incentives under universal health care

Another reason for the rapid expansion of Japan’s anticancer sector lay in R&D incentives, whereby firms were forgiven for a lack of innovation but stood to benefit from launching drugs with limited side effects that could be prescribed to a wide population.⁶⁵⁰ Before the product patent system was introduced in 1975, the criteria for innovation in Japan were lower than in other advanced markets. In addition, the national health insurance system not only guaranteed that the government would underwrite demand, but also incentivised physicians to prescribe newer, higher priced

⁶⁴⁹ Todd S. Elwy, Michael D. Fetters, Daniel W. Gorenflo, and Tsukasa Tsuda, “Cancer Disclosures in Japan: Historical Comparisons, Current Practices,” *Social Science & Medicine*, 46, (September 1998): 1151-1163.

⁶⁵⁰ This was the same reason for the rapid expansion of the antibiotics sector during this period.

drugs to gain from pharmaceutical price differentials that supported their income.⁶⁵¹

Anticancer drugs such as Picibanil and Krestin had high drug prices.⁶⁵² The drugs also offered the promise of a remedy that existing anticancer drugs could not achieve.

Anticancer drugs such as Picibanil and Krestin experienced tremendous success, not only because of their high prices and large pharmaceutical price differentials, but also because they could be prescribed to many patients.

The impact of rudimentary infrastructure

In addition, the infrastructure for developing anticancer drugs remained underdeveloped in Japan. In the early 1980s, for example, the number of cancer specialists in the United States was estimated at 5,000 compared to 100 in Japan.⁶⁵³

The absence of cancer specialists and cancer hospitals meant not only that Japanese pharmaceutical firms found it extremely difficult to conduct clinical trials, it also meant that Japanese physicians were also unable to administer effective yet often highly toxic cancer therapies to Japanese cancer patients.⁶⁵⁴ The scarcity of oncologist training in Japan diminished demand for innovative drugs, as there were few physicians capable of using them. Physicians who administered too little of the drug found the expense to be wasteful, as the drug was ineffective. But those who administered too much of the drug found the serious harm done to patients too

⁶⁵¹ Physician prescribing incentives from pharmaceutical price differentials are not an insignificant. For reference, see “Yakka Kijun Jissei Kakaku yori Ohabadaka: Saeki 4-wari Chikakumo [Official Drug Prices Much Higher than Actual Drug Prices: Pharmaceutical Price Differentials Account for 40 Percent of Drug Prices],” *Asahi Shimbun*, 18 July 1978; and “Yakka Saeki Nen ni 1-chō 300-oku en: Kusuridai Sōgaku no 4-bun no 1 [Pharmaceutical Price Differentials amount to 1.3 Trillion Yen a Year, or a Quarter of Drug Prices],” *Asahi Shimbun*, 9 November 1989. See also Masanori Fukushima, “The Overdose of Drugs in Japan,” 850-851; and “The Strange Ways of Japanese Medicine Makers,” *Fortune*, 29 July 1991, 118.

⁶⁵² *Yakka Kijun* [Official Drug List] (Tokyo: Shin Nihon Hoki Shuppan, 1975-1990).

⁶⁵³ Yano Research Institute, *Iyaku Sangyō Nenkan* [Pharmaceutical Industry Annual] (Tokyo: Yano Research Institute, 1985), 18.

⁶⁵⁴ See Yano Research Institute, *Iyaku Sangyō Nenkan*, [Pharmaceutical Industry Annual] (Tokyo: Yano Research Institute, 1985), 17-19.

devastating to use again.⁶⁵⁵

Another reason for the volume-based expansion of the anticancer drug sector lay in Japan's opaque drug approval system, where the criteria for drug approval was unclear. Scholars such as Lacey Glenn Thomas and Gerald Laubach have argued that clear, rigorous drug approval standards are very important in incentivising firms to develop globally competitive drugs.⁶⁵⁶ A drug approval system that is transparent, stable, and based on scientific criteria incentivises firms to invest in developing quality drugs that can also be approved in other markets. But a more opaque or politically charged drug approval system changes this incentive structure and incentivises firms to invest in political rent-seeking at the expense of R&D.⁶⁵⁷

Indeed, Japan's drug approval process during this period was subject to political influence. Drug regulations were malleable, and drug approval decisions were shaped by powerful individuals. Moreover, the blurring of the boundaries between government, industry, and academia also created conflicts of interest. The governance of the Japanese pharmaceutical industry by a set of administrative guidance, ministerial orders, and quality standards created room for ambiguous interpretation. Firms benefited from forming strategic alliances with key individuals in government and academia to facilitate drug approval. The approval process involved political

⁶⁵⁵ The certification of oncologists began in 2007. See Japanese Board of Cancer Therapy, <http://jbct.jp/index.html>, (accessed 1 December 2007).

⁶⁵⁶ See for example, Lacey Glenn Thomas, "Spare the Rod and Spoil the Industry: Vigorous Competition and Vigorous Regulation Promote Global Competitive Advantage: A Ten Nation Study of Government Industrial Policies and Corporate Pharmaceutical Competitive Advantage," *First Boston Working Paper Series*, 90-03 (1990); Gerald D. Laubach, "Federal Regulation and Pharmaceutical Innovation," *Proceedings of the Academy of Political Science* 33, no.4 (1980): 60-80.

⁶⁵⁷ Anne Kreuger, "The Political Economy of the Rent-Seeking Society," *American Economic Review*, 64 (June 1974): 291-303.

interplay that at times prioritised benefits to select parties rather than the therapeutic effectiveness of the drug.⁶⁵⁸

In the 1980s, the integrity of MHW's drug approval process came to be intensely debated in media and parliament. This was not only because the two leading anticancer drugs of dubious efficacy had experienced a phenomenal rise in production. It was also because the criteria for Picibanil and Krestin's approval and SSM's rejection remained unclear.⁶⁵⁹ The media reports and parliamentary proceedings that followed SSM's rejection in 1981 eventually led to the revisions of Krestin and Picibanil's indications in 1989.⁶⁶⁰ The revisions, which stated that the two drugs could no longer be used as the main component of an anticancer regimen, led to a precipitous fall in production. These discussions remarked upon the political role of linkages formed between government, industry, and academia in facilitating drug approvals.

Links between government, industry, and academia

The volume based expansion of Picibanil and Krestin was supported by their links to powerful individuals with overlapping roles in government, industry, and academia – by excluding competition from drugs that did not have similar links. Scientists who

⁶⁵⁸ "Ososugita Yakujishin Tōshin (Recommendation by the Drug Approval Committee Long Due)" *Yomiuri Shimbun*, 21 December 1989. The article discusses the non-transparent, politicised nature of approval among select parties that neglected patient interests.

⁶⁵⁹ "Maruyama Wakuchin: Sekinin Omoi Gyōsei Tōkyoku [Maruyama Vaccine: Heavy Responsibility of Administrative Authorities]" *Asahi Shimbun*, 6 December 1980. This article elaborates on need for disclosure of documents in the approval process.

⁶⁶⁰ "Maruyama Wakuchin Kōka Nashi [Maruyama Wakuchin Rejected]," *Asahi Shimbun*, 11 July 1981; "Hanagata Kōganzai Kuresuchin, Yakkō Shirabenaoshi [Top Cancer Drug Krestin to be Tested for Effectiveness]," *Asahi Shimbun*, 5 September 1997; "Kōganzai Kuresuchin Pishibanīru, Tandoku deno Yakkō Hobo Hitei [Effectiveness of Cancer Drugs and Picibanil Almost Negligible When Used Alone]," *Asahi Shimbun*, 10 December 1989; "2 Kōganzai Hyōkagae [Revisions to Two Cancer Drugs]," *Yomiuri Shimbun*, 21 December 1989, 30; "Kuresuchin Pishibanīru Kōnō Gentei o Tōshin [Reduction to Effective Range of Krestin and Picibanil Recommended]," *Asahi Shimbun*, 21 December 1990; "Kōnō Gentei o Tōshin; Kuresuchin to Pishibanīru [Reduction of Effective Range Recommended: Krestin and Picibanil]," *Nihon Keizai Shinbun*, 21 December 1989.

developed Picibanil and Krestin, for example, also served on committees that approved these drugs.⁶⁶¹ Prominent individuals such as Yoshio Sakurai bridged important roles across government, academia and industry: as Director of the Chemotherapy Centre at the National Cancer Research Institute, as Chair of the Subcommittee for Drugs against Malignant Tumours, and as Director of Yoshitomi Pharmaceutical. Sakurai's direct involvement in the development of Krestin at the National Cancer Research Institute, and as chair of MHW's drug approval committee, for example, was argued to have created conflicts of interests that facilitated Krestin's approval.⁶⁶²

Links between government and industry were also reinforced by *amakudari*, where MHW bureaucrats retired to directorships in private firms.⁶⁶³ *Amakudari* is a retirement path whereby government bureaucrats gain positions in private or public institutions within the domain of the ministry from which they have originated. While this practice arguably facilitated industrial development under government guidance, it has also led to corrupt ties between government and industry. Chugai, for example, had strengthened its ties to the government when it welcomed MHW vice minister Teiichirō Sakamoto as its vice president.⁶⁶⁴ These practices placed larger firms with

⁶⁶¹ Yoshio Sakurai and Shigeru Tsugakoshi were involved in both the development and approval of Krestin. See "Kōgan-zai Kuresuchin, Yakujishin no 2 Iin Hantei Ronbun ni Kanyo [Two Members of the Drug Approval Committee Involved in Drug Development]" *Asahi Shimbun*, 19 December 1989. See also, Japan, House of Representatives, Labour and Welfare Committee, *Official Report of Debates*, 94th Diet, 20th Session, 30 July 1981; and Japan, House of Representatives, Labour and Welfare Committee, *Official Report of Debates*, 104th Diet, 4th Session, 6 March 1986.

⁶⁶² Similarly, his direct involvement in the development of Yoshitomi Pharmaceutical's anticancer drug, Protectron, was argued to have facilitated its approval in the late 1960s; such ties were strengthened when he later became a director of the company. See "Ninki Kōgan-zai Kuresuchin no Kōnō [Effectiveness of Anticancer Drug Krestin]," *Shūkan Shinchō*, 16 October 1986, 44-45.

⁶⁶³ See for example, Richard A. Colignon and Chikako Usui, *Amakudari: The Hidden Fabric of Japan's Economy* (Ithaca: ILR Press, 2003).

⁶⁶⁴ Japan, House of Representatives, Labour and Welfare Committee, *Official Report of Debates*, 87th Diet, 15th Session, 9 May 1979; Japan, House of Councillors, Labour and Welfare Committee, *Official Report of Debates*, 93rd Diet, 9th Session, 25 November 1980. These proceedings also take note of the wide custom of *amakudari* across the pharmaceutical industry, with a list of 60 former MHW officials retiring as executives in leading firms ranging from Takeda, Sankyo, Daiichi, Shionogi, Fujisawa and

greater financial clout at a political advantage compared to smaller firms. Picibanil and Krestin's performance reportedly benefited from Chugai and Sankyo's links to influential individuals with overlapping roles in government, industry, and academia.

Of course, it is also important to recognise that MHW's rejection of SSM may not have been entirely politically motivated. The MHW, in fact, was justified in its decision to reform anachronistic drug approval standards and begin to reject safe but largely ineffective drugs, given contemporary developments abroad.⁶⁶⁵ With much higher levels of government funding, more transparent and rigorous standards of evaluations, and the existence of medical specialists and facilities for cancer therapy, the American and British anticancer drug markets, for example, were dominated by more innovative yet invasive therapies.⁶⁶⁶ With advances in science, Japanese scientists who had previously held genuinely optimistic hopes for the effectiveness of cancer immunotherapy drugs were more pessimistic by the 1980s.⁶⁶⁷ Given the burden placed by Picibanil and Krestin on national health insurance funds, the MHW was also under pressure by the Ministry of Finance (MOF) to contain costs and not approve similar drugs.⁶⁶⁸ The imposition of more stringent standards for SSM, while perhaps unfair compared to preceding drugs, also resulted in the much needed upgrading of Japan's pharmaceutical R&D. While MHW's rejection of SSM might have been based

Eisai.

⁶⁶⁵ "Maruyama Wakuchin, Yowai Rinshō Shiken Dēta, [Maruyama Vaccine Supported by Weak Clinical Data]," *Asahi Shimbun*, 27 December 1980; "Hyōka Nibun, Maruyama Wakuchin [Divided Opinions on the Maruyama Vaccine]," *Asahi Shimbun*, 22 January 1981.

⁶⁶⁶ Yano Research Institute, *Iyaku Sangyō Nenkan* [Pharmaceutical Industry Annual] (Tokyo: Yano Research Institute, 1985): 17-19.

⁶⁶⁷ "Gan: Men'eki Ryōhō no Jitsuryoku to Genkai [Cancer: The Strengths and Limitations of Cancer Immunotherapy]," *Asahi Shimbun*, 11 July 1981.

⁶⁶⁸ Kazuo Miwa, "Shiseiji Maruyama Wakuchin no 17-nen [A 17 Year History of Our Maruyama Vaccine]," *Bungei Shinjū*, August 1981, 208-236.

on scientific evidence rather than political influence, the criteria for drug approval remained opaque.⁶⁶⁹

Other reasons

There were also other explanations for the proliferation of largely ineffective drugs in Japan during this period. Part of Krestin's dramatic sales record, for example, was attributed to Sankyo's marketing strategy and sales network.⁶⁷⁰ The significance of marketing to firm performance echoed a wider, global trend in the pharmaceutical industry during the early 1980s. Based on a rigorous marketing strategy, Glaxo managed to overtake the antiulcer market, with Zantac (ranitidine) approved in 1981, despite minimal improvements over Smith Kline & French's antiulcer drug, Tagamet (cimetidine) approved in 1979.⁶⁷¹ Glaxo had revolutionised the industry – in which marketing capacity became as important to firm performance as the capacity for drug discovery and development.⁶⁷² Chugai and Sankyo's ability to skilfully market Picibanil and Krestin, respectively, contributed to the drugs' success,

Other factors may have accounted for the growth of Japan's anticancer drug sector through relatively ineffective drugs. Government support for cancer research, for example, was much less in Japan compared to many Western countries such as the

⁶⁶⁹ Kōichi Yoshimoto, "Kagaku to Igaku no Aida: Maruyama Wakuchin o Megutte [Between Medicine and Science: On the Maruyama Vaccine]," *Chūō Kōron*, September 1981, 286-295.

⁶⁷⁰ Sankyo Co., *Sankyo 80-nenshi* [Sankyo, a 80 Year History] (Tokyo, Sankyo Co., 1979), 162.

⁶⁷¹ Ernst R. Berndt, Linda Bui, David R. Reiley and Glen L. Urban, "Information, Marketing, and Pricing in the U.S. Antiulcer Drug Market," *The American Economic Review* 85 (May 1995): 100-105. Davina C. Ling, Ernst R. Berndt, Margaret K. Kyle, "Deregulating Direct-to-Consumer Marketing of Prescription Drugs: Effects on Prescription and Over-the-Counter Product Sales," *The Journal of Law and Economics* 45 (October 2002): 691-723; Filippo Dell'Osso, "Defending a Dominant Position in a Technology Led Environment," *Business Strategy Review* 1 (June 1990): 77-86.

⁶⁷² Matthew Lynn, *The Billion Dollar Battle: Merck vs. Glaxo* (London: Mandarin, 1992).

United States.⁶⁷³ Cancer immunotherapy drugs, like antibiotics, were less costly to develop compared to other types of anticancer drugs. In addition, the government placed little emphasis on coordinating academic and industrial research at a time when the US government, for example, played a major role in coordinating cancer research projects through the National Cancer Institute. But government support for cancer research does not sufficiently explain the causes of Japan's weakness in anticancer drugs. After all, while the government did launch cancer research subsidies through the MHW and the Ministry of Education from 1963, these did not directly translate into the availability of new anticancer drugs.⁶⁷⁴ The nature of R&D incentives, the opacity of the drug approval system, and Japanese medical culture provide a far stronger explanation for the weakness of Japan's anticancer drug sector at this time.

4.4.4 Summary of the period between 1975 and 1990

There are several reasons why the Japanese anticancer sector experienced a phenomenal expansion through anticancer drugs that did not exist in leading Western markets during this period. One of the major reasons lay in Japan's opaque drug approval process and the lack of government funding for research in anticancer drugs. It is important to note, however, that even if innovative drugs had been developed and approved, the Japanese medical system was not prepared to take advantage of such drugs. The development of anticancer drugs is dependent on physicians and

⁶⁷³ Yano Research Institute, *Iyaku Sangyō Nenkan* [Pharmaceutical Industry Annual] (Tokyo: Yano Research Institute, 1985), 13.

⁶⁷⁴ Increases in cancer research funding has not necessarily translated into new drug discoveries. See for example, Gardiner Harris, "New Drug Points Up Problems in Developing Cancer Cures," *The New York Times* 20 December 2005. Michael Reich has also noted the R&D spending does not necessarily correlate with drug discoveries in Michael Reich, "Why the Japanese Don't Export More Pharmaceuticals: Health Policy as Industrial Policy," 124-150.

technicians with expertise in cancer and cancer drugs to administer the drug, as well as hospitals equipped with the relevant equipment to deliver the drug. The lack of such infrastructure not only disincentivised innovation, but they also maintained invisible yet significant barriers to entry to foreign firms despite formal attempts at deregulation – and provided life support for non-innovating firms. The absence of R&D incentives, lack of regulatory transparency, and distinct medical culture helped encourage the development of high priced, safe yet largely ineffective drugs that would not have survived in other advanced markets. These factors were the source of Japan's weakness in anticancer drugs.

4.5 Hollowing out, 1990 onwards

Despite considerable advances in the anticancer drug market over the decades, Japan's anticancer drug sector remained weak compared to countries such as the United States, the United Kingdom and Germany. This was demonstrated clearly in Japan's large trade deficit and trading partners. In 2000, for example, Japanese firms ran a deficit of 27.3 billion yen, as it exported 4.9 billion yen and imported 32.2 billion yen. While imports of anticancer drugs originated from developed countries, led by the United States, the United Kingdom, and France, its exports were primarily destined to developing countries, led by China, Taiwan, and Middle Eastern countries such as Egypt, Syria and Jordan.⁶⁷⁵ Japan remained reliant on Western imports, and its anticancer drug sector was not able to compete in advanced Western markets.

⁶⁷⁵ In nominal terms, Japan exported 5.0 billion yen and imported 33.2 billion yen worth of anticancer drugs in 2000. It should be noted that trade figures for anticancer drugs are not available in the *Tsūshō Hakusho*. Trade data for anticancer drugs were available in Ministry of Health and Welfare, *Yakuji Kogyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Yakugyō Keizai Kenkyūjo, 2001).

Part of this could be explained by the inability of Japanese university professors to commercialise their research, the lack of venture capital for biotechnology start-ups, and the comparably small size of Japanese firms without significant funds for R&D spending. But a much more compelling reason for the weakness of Japan's anticancer drug sector was the comparative lack of research incentives, lack of specialised experts or facilities for drug development, and distinct medical practices that restricted demand for highly innovative anticancer drugs. In the 1990s, Japan's pharmaceutical industry began to observe the hollowing out of R&D in Japan. To circumvent inferior incentives in the home market, Japan's leading pharmaceutical firms began to prioritise drug development in American or European regimes that were more favourable to pharmaceutical innovation.

4.5.1 Lagging drug approvals and problems in infrastructure

In the 1990s, fewer anticancer drugs were approved in Japan compared to other advanced markets. Despite having the second largest cancer market in the world after the United States, 30 cancer therapies approved in the United States had not been approved in Japan.⁶⁷⁶ This was a new development that had not been observed in previous decades.⁶⁷⁷

Some argued that Japan's delayed approval of innovative drugs was a result of

⁶⁷⁶ Matsuyama Kotone, Tetsuji Sadaike, Masanori Fukushima, "The Present Approval State of Anti-tumour Drugs in Japan," *Rinshō Hyōka* [Clinical Evaluation] 31 (2004): 579-86.

⁶⁷⁷ Jeffrey S. Brown, Brigitta Bienz-Tadmor, and Louis Lasagna, "Availability of Anticancer Drugs in the United States, Europe, and Japan from 1960 through 1991," *Clinical Pharmacology and Therapeutics* 58 (September 1995): 243-256.

administrative failure. The government had been reluctant to consult foreign test data or quicken its pace of examination following the criticism over the approval of Krestin and Picibanil in the 1980s and the HIV blood scandal in the early 1990s. While this was true to some extent, the issue was more complex: the Japanese government lacked the resources, funds and capacity – in terms of human capital, facilities, and organisation – to support drug R&D and review drugs efficiently compared to overseas competitors in the United States and Europe.⁶⁷⁸ For one, the Japanese clinical trial system was less equipped in relation to comparable systems abroad. Japan's Pharmaceuticals and Medical Devices Agency in 2005 maintained approximately 250 staff, including 10 clinical examiners, of whom three were biological statisticians. By comparison, the FDA employed approximately 2,300 staff, with 300 clinical examiners, including 100 biostatisticians.⁶⁷⁹ Moreover, there has been no system or standards established to conduct clinical trials in Japanese hospitals; in the past, most were conducted through personal connections, on an ad-hoc basis.⁶⁸⁰

In addition, there were fewer cancer specialists and facilities compared to many other countries. Oncologists, for example, were only certified in 2007, more than 35 years after the United States, and Japan had much fewer cancer hospitals compared to its Western counterparts.⁶⁸¹ The lack of infrastructure long limited the demand for anticancer drugs, as it meant that fewer Japanese physicians were capable of

⁶⁷⁸ Shunsuke Ono, "The Performance of the Japanese New Drug Review System: From the Reviewer's Perspective," *Rinshō Hyōka* [Clinical Evaluation] 31 (2004): 557-66.

⁶⁷⁹ Jon Sigurdson, *Future Advantage Japan?: Chemicals and Pharmaceuticals Report*, (London: Cartermill Publishing, 1996).

⁶⁸⁰ P. Reed Maurer, interview by author, Tokyo, Japan, 11 July 2007.

⁶⁸¹ Japanese Board of Cancer Therapy, "Nintei Seido Kisoku [Certified Oncologist Regulations]," Japanese Board of Cancer Therapy, 2 May 2007, http://www.jbct.jp/sys_regulation01.html (accessed 30 November 2007).

prescribing the drug, and fewer facilities were equipped to administer the drug to cancer patients.

4.5.2 A shift in Japan's anticancer drug market

While it remained weak in global perspective, the anticancer drug sector transformed markedly after 1989. Following public debates over the efficacy of Japan's leading anticancer drugs, the government banned Chugai's Picibanil and Kureha's Krestin from being prescribed as the main drugs in cancer therapy. The composition of Japan's anticancer drug market changed as sales of the two drugs plunged. The impact of the 1989 revisions, as well as the government's cost containment measures are reflected in the production trends after 1990. Anticancer drug production stabilised but decreased slightly due to the biennial price reductions. The slight decrease also reflected delays in the approval process, which limited the availability of drugs already marketed overseas. At the same time, more anticancer drugs of foreign origin were available in the market. As a disease that mostly affects the elderly, Japan's ageing society also contributed to a rising cancer population.⁶⁸²

⁶⁸² Ministry of Health and Welfare, "Patients and Deaths of Infectious Diseases and Food Poisoning (1876 -1999)," <http://www.stat.go.jp/data/chouki/02.htm> (accessed 6 May 2008).

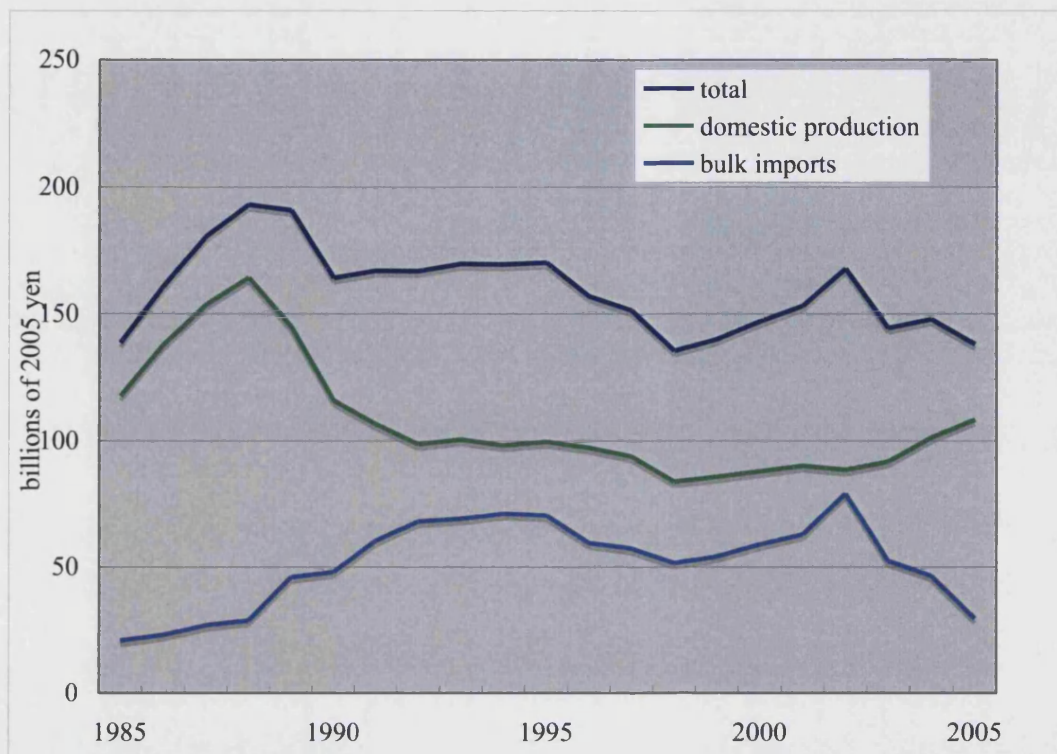


Figure. 22. Value of Anticancer Drug Production, 1985⁶⁸³

Whereas the top three anticancer drugs in 1985 were domestic drugs not approved in the United States or Europe, a decade later, the top three anticancer drugs—Taiho’s UFT, Roche’s Fruturon, and Takeda’s Leuplin—were all therapies recognised beyond Japan.⁶⁸⁴ Although Japan’s anticancer drug market remained undeveloped, it was becoming less backward relative to its Western counterparts.

Taiho

One of the leading anticancer drug makers since the 1980s began as a small import distributor of Western medicines in 1963, a time when the Japanese pharmaceutical

⁶⁸³ Ministry of Health and Welfare, *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Yakugyō Keizai Kenkyūjo, 1968-2000). Ministry of Health, Labour and Welfare, *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Jihō, 2001-2006).

⁶⁸⁴ *Gekkan Mix* [Monthly Medical Information Express] (December 1996): 61. The top three drugs in 1985 were Krestin, Picibanil and Ftorafur. See Yakugyō Jihōsha, *Yakuji Handobukku*, [Pharmaceutical Affairs Handbook] (Tokyo: Yakugyō Jihōsha, 1987), 266.

market was expanding rapidly. Established as a subsidiary of a leading over-the-counter (OTC) drug maker, Otsuka Pharmaceutical Co., Taiho Pharmaceutical Co. offered numerous therapies ranging from anti-allergy to digestive medicines.⁶⁸⁵

Taiho's decision to invest in anticancer drugs was an organic outgrowth of its past in reverse engineering foreign-discovered drugs. Taiho pursued incremental innovations based upon an imported technology made possible through alliances with university researchers and marketing partnerships with foreign firms. In 1969, Taiho formed a partnership with the Latvian Institute of Organic Synthesis in the Soviet Union in 1969 to launch Ftorafur, a drug for colorectal cancer that was patented in the United Kingdom and the United States in 1969 and 1976, respectively.⁶⁸⁶ After conducting Japanese clinical trials from 1970, Taiho launched its drug in 1973. Taiho's collaboration was unique, in that it sought new market opportunities through licenses with a Soviet organisation at a time when the majority of firms imported technologies from the United States or Europe. For Taiho, this collaboration proved a strategic success. Ftorafur sales rode on the tails of Krestin and Picibanil sales in the 1980s and placed Taiho firmly as a key player in the Japanese anticancer drug market by the 1980s.⁶⁸⁷

⁶⁸⁵ Tadamasu Matsumoto, "Wagasha ni Okeru Kōgan-zai no Kaihatsu," *Kagaku to Kōgyō* (April 1976): 105-107; Letter from Valdis Jākobsons, Chairman of the Board, AS Grīdeks (successor to Latvian Institute of Organic Synthesis) to author, dated 10 May 2006; Taiho Pharmaceutical Co., "Taihō Yakuhin no Ayumi," <http://www.taiho.co.jp/corporation/history/index.html> (accessed 2 December 2007).

⁶⁸⁶ Yakuji Nippōsha, "N1(2Tetrahydrofuryl-5-fluorouracil)," in *Saikin no Shinyaku* [New Drugs in Japan] (Tokyo: Yakuji Nippōsha, 1974), 53-61. Solomon Aronovich Giller, Regina Abramovna Zhuk, Marger Jurievich Lidak, Aina Avgustovna Zidermane, "Substituted Uracils," British Patent 1,168,391 filed 8 January 1968 and issued 22 October 1969; Leroy B. Townsend, Robert A. Earl, Steven J. Manning, "Method of Synthesizing 1-(tetrahydro-2-furanyl)-5-fluorouracil," U.S. Patent 3960864 filed 6 May 1974 and issued 1 June 1976.

⁶⁸⁷ "UFT," in *Gekkan Mix* [Monthly Medical Information Express] (December 1996): 60-61.

Taiho developed UFT in collaboration with Setsurō Fujii and others at Osaka University, who strengthened the anticancer properties of Ftorafur by adding a substance called uracil in 1978.⁶⁸⁸ In 1984, UFT was approved for wide range cancers – from the head, lung, and breast, to neck – and featured few adverse effects compared to many existing therapies.⁶⁸⁹ Its wide range of approval, limited side effects, and ease of use helped Taiho record robust sales in Japan for well over a decade – with annual sales exceeding 80 billion yen in the mid 1990s.⁶⁹⁰

In many ways, Taiho's UFT reflected a transitional phase in the government's commitment to pharmaceutical R&D. UFT was met with mixed reception abroad. The drug was approved in more than 15 countries, and was marketed by Merck in countries such as UK, France, and Germany by 2005.⁶⁹¹ It was, however rejected in the United States in 2001, as the FDA cited insufficient evidence regarding efficacy or superiority over existing drugs.⁶⁹² UFT was not an entirely new therapy, but a product of incremental improvements on an existing anticancer drug. While it was more effective compared to Japan's previous anticancer drugs, it had yet to be fully recognised internationally. This was similar to the status of Japan's drug approval standards, in which criteria had improved, but had yet to become comparable to those of the

⁶⁸⁸ S. Fujii, K. Ikenaka, M. Fukushima, and T. Shirasaka, "Effect of Uracil and its Derivatives on Antitumor Activity of 5-fluorouracil and 1-(2-tetrahydrofuryl)-5-fluorouracil," *Gann* 69 (1978): 763–72; See also, Tetsuhiko Shirasaka, *SI Tanjō* [Creating S-1] (Tokyo: Evidensu, 2006), 74–88.

⁶⁸⁹ Yakuji Nippōsha, "Tegafur-Uracil," in *Saikin no Shinyaku* [New Drugs in Japan] (Tokyo: Yakuji Nippōsha, 1985), 110–113.

⁶⁹⁰ This value is in nominal terms. "UFT," *Gekkan Mix* [Monthly Medical Information Express] (December 1996): 60–61.

⁶⁹¹ Merck KGaA, "2006 Online Report: Commercial Unit Oncology," Merck KGaA, <http://www.merck.de/servlet/PB/menu/1647870/index.html>. (accessed 6 December 2007).

⁶⁹² U.S. Food and Drug Administration, Center for Drug Evaluation and Research, "Colorectal Cancer Endpoints Workshop Summary, 12 November 2003," U.S. Food and Drug Administration, http://www.fda.gov/cder/drug/cancer_endpoints/colonEndpointsSummary.htm (16 May 2006).

advanced Western markets.

As a means to counter the government's periodic price reductions of existing therapies, Taiho continued to invest in R&D and launch new drugs. The firm's continuous efforts at improving existing therapies resulted in the launch of another anticancer drug TS-1, in 1999. In step with improvements in Japanese approval standards, TS-1 was recognised with a license for worldwide distribution by Sanofi-Aventis in 2006.⁶⁹³

Yakult Honsha

It was during these times that Yakult Honsha Co. launched its successful anticancer drugs, irinotecan and oxaliplatin. Yakult Honsha is a food company known for its probiotic drink, "Yakult," that entered pharmaceuticals and cosmetics in the 1970s. The drink, "Yakult," was first launched in 1935 by the bacteriologist Minoru Shirota as a nutritional supplement that would promote a healthy intestinal tract in a still poor economy. The company had been established in 1955 in order to manufacture and sell "Yakult." Yakult Honsha expanded over the decades through its operations in food and beverage, pharmaceuticals and cosmetics, with international operations spanning the continents.⁶⁹⁴

Facing saturation in the food and beverages market, Yakult Honsha planned to build upon its core competencies, take advantage of new developments in biotechnology,

⁶⁹³ Datamonitor, "Taiho Pharmaceuticals Co Ltd.," *Company Profile* (London: Datamonitor, 2007).

⁶⁹⁴ Yakult Honsha Co., *Yūka Shōken Hōkokusho* [Annual Securities Report] (Tokyo: Ōkurashō Insatsukyoku, 1990), 1; Yakult Honsha Co., "Enkaku [History]," <http://www.yakult.co.jp/front/company/profile/htm/index03.html>, (accessed 15 November 2007); Datamonitor, "Yakult Honsha Co., Ltd.," *Company Profile* (London: Datamonitor, 2007).

and gain an edge in a niche sector. As observed in the overview chapter, the entry of Yakult Honsha into pharmaceuticals represented a wider phenomenon in the 1970s and 1980s, when Japanese firms from a range of sectors began to diversify into this industry for the same reason.⁶⁹⁵ The firm invested heavily to develop its research capacity by hiring new scientists and forming alliances with universities and other firms to supplement its lack of expertise in drug development and distribution.⁶⁹⁶ Yakult hoped that its new investments in cancer therapy would help the firm gain a foothold in the pharmaceutical industry.

The research that led to Yakult's anticancer drug, irinotecan, in fact, had begun decades earlier, in America during the mid 1960s. In 1966, researchers led by M.E. Wall at the Research Triangle Institute in North Carolina isolated camptothecin, an extract from a Chinese tree which was found to be effective against certain mouse cancers.⁶⁹⁷ Clinical trials, initiated at the National Cancer Institute in the United States during the 1970s, were withdrawn due to the high toxicity of the substance. But worldwide, research continued on camptothecin compounds and derivatives in search for a potential anticancer drug.⁶⁹⁸

During the 1970s, Yakult Honsha invested heavily in the recruitment of capable scientists and forming academic and corporate alliances in order to make its new

⁶⁹⁵ Yano Research Institute, *Iyaku Sangyō Nenkan* [Pharmaceutical Industry Annual] (Tokyo: Yano Research Institute, 1980), 12-15.

⁶⁹⁶ David Drutz, phone interview by author, 15 November 2005.

⁶⁹⁷ Monroe E. Wall, M. C. Wani, C. E. Cook, Keith H. Palmer, A. T. McPhail, and G. A. Sim, "Plant Antitumour Agents 1: The Isolation and Structure of Camptothecin, a Novel Alkaloidal Leukemia and Tumour Inhibitor from *Camptotheca Acuminata*," *Journal of American Chemical Society* 88 (20 August 1966): 3888-3890; Monroe Wall and Mansukh Wani, "Camptothecin: Discovery to Clinic," *Annals of the New York Academy of Sciences*, 803 (13 December 1996): 1.

⁶⁹⁸ Yakuji Nippōsha, "Irinotecan," in *Saikin no Shinyaku* [New Drugs in Japan] (Tokyo: Yakuji Nippōsha, 1995), 72-76.

venture in pharmaceuticals a success.⁶⁹⁹ At the firm's Central Institute for Microbiology Research in Tokyo, researchers worked with scientists at the School of Pharmaceutical Sciences at Showa University.⁷⁰⁰ By 1979, researchers at Yakult were able to reduce the toxicity of camptothecin, and an effective substance was synthesised in 1983. To compensate for its lack of experience in drug development, the company formed an alliance with Daiichi Pharmaceuticals from 1984.⁷⁰¹

Yakult experienced phenomenal success when it launched its new anticancer drug, irinotecan in 1994. Yakult's anticancer drug was a truly innovative therapy – the first drug that was found to be effective for colorectal cancer in 40 years. In fact, Yakult's anticancer drug became a global blockbuster drug. In the domestic market, irinotecan was launched as Campto by Yakult and Topotecin by Daiichi in April 1994.⁷⁰² Overseas, irinotecan was introduced in France as Campto by Rhône-Poulenc in 1995, and as Camptosar in the United States by Pharmacia & Upjohn in the following year. As of March 2006, irinotecan was approved in 100 countries, and sold in 88. Until the introduction of its successor drug, oxaliplatin, irinotecan formed the backbone of Yakult's pharmaceutical operations; with annual sales over 15 billion yen, it comprised over 90% of Yakult's pharmaceutical sales.⁷⁰³ With 80% of its sales from overseas markets, it was more of a global, rather than Japanese drug.⁷⁰⁴ Yakult's success with irinotecan solidified the firm's position in the anticancer drug market, and

⁶⁹⁹ Kiyoshi Terada, "Ensan Irinotecan," *Fine Chemical* 29 (September 2000): 31-41.

⁷⁰⁰ Yakuji Nippōsha, "Irinotecan," 72-76.

⁷⁰¹ T. Miyasaka and S. Sawada, "Anticancer Agent Irinotecan," *Gendai Kagaku* [Current Chemistry] 343 (1999): 58-66.

⁷⁰² Yakuji Nippōsha, "Irinotecan," 72-76.

⁷⁰³ Yakult Honsha, Co., "Yakult Honsha Iyakuhin Jigyō Setsumeikai [Yakult Honsha Discussion of Pharmaceutical Operations]," 14 June 2006.

⁷⁰⁴ Rosemary C. Bonney, *SCRIP's Guide to Cancer Therapies: A Biotech Revolution?* (Richmond: Scrip Reports, 2001).

helped the launch of a new anticancer drug.

This new drug, oxaliplatin, was a platinum-based anticancer drug that was actually discovered in 1976 by Kidani Yoshinori at Nagoya City University.⁷⁰⁵ But with limited success in preclinical tests, Japanese researchers had abandoned clinical testing in the 1970s. In 1989, however, Debiopharm, a Switzerland-based pharmaceutical firm, licensed-in oxaliplatin. Debiopharm was a firm that specialised in ethical drug development and registration; the firm licensed-in potential compounds and licensed-out the developed drug. Debiopharm was able to develop oxaliplatin into a successful drug, which was approved as a therapy for colorectal cancer in France, the UK, and the US in 1996, 1999, and 2004, respectively.⁷⁰⁶ But in Japan, Yakult did not gain approval for oxaliplatin, branded as Elplat, until March 2005.⁷⁰⁷

Reforms in R&D incentives, the drug approval process, and the modernisation of cancer therapy in Japan over the 1990s resulted in the approval of drugs such as oxaliplatin. As with irinotecan, oxaliplatin's strong performance in global sales generated considerable revenues for Yakult. At a high launch price, oxaliplatin gained sales of 9 billion yen in 2005 in Japan, and surpassed irinotecan sales in Japan during 2006.⁷⁰⁸

⁷⁰⁵ Yakult Honsha, Co., "Yakult Honsha Iyakuin Jigyō Setsumeikai [Yakult Honsha Discussion of Pharmaceutical Operations]."

⁷⁰⁶ Yakuji Nippōsha, "Oxaliplatin," in *Saikin no Shinyaku* [New Drugs in Japan] (Tokyo: Yakuji Nippōsha, 2006), 68-77.

⁷⁰⁷ As mentioned earlier, the drug's belated approval in Japan was not simply due to the absence of R&D incentives or fully modern, transparent criteria for drug approval. It was also due to delays to the drug approval process following the HIV blood scandal in the early 1990s. As well, Japanese medical system still had much smaller demand for rigorous chemotherapy. Moreover, the infrastructure to develop and approve anticancer drugs remained much less developed compared to the leading Western pharmaceutical markets. The Japanese anticancer drug sector had fewer physicians capable of providing rigorous cancer treatment or coordinating clinical trials. It also had fewer experts capable of evaluating innovative cancer drugs.

⁷⁰⁸ Yakult Honsha Co., "Yakult Honsha Iyakuin Jigyō Setsumeikai Sankō Shiryō [Reference Materials for the Informational Meeting on the Pharmaceutical Business at Yakult Honsha]," 14 June 2006.

4.5.3 Technology, patient empowerment, and the modernisation of medical practice

While Japanese physicians did not historically disclose to cancer patients their full and accurate diagnoses, Japan's medical culture began to change over the 1990s. The growth of Internet use, in particular, empowered patients who accumulated information on cancer and cancer therapies. This meant that physicians were more likely to prescribe drugs with the conspicuous side effects of cancer chemotherapy, and that there was more demand for such drugs. Japanese cancer patients began to help expand demand for innovative anticancer drugs and pressure authorities to accelerate drug approval.

The Internet not only empowered cancer patients with knowledge of their condition and possible therapies, but also fostered patient networks that campaigned for anticancer drugs that had yet to be approved in Japan. Patient groups such as Japan's Cancer Patients Support Organization (CANPS), for example, were instrumental in obtaining approval for oxaliplatin in Japan.⁷⁰⁹ The national organisation for cancer patients was only established in 2005, but quickly gained political influence through connections with government, firms and academia.⁷¹⁰ Patient groups concentrated primarily on the rapid approval of drugs for cancer or orphan diseases that were not

⁷⁰⁹Ministry of Health and Welfare, *Mishōninyaku Kentō Kaigi* [Committee on Non Approved Drugs in Japan], "Kako 5-nenkan ni Gakkai/Kanjadantai kara no Sōki Shōnin no Yōbō ga Ari, katsu Heisei 17-nen 3 gatsu Izen ni Ōbei 4 kakoku de Shōnin Sareta Mishōninyaku [Drugs Requested by Academic / Patient Organizations for Accelerated Approval Within the Past 5 years, that were Approved in the 4 American and European Countries Prior During or Before March 2005]," <http://www.mhlw.go.jp/shingi/2005/03/s0331-13.html> (accessed 1 December 2007).

⁷¹⁰Gankanja Dantai Shien Kikō, "Shui [Statement]," <http://www.canps.net/> (accessed 10 August 2007). Naoko Wakao, Representative of Japan's Cancer Patients Support Organization (CANPS), letter to author, 7 September 2007.

available in Japan but already approved in other countries.⁷¹¹ For pharmaceutical firms, patient groups could also act as a vehicle to promote potential approvals. Much of the funding for CANPS campaigns, for example, came from pharmaceutical firms, and foreign pharmaceutical firms have been particularly keen in funding and disseminating information on new drugs yet to be approved in Japan.⁷¹² The absence of empowered cancer patients in earlier times indirectly undermined the development of Japan's anticancer drug sector.

4.5.4 Barriers to entrepreneurship

The legal barriers to entrepreneurship faced by Japanese university academics until the late 1990s also hindered the translation of innovative research in anticancer drugs into commercial therapies. As mentioned in the overview chapter, until 1998, academics at national or public universities were prohibited from receiving income in private industry or establishing firms to commercialise their research.⁷¹³ In the meanwhile, American academic start-ups such as Genentech had played a key role in launching new anticancer drugs in the United States.⁷¹⁴

The comparatively smaller size of Japanese firms also disadvantaged prospects for innovative discoveries due to the limited size of R&D that smaller firms could

⁷¹¹ P. Reed Maurer, interview by author, Tokyo, Japan, 11 July 2007. While specific definitions vary according to country, orphan diseases refer to life-threatening or debilitating conditions that are rare. In general, few remedies are available for orphan diseases, as pharmaceutical firms do not expect to be adequately compensated for investments on drug R&D through sales.

⁷¹² Naoko Wakao, Representative Japan's Cancer Patients Support Organization (CANPS), letter to author, 7 September 2007.

⁷¹³ The Law for Promoting University Technology Transfer was introduced in 1998. An assessment of recent changes in legislation has been written by Michael Lynskey, "The Commercialisation of Biotechnology in Japan: Bioventures as a Mechanism of Knowledge Transfer from Universities," *International Journal of Biotechnology* 6 (2004): 155-185. As noted in the overview chapter, university professors lost their civil servant status in 2004.

⁷¹⁴ Rosemary C. Bonney, *SCRIP's Guide to Cancer Therapies: A Biotech Revolution?*

possibly afford. Dominant players in the Japanese anticancer drug market such as Taiho, Nippon Kayaku, and Kyowa Hakko were not only much smaller than global leaders such as Novartis, Bristol-Myers Squibb, or Aventis, but were also more diversified firms with considerable business outside of pharmaceuticals.⁷¹⁵ Still, less R&D investment does not directly lead to an inability to innovate. After all, from a historical perspective, drug discovery has not been as fruitful in recent years despite massive increases in R&D investment, advances in technology, and greater knowledge of both drugs and disease.⁷¹⁶

4.5.5 Opening up

Japan's protectionist policies had created a distinctly domestic anticancer drug market. At the turn of the century, it remained the only market where domestic firms, rather than global multinationals dominated the market. Global leaders such as Bristol-Myers Squibb, Johnson & Johnson, AstraZeneca, and Aventis had remarkably little presence in Japan.⁷¹⁷ Aside from Takeda, most of the leading firms such as Kyowa Hakko, Taiho, and Nippon Kayaku were younger, mid sized, less renowned firms. In addition to differences in language and culture, with an intricate distribution network and distinct domestic laws, most foreign firms found entry barriers still high enough to opt for licensing contracts rather than direct entry, despite substantial reforms since the 1990s.

⁷¹⁵ Datamonitor, "Japan – Cancer drugs," *Industry Profile* (London: Datamonitor, 2002), 8-9; Datamonitor, "Global – Cancer drugs," *Industry Profile* (London: Datamonitor, 2002), 9-10.

⁷¹⁶ Jürgen Drews, "Drug Discovery: A Historical Perspective," 1960-1964.

⁷¹⁷ Datamonitor, "Global – Cancer drugs," 9-10.

But Japan's anticancer drug sector had begun to open up and modernise in the 1990s. R&D incentives to innovate improved significantly following the modernisation of Japanese pharmaceutical regulations, the Market Oriented Sector Selective discussions of the 1980s, distribution reforms, and the harmonisation of regulation with the United States and Europe in the early 1990s.⁷¹⁸ Criteria for drug approval were more transparent, quality, safety, and efficacy guidelines were modernised, and innovative drugs were priced with a much higher premium compared to less innovative drugs. But while incentives had improved, conditions remained more favourable in other advanced nations. In the United States, for example, drug evaluation times were shorter, and while approval standards were more rigorous, approval decisions were based more on science than politics.⁷¹⁹ Moreover, compared to the medical practices in many Western countries, it was less common for Japanese physicians to provide cancer patients with complete and accurate disclosure of their illness.⁷²⁰ In medical systems where the practice of informed consent was more common, patient demand was higher for potentially effective therapies, which tended to be highly invasive and toxic.

In a more global economy, where better incentives existed abroad, leading Japanese firms such as Takeda moved some of their core operations – such as R&D and

⁷¹⁸ United States Department of Commerce, International Trade Administration, Market Access and Compliance, "MOSS Agreement on Medical Equipment and Pharmaceuticals." United States Department of Commerce. <http://www.mac.doc.gov/japan/source/menu/medpharm/ta860109.html> (accessed 15 May 2007)

⁷¹⁹ See for example, Office of Pharmaceutical Industry Research, "Sōyaku no Ba to shite no Kyōsōryoku Kyōka ni Mukete [Creating a Stronger, More Competitive Environment for Drug Discovery]" *Office of Pharmaceutical Industry Research, Japan Pharmaceutical Manufacturers Association* (November 2005); Office of Pharmaceutical Industry Research, "Seiyaku Sangyō no Shōrai-zō [The Future Image of the Pharmaceutical Industry]" *Office of Pharmaceutical Industry Research, Japan Pharmaceutical Manufacturers Association* (May 2007).

⁷²⁰ Emiko Ohnuki-Tierney, *Illness and Culture in Contemporary Japan* (Cambridge: Cambridge University Press, 1984), 62.

marketing – overseas, hollowing out innovation in Japan. While these outward oriented firms grew stronger, the more domestically oriented firms began to suffer in the face of foreign competition at home. Whether to strengthen their global reach or merely to survive, Japanese firms actively formed alliances with other firms during this period. Despite considerable reforms, comparatively inferior incentives facing the Japanese firms hindered the development of a strong anticancer drug sector in Japan. Entrepreneurial initiatives taken by firms such as Takeda also reflected diverging fortunes among Japanese firms, whereby outward looking firms prospered from expanding opportunities and inward looking firms suffered from a shrinking home market.

Takeda

While one of the oldest of Japanese pharmaceutical firms, Takeda was also an entrepreneurial firm that invested in R&D and adopted an export orientation, even before the Second World War.⁷²¹ Founded in 1781 as wholesaler of Chinese medicines, Takeda had established its position as one of Japan's leading pharmaceutical firms by the Second World War – primarily through the import and distribution of Western medicines. In the post war period, the firm grew primarily through its strengths in vitamins and antibiotics, the leading therapeutic sectors of the early post war period. As evident from the writings of its chairman in 1949, Takeda's managers adopted an export orientation from relatively early period.⁷²² By 1962, the firm re-expanded into

⁷²¹ Takeda Pharmaceutical Co., *Takeda 180-nenshi* [A 180 Year History of Takeda] (Osaka: Takeda Pharmaceutical Co., 1962).

⁷²² Chōbei Takeda, "Wagakuni no Iyakuin Kōgyō to Bōeki [Pharmaceutical Industry and Trade in Our Country]," *Kankeiren* 16 (January 1949): 19-21.

South East Asia, a region where it had developed extensive operations during the interwar era.⁷²³ In 1978, Takeda entered the European market and launched its first antibiotics in the United States in 1980.⁷²⁴

Takeda's decision to invest in anticancer drugs was a product of Takeda's strategies to invest in R&D to strengthen the firm, rather than an attempt to develop anticancer drugs in particular. Over the decades, Takeda had cultivated scientific and organisational capacities for R&D by forming ties with university scientists who could lead innovative research. In 1961, for example, Takeda launched its anticancer antibiotic, Toyomycin, under the advice of Morizō Ishidate at the University of Tokyo, who had developed Nitromin in the early 1950s.⁷²⁵

The development of its main anticancer drug, leuprorelin, also emerged out of Takeda's investments in R&D, which involved sending its key scientists to learn from foreign research institutes. In a manner similar to many large Japanese firms, Takeda had adopted the practice of sending its best scientists to study abroad to learn, adopt, and build upon cutting edge technologies. In the mid 1960s, Takeda had sent Fujino Masahiko, who later became Takeda's chairman, to study at the Baylor College of Medicine in Houston, Texas.⁷²⁶ At the time, Baylor was pursuing research on the potential therapeutic effects of two substances: TRH (thyrotropin releasing hormone)

⁷²³ Takeda Pharmaceutical Co., *Takeda 200-nen* [200 Years of Takeda] (Osaka: Takeda Pharmaceutical Co., 1984).

⁷²⁴ Takeda Pharmaceutical Co., "Takeda no Rekishi [A History of Takeda]," http://www.takeda.co.jp/about-takeda/history/article_79.html (accessed 30 November 2007).

⁷²⁵ Takeda Pharmaceutical Co. *Takeda 180-nenshi* [A 180 Year History of Takeda]; Takeda. Pharmaceutical Co., *Takeda 200-nen* [200 Years of Takeda].

⁷²⁶ Yakuji Nippōsha, "Leuprorelin," in *Saikin no Shinyaku* [New Drugs in Japan] (Tokyo: Yakuji Nippōsha, 1993), 127-130.

and LH-RH (luteinizing hormone releasing hormone). Back in Japan, Fujino continued this research to consider possible applications to infertility and other hormone-related afflictions, and eventually found a potential therapy for prostate cancer.⁷²⁷ Takeda's leuprorelin, in fact, marked a major therapeutic innovation in the treatment of prostate cancer.

But facing few rewards for innovation in Japan, Takeda looked abroad to develop this drug. Leuprorelin marked one of the first of Japan-origin drugs to be developed and launched abroad, as firms such as Takeda sought to capture the gains of greater market size, swift drug approval processes, and the more favourable pricing regimes of countries such as the United States. To compensate for the lack of experience in the US market, Takeda formed a joint venture with Abbot in 1977 – TAP Pharmaceutical Products Inc. – in order to develop drugs in the United States.⁷²⁸ Taiho, too, established Taiho Pharma, its US subsidiary in 2002 to prioritise drug development in the United States.⁷²⁹

Leuprorelin was recognised for its effectiveness toward a wide range of cancers in international markets. Following FDA approval, leuprorelin was launched in the United States as Lupron Injection in May 1985 by TAP Pharmaceutical. Leuprorelin

⁷²⁷ Satoshi Sasaki, Toshihiro Imaeda, Yoji Hayase, Yoshiaki Shimizu, Shizuo Kasai, Nobuo Cho, Masataka Harada, Nobuhiro Suzuki, Shuichi Furuya and Masahiko Fujino, "A New Class of Potent Nonpeptide Luteinizing Hormone-releasing Hormone (LHRH) Antagonists: Design and Synthesis of 2-phenylimidazo[1,2-a]pyrimidin-5-ones," *Bioorganic & Medicinal Chemistry Letters* 12, (August 2002): 2073-2077.

⁷²⁸ "Kaigai Shijō e Mukau Nihonsei Shinyaku [Japan-origin Drugs Expanding into Overseas Markets]," *Gekkan Mix* (September 1991): 29; "Leuprorelin," *Gekkan Mix* (June 1996): 44-45. This joint venture concluded on 30 June 2008. See Takeda Pharmaceutical Co., "Beikoku Jigyō Saihen ni Tsuite [On the Reorganisation of US Operations]," Takeda Pharmaceutical Co., news release dated 2 July 2008, http://www.takeda.co.jp/press/article_28213.html (accessed 30 July 2008).

⁷²⁹ Datamonitor, "Takeda Pharmaceutical Company Limited," *Company Profile*. (London: Datamonitor, 2007).

was improved and approved for a wider range of indications in the following years, as Lupron Depot, Viadur, and Eligard, in 1989, 2000, and 2002, respectively. Takeda's drug was only launched in Japan 9 years after the United States, as Leuplin in September 1994. Both in the international and domestic market, leuprorelin proved highly successful. Between 1988 and 1995, overseas sales soared from approximately 3.3 billion yen to 78.6 billion yen.⁷³⁰ In 2004, Leuplin was still the top selling anticancer drug in Japan at 44.3 billion yen.⁷³¹

The government's introduction of improved safety, quality, and efficacy standards over the 1970s and 1980s had coincided with the development of leuprorelin. The introduction of GMP (1974), GLP (1982), and GCP (1989) helped raised the quality of Japan origin drugs. As leuprorelin's development history suggests, however, anticancer drug development in Japan was often an ad-hoc product of corporate strategies to invest in R&D by individual firms who decided to invest in R&D – rather than a product of clearly defined research strategies by government or firms. As the trend among Japanese firms to prioritise drug development and marketing abroad suggests, government policies were less than optimal in incentivising firms to develop a strong anticancer drug sector in Japan.

Japanese firms that developed drugs abroad also stood to benefit from superior pricing regimes. The development of Takeda's cancer therapy leuprorelin demonstrated that,

⁷³⁰ In nominal terms, overseas sales increased from approximately 3 billion yen to 80 billion yen. "Leuprorelin," *Gekkan Mix* (June 1996): 44–45.

⁷³¹ In nominal terms, Leuplin's 2004 sales reached 44.5 billion yen. Fuji Keizai, *Iryōyō Iyakuhin Dētabukku* [Prescription Medicine Databook] 5 (Tokyo: Fuji Keizai, 2005), 12.

while firms operated within a highly regulated environment under a common set of incentives and disincentives, firm responses varied significantly. For example, one response to a system that rewarded incremental innovation was to develop me-too drugs; another was to seek opportunities where product innovation was rewarded.⁷³² Poor economic conditions, downward price revisions, and rising foreign competition in the home market, disincentivised firms such as Takeda from developing anticancer drugs in Japan. Instead, they increasingly sought opportunities abroad by investing heavily in R&D and strengthening overseas distribution networks.⁷³³ The Japanese government had been loath to place initial high prices on drugs due to financial constraints of the Japanese health insurance system. But if a drug was already approved abroad, the government set prices to minimise the difference between domestic and overseas prices.⁷³⁴ These policies incentivised stronger firms like Takeda to prioritise drug development outside of Japan. Without the profit potentials offered by larger cancer markets, and the absence of a generous pricing regime to reward innovation, the Japanese market could not support the development of a strong anticancer drug sector.

4.5.6 Summary of the period between 1990 and 2005

Over the 1990s, the Japanese cancer market had evolved markedly in both size and content. By 2001, the Japanese anticancer drug market stood at 14.4 % of the global market at \$3.3 billion, compared to \$10.9 billion in the United States and \$1.6 billion

⁷³² Me-too drugs refer to drugs with minor improvements over existing alternatives.

⁷³³ See for example, Michiyo Nakamoto, "Global Reach through Tie-ups: Japan," *Financial Times*, 30 April 2002; "Looking West," *The Economist*, 18 June 2005.

⁷³⁴ "Kaigai Shijō e Mukau Nihonsei Shinyaku [Japan-origin Drugs Expanding into Overseas Markets]," *Gekkan Mix* (September 1991): 29.

in the United Kingdom.⁷³⁵ The cancer market expanded amid an ageing population, wider options in pharmacological treatments, and increased survival rates – as well as the comparatively high prices for new, innovative cancer therapies. By 2004, the Japanese anticancer drug market had expanded to 460.0 billion yen, led by Takeda's Leuplin, Taiho's UFT, and AstraZeneca's Kasodex, which recorded sales of 44.3 billion yen, 30.8 billion yen, and 20.9 billion yen, respectively.⁷³⁶ For firms, there were considerable pressures to invest in innovative therapies and survive intense competition.

Case studies from the three firms that launched leading anticancer drugs during this period indicated that initial decisions to invest in anticancer drug research were the product of entrepreneurial initiative rather than government policy. Drug development, however, was very much influenced by government incentives. Under a system that rewarded incremental innovations more than other Western countries, some firms such as Taiho, developed a series of improved, domestic versions of anticancer drugs that were discovered abroad.

Other anticancer drug makers, such as Yakult and Takeda, began to circumvent inferior rewards to R&D in the Japanese market and sought opportunities overseas.

These firms began to transfer their core R&D operations to countries where R&D was

⁷³⁵ In nominal terms, the value of the anticancer drug markets in 2001 in Japan, the United States, and the United Kingdom were \$3.4 billion, \$11.1 billion, and \$1.6 billion, respectively. Datamonitor, "Japan – Cancer drugs," 4; Datamonitor, "Global – Cancer drugs," 4; Datamonitor, "United States – Cancer drugs," *Industry Profile* (London: Datamonitor, 2002), 4; Datamonitor, "United Kingdom – Cancer Drugs," *Industry Profile* (London: Datamonitor, 2002), 4.

⁷³⁶ In nominal terms, the size of Japan's anticancer drug market in 2004 was 461.8 billion yen. Nominal sales values in 2004 for Leuplin, UFT, and Kasodex were 44.5 billion yen, 31.0 billion yen, and 21.0 billion yen, respectively. Fuji Keizai, *Iryōyō Iyakuhin Dētabukku* [Prescription Pharmaceutical Databook], 12.

more rigorous and costly but where rewards to innovation were higher – and where their drugs could be translated more easily into multiple pharmaceutical markets. These firms were increasingly rootless: most of the managerial and sales operations were based in Japan, but the sources of innovation and potential for future growth was now based overseas.

While a handful of Japanese firms were able to launch innovative anticancer drugs, these were exceptions. There were several reasons for the relative weakness of Japan's anticancer drug sector. It was true that more drugs were approved on the basis of efficacy, even if they had significant side effects. The government did improve incentives to innovate by placing higher prices, for example, on innovative drugs – and many firms responded by investing more heavily in R&D. But innovation among many domestic firms suffered from lower prices than abroad, biannual price reductions, lack of venture capital, an undeveloped clinical testing environment, and considerable delays in the drug approval process. Remnants of protectionist policies and the persistence of some non-tariff barriers, too, allowed comparatively weaker firms and drugs to survive in the domestic market. Finally, it was only after the millennium that the Japanese medical system was more equipped with the expertise and the facilities, or catered to patients empowered with knowledge over their condition, which created the final demand for innovative therapies.

4.6 Analysis of the anticancer drug sector

The Japanese anticancer drug sector was far less successful in drug discovery,

development or sales – both in comparison with leading Western counterparts and the Japanese antibiotics sector. The experience of the anticancer drug sector sheds light upon the causes for the weakness in Japan's pharmaceutical industry. This section considers why Japan's anticancer sector remained underdeveloped.

Some scholars have suggested that the relative weakness of the Japanese anticancer drug sector stems from Japan's weak foundation in science compared to countries with stronger performance in this sector. Samuel Collins and Steven Collins have argued that the Japan's weakness in pharmaceutical innovations stems from lack of investment in basic science and research at universities.⁷³⁷ But Japanese universities engaged in rigorous cancer research in collaboration with government and industry since the early 20th century.⁷³⁸ In addition, most Japan-origin anticancer drugs of global repute originated in academic laboratories. Japan's weakness in the anticancer drug sector cannot be explained by a weakness in basic science.

Another possible explanation for the weakness of the anticancer drug sector in Japan relates to industrial structure. The Japanese pharmaceutical industry was dominated by smaller firms for a longer period than in the leading pharmaceutical markets. Of the nearly 500 Japanese prescription drug makers in 2005, the leading firm, Takeda, was only a quarter of the size of the leading global firms, such as Pfizer or

⁷³⁷ Samuel Collins, *Japanese Science: From the Inside* (London: Routledge, 1999), 56; Steven W. Collins, *The Race to Commercialize Biotechnology: Molecules, Markets, and the State in the United States and Japan* (London: RoutledgeCurzon, 2004), 151.

See also "Pioneers of Cancer Research in Japan," *Japanese Journal of Cancer Research* 82 (December 1991): 1448- 1449.

⁷³⁸ Japan Cancer Association, "Nihon Gangakkai no Rekishi [History of the Japan Cancer Association]," <http://www.jca.gr.jp/b01.html>, (accessed 1 December 2007).

GlaxoSmithKline.⁷³⁹ The difference between the market concentration of Japanese and other advanced Western markets, however, has not been significantly different.⁷⁴⁰

There is some value in explaining the weakness of Japan's anticancer drug sector in light of its industrial structure. Large firms would have an advantage in developing anticancer drugs, which involve a much more costly and complex process compared to antibiotics. After all, producing cutting edge anticancer drugs requires a much higher R&D investment than in antibiotics.

But smaller firms are not necessarily disadvantageous to the development of an anticancer drug sector. After all, smaller pharmaceutical ventures in the United States have launched globally successful anticancer drugs and have contributed to the strength of the American industry. Firms may realise economies of scale in R&D. But the benefits of larger firm size are less clear in production or marketing. This is because anticancer drugs generally target a very particular type, stage and location of cancer, which limits the demand for each type of anticancer drug. Each anticancer drug also targets a niche market. Industrial structure only provides a partial explanation for the weakness of Japan's anticancer drug sector.

⁷³⁹ In sales. See Takeda Pharmaceutical Co., *Annual Report 2006* (Tokyo: Takeda Pharmaceutical Co., 2006), 2; Pfizer, Inc., *Annual Review 2006* (New York: Pfizer, Inc., 2007), 9; GlaxoSmithKline plc., *Annual Report 2006* (London, GlaxoSmithKline plc., 2007), 2. See also, Ministry of Health, Labour and Welfare, *Iyakuhin Sangyō Jittai Chōsa Hōkoku* [Report on the Status of the Pharmaceutical Industry] (Tokyo: Ministry of Health, Labour and Welfare, 2006), <http://www.dbtk.mhlw.go.jp/toukei/kouhyo/index-kousei.html>.

⁷⁴⁰ To 1994, Japan Fair Trade Commission, *Shuyō Sangyō ni Okeru Ruiseki Seisan Shūchūdo* [Concentration Ratio of Main Industries] (Tokyo: Japan Fair Trade Commission, 1975-1994), <http://www.jftc.go.jp/katudo/ruiseki/ruisekidate.html> (accessed 1 June 2008). From 1995, Ministry of Health and Welfare, *Iyakuhin Sangyō Jittai Chōsa Hōkoku* [Report on the Status of the Pharmaceutical Industry] (Tokyo: Ministry of Health and Welfare, 1988-2000); Ministry of Health, Labour and Welfare, *Iyakuhin Sangyō Jittai Chōsa Hōkoku* [Report on the Status of the Pharmaceutical Industry] (Tokyo: Ministry of Health, Labour and Welfare, 2001-2006). Also, U.S. Census Bureau, "Concentration Ratios in Manufacturing," Economic Census: Concentration Ratios <http://www.census.gov/epcd/www/concentration.html>, (accessed 1 December 2007).

A more convincing explanation for the weakness of Japan's anticancer drug sector lies in the incentives facing university professors, who faced considerable barriers in commercialising their research until 1998. The Law on National Public Employees, for example, effectively banned outside employment, while rigid labour markets and bankruptcy laws penalised failures in entrepreneurship.⁷⁴¹ The pre-1998 rules governing academics had a particularly acute impact on the anticancer drug sector.

Because the development of antibiotics was depended upon linear, incremental and evolutionary learning, restrictions to the transfer of academic know-how had a limited impact on the development of the antibiotics sector.⁷⁴² Antibiotic discovery had long been based on the random screening of a vast number of soil samples, and – while labour intensive – did not require the human capital and equipment needed to develop anticancer drugs. In contrast, anticancer drug development was much more sophisticated, and required more specialised expertise, equipment and more revolutionary knowledge spillovers from universities. Indeed, university affiliated start-ups such as Genentech played a large role in stimulating innovation and discoveries of anticancer drugs in the United States. While the pre-1998 rules hampered the development of the anticancer drug sector, it is not yet clear whether the change in the rules will result in a strong anticancer drug sector in Japan.

⁷⁴¹ See Steven Collins and Hikoji Wakoh, "Universities and Technology Transfer in Japan: Recent Reforms in Historical Perspective," *The Journal of Technology Transfer* 25 (June 2000); Kenji Kushida, "Japanese Entrepreneurship: Changing Incentives in the Context of Developing a New Economic Model," *Stanford Journal of East Asian Affairs* 1 (Spring 2001).

⁷⁴² Steven W. Collins, *The Race to Commercialize Biotechnology: Molecules, Markets, and the State in the United States and Japan*, 151.

One of the most powerful reasons for the relative weakness of Japan's anticancer drug sector was unhelpful government policy. More specifically, the weakness of Japan's anticancer drug sector stemmed largely from inferior R&D incentives, an undeveloped drug approval system, and Japanese medical practice. It was true that other factors, such as industrial structure, or legal barriers to entrepreneurship facing university professors, hindered the development of a strong, innovative industry. But these factors mattered less in explaining the causes for Japan's weakness in the anticancer drug sector.

To a certain extent, the ineffectiveness of government intervention in Japan's anticancer drug sector might be explained by the country's belated demand for drugs that treated diseases of affluence such as cancer compared to other advanced nations. On a practical level, it is also much more difficult for a government to intervene in the development of a complex product. Only a handful of firms equipped with high levels of human capital, capable and willing to undertake extraordinary risk and cost in the R&D process could acquire the capacity to discover and develop innovative anticancer drugs. Government policy is more effective and conducive in sectors such as antibiotics that can involve numerous firms in low-cost, labour-intensive, and serendipitous methods of drug discovery for mass production.

The weakness of Japan's anticancer drug sector is most convincingly explained by its inferior R&D incentives. Japan's post-war pharmaceutical industry was shaped by the endurance of MHW's developmental health policies that prioritised improvements in

public health over the development of industry. Public health objectives to deliver low cost drugs to Japanese citizens under universal health insurance encouraged the government to set – and effectively cap – prices and conduct periodic price reductions. While this helped contain health care costs for the government and facilitated public access to medicines, it also encouraged firms to long pursue incremental innovations rather than invest heavily in R&D. The introduction of product patents and capital liberalisation should have incentivised firms to invest more heavily in R&D and develop more competitive drugs. But Japan's unique product standards, lower criteria for innovation, and medical culture protected drugs of lesser quality from foreign competition. Japanese government policies that sustained less competitive drugs in the market help explain why Japan's anticancer drug remained weak.

At times, Japan's politicised, unscientific, and non-transparent drug approval system also reduced R&D incentives and undermined the industry's prospects for growth. For firms, alliances with other firms and universities could substitute for or complement their lack of capacities in drug discovery, development, or distribution, while affiliations with the government could facilitate drug approval. But in the 1970s and 1980s, firms unable to assess the government's approval criteria invested in developing political ties rather than R&D to facilitate drug approval. This helped prompt a massive expansion of the anticancer drug sector, which was supported by Japan's distinct product standards and medical system. If the safety and efficacy criteria for drug approval had been more transparent, more firms might have invested in R&D despite lower drug prices. At a time when many Western markets were

launching new, innovative anticancer drugs, Japan's undeveloped drug approval system misdirected investments and undermined the industry's potential at a crucial time in its development.⁷⁴³

Just because a drug received approval in Japan, did not mean it was recognised in other countries. A major factor limiting the ability of Japanese drug companies to export anticancer drugs was the fact that Western governments long viewed the Japanese regulatory system with scepticism. Until its pharmaceutical regulations were harmonised with the United States and Europe in the early 1990s, Japan's drug approval standards lacked the rigour and credibility of its Western counterparts. As a result, it was difficult for Japanese firms to use Japanese approval as a precedent to gain approval in other countries. Japan's drug approval process lacked credibility because of its non-transparent approval process and lack of clear, rigorous standards for laboratory or clinical trials.

Gaining recognition from regulatory authorities in advanced Western markets was particularly important in anticancer drugs. Cancer is a disease of affluence with most of its patients in the developed world. Japanese firms in the antibiotics sector could export their products to developing countries with less rigorous standards and higher demand for therapies to treat infectious diseases. But Japanese firms in the anticancer drug sector could not export their products to the developed world. Japanese

⁷⁴³ The importance of drug approval standards in advancing pharmaceutical industries has been discussed by Lacy Glenn Thomas, who compared the British and French pharmaceutical industries. See, Lacy Glenn Thomas, III., "Implicit Industrial Policy: The Triumph of Britain and the Failure of France in Global Pharmaceuticals," 451-489.

antibiotics makers were therefore able to enjoy a degree of success in exports that their counterparts in the anticancer drug sector could not.

The weakness of the anticancer drug sector was also affected by Japan's medical system. Many physicians in Japan also dispensed drugs, and derived a portion of their income from dispensing drugs. Physicians were therefore incentivised to prescribe drugs that could be prescribed widely and had a greater difference between wholesale and retail prices. The cancer immunotherapy drugs of the 1970s and 1980s – unlike most anticancer drugs – had few side effects and were approved for various types of cancer. These drugs were popular because they could be prescribed to a large population of cancer patients who remained ignorant of their diagnosis, and could neither ascertain nor question the efficacy of drugs until long after they were taken. Cancer immunotherapy drugs were also popular because anticancer drugs were highly priced drugs that tended to have greater pharmaceutical price differentials. As a result, Japanese firms developed anticancer drugs of limited efficacy that could neither be approved in other advanced nations nor be delivered beyond the Japanese medical system.

The lack of oncologists, cancer hospitals, and proper patient diagnoses, not only undermined the capacity to conduct accurate clinical trials in Japan, they also limited demand for innovative cancer therapies in Japan. Physicians and technicians, as well as hospitals and facilities, provided the infrastructure that determined not only the manner of drug development but also the size of demand. As a complex, hospital

based therapy, the development of anticancer drugs was dependent on physicians and technicians with expertise in cancer and anticancer drugs to administer the drug – as well as hospitals equipped with the relevant equipment to deliver the drug. A strong anticancer drug sector also required a medical culture where physicians would provide patients with an accurate diagnosis to generate demand for an arduous treatment. The lack of such infrastructure for much of the post war period also long hindered the development of Japan’s anticancer drug sector.

With a history of solid, active cancer research in universities, and strong networks of collaboration between academia and industry to translate academic research into commercial products, Japan had the potential to develop a strong, competitive anticancer drug sector. During the 1950s and 1960s, it appeared capable of doing so. But the Japanese industry failed to fulfil its promise. Without clear or rigorous R&D incentives or a medical culture to deliver innovative cancer therapies, Japan’s anticancer drug sector did not capitalise on its potential.

5 Conclusion

This thesis has traced the history of the Japanese pharmaceutical industry since 1945. It explained how Japanese pharmaceutical firms recovered from the Second World War and caught up with Western firms by importing technologies. The two case studies have also shown that Japanese pharmaceutical firms were able to develop a number of original, innovative therapies, some of which have proven successful in overseas markets.

The emphasis of this thesis, however, has not been on the achievements of the Japanese pharmaceutical industry, but rather on its relative weakness. I argue that while Japanese firms were able to catch up with Western pharmaceutical firms by the 1970s and acquired the capacity to discover innovative drugs, they did not exploit the potential to become global leaders. Rather than invest heavily in R&D to pursue breakthrough discoveries, most opted to launch many new drugs with limited innovative value that could not be sold in other advanced markets. It was true that a handful of leading firms began to develop global blockbuster drugs and increase their overseas presence. But Japanese firms remained much smaller in terms of sales, workforce, or R&D expenditures, and Japan remained a net importer of pharmaceuticals.

The aim of this thesis has been to explain why Japan's pharmaceutical industry did not become a global leader, and continues to lag behind the pharmaceutical industries of countries such as the United States, the United Kingdom and Switzerland. I used two

classes of medicines, antibiotics and anti-cancer drugs, as case studies for exploring the overall history of the Japanese pharmaceutical industry. I showed that the experiences of these two sectors were very different, and that the antibiotics sector was the stronger of the two. Japanese pharmaceutical firms were able to develop many antibiotics that came to be produced under license in other industrialised countries. Japan's anticancer drug sector was far less successful; it developed fewer globally competitive drugs and remained heavily reliant on imports.

There were several reasons why Japan's antibiotics sector became stronger than the anticancer drug sector. Both sectors were heavily shaped by government policy. But the government did not necessarily plan to foster the antibiotics sector over the anticancer drug sector. Policies governing the pharmaceutical industry – whether it be on intellectual property or capital liberalisation – applied to all therapeutic sectors. The MHW's tendency to prioritise universal access to prescription drugs, however, had a disproportionate impact on the anticancer drug sector. The government's cost containment measures, to set drug prices and reduce them regularly, limited the profits that pharmaceutical firms in Japan could gain from launching new therapies. Japanese firms were reluctant to invest in anticancer drugs, which were much more expensive and difficult to develop compared to antibiotics.

As the previous chapters showed, the search for new antibiotics was a more low-cost, labour-intensive, and serendipitous process compared to the search for new anticancer drugs. In addition, whereas a given antibiotic could treat many infectious

ailments, a given anticancer drug could only treat a particular type and stage of cancer. Antibiotics were more suited to mass production and allowed R&D expenses to be recovered over a larger number of consumers.

Other characteristics that were specific to antibiotics or anticancer drugs also led to differences in performance between the two sectors. The efficacy of many antibiotics were long-established, and few had significant side effects. On the other hand, the efficacy of many anticancer drugs had yet to be established, and most had severe side effects. As a treatment for an acute ailment, the efficacy of antibiotics could also be more swiftly and easily determined compared to that of anticancer drugs. The ease of evaluating the safety and efficacy of antibiotics made it easier for Japanese firms to obtain approval from drug regulators abroad, and export these drugs into overseas markets.

Pharmaceutical firms in Japan had much less incentive to develop anticancer drugs compared to antibiotics. The undeveloped medical infrastructure and opaque drug approval process increased the risk and cost of drug development. Moreover, well into the 1980s, there was little demand in Japan for efficacious anticancer drugs, as these tended to have strong side effects. Japanese physicians did not inform patients of their cancer diagnosis, and prescribed drugs with few side effects but of limited efficacy. Only in the 1990s did Japanese patients begin to make more informed decisions and generate final demand for more effective anticancer drugs. The antibiotics sector outperformed the anticancer drug sector in Japan because the returns to

pharmaceutical R&D were limited; because antibiotics were easier to export compared to anticancer drugs; and because Japan's medical system did not generate demand for more effective anticancer drugs.

The problems observed in the anticancer drug sector of the Japanese pharmaceutical industry illustrate some of the reasons why Japan did not become a leader in the global pharmaceutical industry. Japanese pharmaceutical firms were able to dominate the domestic market and remain highly profitable over the post-war period. But Japan's pharmaceutical industry did not become a world leader, as did its automobile and consumer electronics industries. Even after the millennium, Japan remained a net importer of pharmaceuticals.

I begin this conclusion with a summary of my explanations for why Japan's pharmaceutical industry did not realise its potential and become a global leader. I then move to expand upon the broader significance of this study to the existing scholarship. I conclude by outlining some directions for future research.

5.1 Reasons for the unrealised potential of the Japanese pharmaceutical industry

As I have shown in the previous chapter, there are several reasons why Japan did not develop a strong, globally-competitive pharmaceutical industry. The major reasons for the weakness of the industry are: the weak incentives for pharmaceutical firms to invest in R&D, the government's protectionist policies, the industrial structure of the Japanese pharmaceutical industry, and Japanese medical culture. There are several

factors of secondary importance that also help to explain the underperformance of Japan's pharmaceutical industry. These include differences in therapeutic demand conditions between Japan and its potential export markets; different drug standards that essentially acted as trade barriers; the historical origins of Japanese pharmaceutical firms; barriers to entrepreneurship among university academics; and the lack of initiative taken by Japanese firms to expand into overseas markets.

The single most important reason for the underperformance of Japan's pharmaceutical industry lay in weak R&D incentives. The government did not offer strong incentives to invest in the discovery of innovative new drugs. The weakness of these R&D incentives stemmed from the fact that the industry was governed by the Ministry of Health and Welfare (MHW), rather than the Ministry of International Trade and Industry (MITI). Whereas the MITI prioritised the growth of industry, the MHW prioritised improvements in public health. In order to increase access to drugs among Japanese citizens, the MHW set drug prices rather than allow pharmaceutical firms to determine prices in a free market. Under universal health care, the MHW continued to place downward pressures on drug prices. From the 1980s in particular, the government legislated regular reductions in drug prices so as to contain rising health care costs.

The previous chapters showed how the government's tendency to prioritise the needs of consumers over industry reduced incentives among firms to develop innovative drugs that would succeed in world markets. As well, the lack of government funding

for industrial R&D limited the scale of projects firms could undertake. The government also protected the domestic market long after Japanese firms were capable of competing with Western firms. In an environment where firms could remain highly profitable while launching imitative drugs, few invested in developing more innovative drugs that could have been marketed abroad. The endurance of developmental health policies and the lack of sector-specific industrial policies disadvantaged Japanese firms in developing a strong pharmaceutical sector.

For many years, Japan's intellectual property regime disincentivised Japanese firms from investing in the discovery of truly innovative therapies. Until 1975, Japan had a process patent regime. This was very different from the product patent regime that had already been adopted in Western countries such as the United States and the United Kingdom. Japan's patent regime encouraged firms to reverse engineer foreign-discovered drugs, because new patents could be filed for an alternative path to an existing product. While many Japanese firms began to invest in R&D to discover original therapies after product patents were introduced in 1976, most continued to pursue incremental improvements rather than breakthrough discoveries. Japanese firms therefore developed drugs similar to drugs available abroad – and could not gain approval in these markets.

I showed that Japan's drug approval process was, at times, politicised and non-transparent. For pharmaceuticals firms, this reduced the incentive to invest in R&D because it was difficult to determine the risk involved in gaining drug approval.

The development of anticancer drugs during the 1970s, in particular, revealed how firms unable to assess the government's drug approval criteria invested in forming political ties to facilitate drug approval. These misdirected investments undermined the industry's potential at a crucial time in its development. The very distinct features of the Japanese market also made Japanese firms reluctant to make the costly investments necessary to expand into overseas markets. The Japanese pharmaceutical industry remained relatively weak because firms invested little in R&D, and were content to profit from incrementally innovative drugs that were mostly recognised only in Japan.

Had Japan's intellectual property regime introduced product patents earlier and penalised imitation, Japanese firms would likely have developed more original drugs that might have been recognised abroad. Had Japanese firms faced clearer standards and a more transparent and unbiased drug approval process, they might have invested in more pharmaceutical R&D to develop more original therapies. Had policies been different, firm responses and industrial performance would not have been the same. Institutions played a critical role in the shaping of Japan's post-war pharmaceutical industry.

The second major reason for the weakness of the Japanese pharmaceutical industry lay in the government's protectionist policies. Well into the 1970s, the government protected Japanese firms from foreign competition through a combination of capital controls, intellectual property laws, and distinct product standards. Japanese firms

could prosper without introducing original drugs. Had the government implemented less protectionist policies tailored to a more developed economy by the 1970s, Japanese firms might have pursued the discovery of highly innovative drugs that could have been marketed overseas. Had the government accounted for the idiosyncrasies of different therapeutic sectors to implement sector specific policies, Japan might have developed stronger sectors in anticancer drugs or other therapies. Japan's pharmaceutical industry remained relatively weak, partly because the mix and degree of interventions by the state was less than optimal – for its level of development and for specific therapeutic sectors.

The third major cause of the weakness of Japan's pharmaceutical industry lay in industrial structure. Compared to countries such as the United States, the United Kingdom, and Switzerland, the Japanese industry was dominated by numerous smaller firms. But in the pharmaceutical industry, larger firms have a crucial advantage in achieving economies of scale in R&D, production, and marketing. As observed in the antibiotics and anticancer drug sectors, the size of pharmaceutical firms became increasingly important over the years. This was because R&D processes became more costly and complex, manufacturing processes incorporated rigorous quality controls, and sophisticated marketing strategies came to play a crucial role in drug sales. The smaller size of Japanese firms compromised their ability to compete with the larger firms in Western countries.

The fourth major cause for the weakness of Japan's pharmaceutical industry involves

medical culture. The traditional practice among Japanese physicians to both prescribe and dispense pharmaceuticals created strong demand for newer drugs with higher prices, even if they had minimal innovative value. This was because Japanese physicians could profit from the difference between the wholesale and retail prices of drugs, and high priced drugs tended to have greater price differentials. In addition, culturally specific approaches to medical therapy, most notably in the area of cancer treatments, created demand for pharmaceuticals that were not recognised beyond Japan. The Japanese pharmaceutical industry remained a domestic, rather than global industry, because Japanese firms developed drugs that were not recognised by drug regulators abroad.

Several secondary factors also accounted for the weakness of Japan's pharmaceutical industry. As shown in an earlier chapter, the historical origins of Japanese pharmaceutical firms are part of the explanation. Many Japanese pharmaceutical firms began as import houses specialising in the distribution of German drugs. When these firms later began to produce these drugs for the Japanese market, many remained reliant on foreign technology and launched domestic versions of foreign-discovered drugs. A distinct feature of Japan's pharmaceutical industry was its development, not through the discoveries of original therapies, but through the borrowing of foreign technologies. The importation of technology allowed Japanese firms to leapfrog over earlier phases of pharmaceutical innovation. But Japanese pharmaceutical firms were path-dependent, and many firms continued to focus on acquiring or improving the capacity to produce rather than discover or develop leading drugs.

This focus on manufacturing, often found among late industrialisers, distinguished Japan's pharmaceutical industry in two ways. First, Japanese firms pursued process innovations and incremental product innovations in developing their industry. Second, Japanese firms were less vertically integrated than their American or European counterparts. As manufacturing concerns, fewer Japanese firms were historically engaged in R&D; it was only later that firms undertook backward integration into R&D.

In addition, the incidence of diseases in Japan was different from other industrialised countries. Infectious diseases such as tuberculosis, for example, remained common causes of death in Japan for much longer than other developed countries. Even after diseases of affluence became the leading causes of death, patterns of disease in Japan were not identical to other markets. As a result, Japanese pharmaceutical firms launched therapies in response to domestic needs, which were not necessarily the same as those abroad.

As I showed above, drug standards in Japan were not harmonised with those of the United States and the European Union until the 1990s. Before that time, drugs developed in Japan were not recognised as drugs that could be launched in these markets, and vice versa. The immense cost involved in re-developing drugs for overseas markets both deterred Japanese firms from expanding abroad, and protected Japanese firms from foreign competition.

I also showed that barriers to entrepreneurship imposed on university academics in Japan prevented the translation of academic research into commercial products. For several decades, academics could not work in private enterprise. In addition, the lack of infrastructure – the absence of qualified physicians, the low numbers of examiners, and a less rigorous clinical trial system – undermined the ability of Japanese firms to develop highly innovative drugs.

Finally, the belated initiative taken by Japanese firms to seek opportunities abroad hindered the development of a more globally competitive pharmaceutical industry. Since 2000, Japanese firms such as Takeda and Astellas have transferred their core R&D operations to the United States to develop drugs for the American, European and Japanese markets.⁷⁴⁴ Had these firms taken the initiative at an earlier stage to develop drugs that could have been marketed in multiple markets, Japan might have developed a pharmaceutical industry with a stronger international profile.

5.2 Contributions to existing scholarship

This thesis contributes to five areas of scholarship. This refers to the global histories on the pharmaceutical industry; works on Japanese industrial policy; the literature on late economic development; and existing works that highlight the relevance of New Institutional Economics in economic growth. It also contributes to existing debates on

⁷⁴⁴ See Takeda Pharmaceutical Co., “Takeda Establishes new Global Pharmaceutical R&D Center in US,” Takeda Pharmaceutical Co. newsroom release dated 25 December 2003, http://www.takeda.com/press/article_801.html (accessed 16 July 2008); “Asuterasu, Bei ni Shinyaku Kaihatsu Kyoten [Astellas Establishes New Drug Development Centre in the United States],” *Nihon Keizai Shimbun*, 4 March 2008.

Japanese capitalism and discussions on the role of cultural variables in shaping economic development.

My first contribution is to broaden our understanding of the global history of the pharmaceutical industry by expanding the geographic coverage beyond the North Atlantic region. While much has been written on the histories of the pharmaceutical industries of the United States and Europe, little has been published on the history of Japan's pharmaceutical industry.⁷⁴⁵ This thesis aims to help fill this gap in the existing literature. As one of the world's largest pharmaceutical markets, incorporating the history of Japan's pharmaceutical industry is essential to building a more complete understanding on the history of the global pharmaceutical industry.

The second contribution of this thesis is to illustrate the role of government policy on the development of the Japanese pharmaceutical industry. I argue that the weak R&D incentives created by the government led to the industry's weak performance. Japanese firms opted to develop drugs that would not necessarily gain approval in foreign drug regimes because they could profit from less innovative drugs in a protected home market. However, there were other reasons why Japanese firms developed less innovative drugs. These reasons included industrial structure, medical culture, as well as lack of entrepreneurship.

⁷⁴⁵ As mentioned in the overview chapter, most works on the Japanese pharmaceutical industry have been limited to corporate histories. A few other works were recently published, such as Nihon Yakushi Gakkai, *Nihon Iyakuhin Sangyōshi* [The History of the Japanese Pharmaceutical Industry]; and Takashi Nishikawa, *Kusuri Kara Mita Nihon; Shōwa 20-nendai no Genfūkei to Komichi* [Looking at Japan from "Medicine": Scenes from the 1940s to the Present] (Tokyo: Yakuji Nippōsha, 2004).

The experience of the Japanese pharmaceutical industry demonstrates not only that industrial policy played a powerful role in shaping the industry, but also that unhelpful policies harmed its development. In the early post-war period, for example, the government's import substitution policy was crucial to enabling Japanese firms to produce modern pharmaceuticals. Indeed, by the 1970s, Japanese firms were prepared to compete with Western rivals. But as the government continued to protect the domestic market and introduced few incentives to innovate, many Japanese firms remained content to profit from incrementally innovative drugs from the domestic market. This type of state intervention did not help Japan develop a globally competitive pharmaceutical industry.

The third contribution of this thesis is to show that the concept of late development advanced by Alexander Gerschenkron can be applied to the pharmaceutical sector. Gerschenkron argued that the state took a greater role in backward economies to substitute for lacking institutions and promote economic development.⁷⁴⁶ More recent works by Alice Amsden and Takashi Hikino examined how late developers industrialised by borrowing and improving foreign technologies.⁷⁴⁷ They also highlighted the role of the interventionist state and the firms' focus on production-related R&D in these economies. The Japanese pharmaceutical industry adheres to the patterns of late development discussed in these works. Unlike Germany,

⁷⁴⁶ Alexander Gerschenkron, *Economic Backwardness in Historical Perspective: A Book of Essays* (Cambridge: Harvard University Press, 1962).

⁷⁴⁷ Alice H. Amsden, *The Rise of "The Rest": Challenges to the West From Late-industrialization Economies* (Oxford: Oxford University Press, 2001); Alice H. Amsden and Takashi Hikino, "Staying Behind, Stumbling Back, Sneaking Up, Soaring Ahead: Late Industrialization in Historical Perspective," in *Convergence of Productivity: Cross-national Studies and Historical Evidence*, eds. William J. Baumol, Richard R. Nelson, and Edward N. Wolff (Oxford: Oxford University Press, 1994), 285-315.

Britain, or the United States, the history of Japan's pharmaceutical industry was shaped by a developmental state, the borrowing of foreign technology, and incremental innovations of production technology. Compared to the earlier industrialisers, Japan pursued a very different path in developing a modern pharmaceutical industry.

The highly interventionist and developmental state had a particularly prominent role in nurturing Japan's pharmaceutical industry. As a heavily regulated industry, the state plays a central role in the development of any pharmaceutical industry. Nevertheless, the extent and manner of state intervention in Japan was different from the earlier developers. While the Japanese government did not target the pharmaceutical industry for growth, it nurtured the industry by facilitating technology transfers to firms and promoting the diffusion of technology through process patents. The government also protected the domestic industry by restricting capital controls and creating distinct product standards in Japan.

The Japanese experience sheds light upon how a late developing economy might experience a different path to developing a modern pharmaceutical industry. At a time when Japanese firms are moving abroad and pharmaceutical regulations are becoming harmonised, Japan appears to be converging with the global leaders. The challenge to Japanese pharmaceutical firms has remained the shift to a more research-oriented industry: from the borrowing of foreign technologies to generating their own discoveries.

The fourth contribution of my thesis is to show the importance of strong, rigorous, and credible institutions in developing a world-leading pharmaceutical industry. I have drawn on the insights of New Institutional Economics and have illustrated its relevance to business history. Douglass North and other proponents of New Institutional Economics have argued that institutions such as property rights play a crucial role in explaining economic growth.⁷⁴⁸ The case studies demonstrate that Japan's intellectual property regime had a fundamental impact on technological innovation, diffusion, and industrial performance. Japan's process patent regime long incentivised firms to reverse engineer products and find an alternative path to producing the same product. Most Japanese firms only began to invest in R&D to discover new original therapies when product patents were introduced in 1976.

I also showed how the lack of transparent, credible institutions influenced firm behaviour. As observed in the experience of the anticancer drug sector, Japanese drug standards until the 1990s were opaque, and its drug approval processes were politicised and non-transparent. Without clear standards, Japanese firms were unable to ascertain the risk involved in undertaking R&D, and were therefore less willing to engage in large R&D projects. Governed by a non-transparent and politicised drug approval process, some Japanese firms also invested in forming political ties that would facilitate drug approval, rather than invest in developing drugs that could be marketed abroad.

⁷⁴⁸ Douglass Cecil North, *Institutions, Institutional Change and Economic Performance* (Cambridge: Cambridge University Press, 1990).

The fifth contribution of my thesis relates to debates on whether the distinct features of Japanese capitalism are suitable to economic development in a high technology age. I make several points on the debate on how Japanese capitalism has differed from other varieties of capitalism. Japanese capitalism has been most strongly characterised by the long-term relationships of firms with the government, other firms, and their employees, such as through industrial policy, *keiretsu* structures, and lifetime employment. While Japanese industries have ranged in their degree of success, existing scholarship in Japanese capitalism has been much less interested in studying the country's weaker or declining industries, whether it be petrochemicals or pharmaceuticals. Given this, the study of weaker industries provides a more intricate understanding of the dynamics of Japanese capitalism.

Many scholars have concluded that the Japanese economic system was helpful in enabling the country to achieve phenomenal growth until the 1980s, but became a burden thereafter. Marie Anchooguy, for example, argued that Japan's style of capitalism undermined growth in the more recent period of globalisation and rapid technological change.⁷⁴⁹ My research on the pharmaceutical industry largely supports this argument. But it also argues for a more nuanced understanding on advantages and disadvantages of coordinated and liberal market economies.

In the early post-war period, the collaborative, long-term relationships between

⁷⁴⁹ Marie Anchooguy, *Reprogramming Japan: The High Tech Crisis Under Communitarian Capitalism* (Ithaca: Cornell University Press, 2005).

government, firms, and employees were helpful in enabling Japanese firms to catch up with Western pharmaceutical firms. The government's industrial policies, for example, nurtured Japanese firms. Practices such as *amakudari*, where government bureaucrats retire to firms or agencies under their ministries' jurisdiction, helped cement ties and align the interests of government and business in pursuing growth. The *keiretsu* ties between pharmaceutical manufacturers and wholesalers not only ensured the survival of many small wholesalers, they also long protected the Japanese market from foreign penetration.

But the Japanese economic system was not always beneficial to industrial development, even before the 1980s. The experience of the anticancer drug sector showed that the collaborative relationship between government and firms could also lead to investment in political rent-seeking over R&D. Compared to firms in more liberal economies, Japanese firms tended to be less inclined to undertake significant risk and develop a research-oriented pharmaceutical industry.

It is true that many features of Japanese capitalism were less helpful in supporting the industry in later years – particularly as science and technology became more advanced, and the domestic market became more open to global competition. Low labour mobility and limited access to venture capital, for example, made it difficult for firms to respond swiftly and flexibly to market conditions or pursue radical innovations. Japanese firms were also less likely to implement dramatic job cuts or undertake significant risk in R&D compared to their overseas rivals. These features of Japanese

capitalism weakened the capacity of Japanese firms to compete with foreign firms.

As the leading Japanese firms globalise and prioritise overseas markets for drug development, they appear to be converging with leading global pharmaceutical firms. After all, these firms are governed by the same laws to develop, manufacture, and distribute drugs, and compete in the same markets – as with leading American and European firms. But this convergence remains partial. Since the 1990s, Japanese firms have loosened their *keiretsu* ties, streamlined their business operations, and have merged to invest in large-scale R&D projects. At the same time, however, Japanese firms retain *amakudari* practices, workers are employed for long periods, and downsizing often occurs in the milder form of voluntary retirement.

These findings have contemporary relevance, particularly at a time when Japan has been shifting to a more market-oriented model. But it remains questionable whether the Japanese model should be so hastily discarded. Japanese economic institutions tend to be embedded in Japan's distinct political and cultural trajectory, and are integrated with the larger social environment. As Richard Freeman has noted, this makes the cost of switching systems expensive.⁷⁵⁰ In addition, as Kozo Yamamura has suggested, collective capitalist systems may be more conducive to development as new technologies mature, and innovations take on a more incremental or applied nature.⁷⁵¹ Given the benefits of both liberal and less liberal capitalist systems, partial

⁷⁵⁰ Richard B. Freeman, "Single Peaked vs. Diversified capitalism: The Relation Between Economic Institutions and Outcomes," *NBER Working Paper* No. 7556, February 2000.

⁷⁵¹ Kozo Yamamura, "Germany and Japan in a New Phase of Capitalism: Confronting the Past and the Future, in *The End of Diversity?: Prospects for German and Japanese Capitalism*," eds. Kozo Yamamura and Wolfgang Streeck (Ithaca: Cornell

convergence is likely most suitable for further development.

The sixth contribution of my thesis is to demonstrate the role of culture in shaping the development of Japan's pharmaceutical industry. Scholars such as Mark Granovetter and Lawrence Harrison have emphasised how cultural factors shape the economic development of countries.⁷⁵² The business historian Kenneth Lipartito has argued that a cultural approach is fundamental to understanding the history of business and the differences in industrial performance across nations.⁷⁵³ Of course, definitions of "culture" have varied. While culture might generally be defined as shared values, norms, ideas and behaviours, this thesis has referred to culture more narrowly in terms of Japanese medical culture. This thesis has shown that some aspects of Japan's medical culture – such as physician dispensing and prescribing practices, distinct approaches to medical therapy, and the doctor-patient relationship – played a particularly strong role in shaping its pharmaceutical industry.

The two case studies, for example, showed that the traditional practice upheld by Japanese physicians to both prescribe and dispense medicines fundamentally altered the type of drugs demanded in Japan. Physicians in Japan often prescribed higher priced medicines to gain from greater pharmaceutical price differentials. Japanese firms responded to this environment by continuously launching higher priced drugs with minimal innovative value. While it is true that patients in most medical cultures

University Press, 2003), 115-146.

⁷⁵² For example, Mark Granovetter, "Economic Action and Social Structure: The Problem of Embeddedness" *The American Journal of Sociology* 91, no. 3 (1985): 481-510; Samuel P. Huntington and Lawrence E. Harrison, *Culture Matters: How Values Shape Human Progress* (New York: Basic Books, 2000).

⁷⁵³ Kenneth Lipartito, "Culture and the Practice of Business History," *Business and Economic History* 24, no. 2 (1995): 1-41.

likely defer to the expert advice of physicians, in a hierarchical society where few patients questioned physicians' authority, physician demand also led more easily to patient consumption.

As I observed in the anticancer drug section of this thesis, distinct approaches to medical therapy also had a substantial impact on the type of drugs demanded, developed and launched in Japan. The preference for milder forms of cancer therapy in Japan diminished the development of more rigorous yet innovative forms of therapy, while the cultural reluctance of physicians to diagnose patients of terminal conditions dampened demand for more interventionist remedies. Again, given the information asymmetries in the doctor-patient relationship and the hierarchical culture in Japan, distinct approaches in medical therapy led readily to a pharmaceutical market where the leading medicines could only be found in Japan. To this extent, this thesis has illustrated how Japanese medical culture had a profound impact on the development of the pharmaceutical industry.

5.3 Future directions

As there are few works on the history of Japan's post-war pharmaceutical industry, it is hoped that there will be further research on this topic. There are several possible directions for future research on the history of the Japanese pharmaceutical industry that lie outside the scope of thesis. I will consider each in turn.

My thesis has looked at antibiotics and anticancer drugs. One direction for future

research would be to examine the history of other categories of drugs in Japan. Possible choices for research might be the markets for cardiovascular drugs, central nervous system-related drugs, or vitamins. These sectors have grown dramatically over the post-war period.

An examination of the cardiovascular sector, for example, could offer a better understanding of drug development trends in Japan. Many Japanese firms have launched cardiovascular drugs, some of which have become blockbuster drugs.⁷⁵⁴ Given the large volume of cardiovascular drugs produced and developed in Japan, a study of this sector provide ample opportunities to investigate the experience of more pharmaceutical firms.⁷⁵⁵ These case studies would allow us to better appreciate the evolution of pharmaceutical innovation in Japan.

Research into central nervous system drugs that treat conditions such as Alzheimer's or depression could shed greater light on the impact of Japan's ageing population and Japanese medical culture on the evolution of the pharmaceutical industry. Japan's ageing population has increased demand for drugs to treat conditions such as Alzheimer's.⁷⁵⁶ The study of Alzheimer's drugs would provide an opportunity to consider the impact of a rapidly ageing population, the impact of elderly health care policy, and the infrastructure of medical care for the elderly, on shaping therapeutic

⁷⁵⁴ Yakugyō Jihōsha, *Yakuji Handobukku* [Pharmaceutical Affairs Handbook] (Tokyo: Yakugyō Jihōsha, 1968-1999); Jihō, *Yakuji Handobukku* [Pharmaceutical Affairs Handbook] (Tokyo: Jihō, 2000-2007).

⁷⁵⁵ Ministry of Health and Welfare, *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Yakugyō Keizai Kenkyūjo, 1968-2000); Ministry of Health, Labour and Welfare, *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Jihō, 2001-2006).

⁷⁵⁶ Yakugyō Jihōsha, *Yakuji Handobukku* [Pharmaceutical Affairs Handbook] (Tokyo: Yakugyō Jihōsha, 1968-1999); Jihō, *Yakuji Handobukku* [Pharmaceutical Affairs Handbook] (Tokyo: Jihō, 2000-2007).

sectors.

Antidepressants would be a particularly interesting category of drug to study because it is a sector of drugs in which cultural variables are salient. Japanese citizens have used antidepressants at a lower rate than citizens of other industrialised countries even though Japan's suicide rate has been one of the highest in the world.⁷⁵⁷ This has been frequently attributed to Japanese cultural attitudes toward depression, the treatment of depression in Japan, and the lack of a satisfactory clinical trial system.⁷⁵⁸ Further research on this topic would allow for a better assessment on the impact of medical culture and regulatory infrastructure on the pharmaceutical industry in Japan.

A study of the vitamins sector could offer additional insights. Between 1958 and 1969, vitamins were the most produced drugs in Japan.⁷⁵⁹ This was a time when Japan was still concerned with nutritional deficiencies among a large proportion of its population.⁷⁶⁰ A study of this sector could illuminate how changing health needs shape therapeutic sectors. In addition, vitamins in Japan qualify as both prescription and over-the-counter drugs. While the vitamins sector has become less prominent over the decades, further research would also provide an opportunity to investigate the

⁷⁵⁷ World Health Organization, "Suicide Rates (per 100,000), by Country, Year, and Gender." World Health Organization, http://www.who.int/mental_health/prevention/suicide/suiciderates/en/ (accessed 2 August 2008); Edward Norbeck and Margaret Lock, ed., *Health, Illness, and Medical Care in Japan: Cultural and Social Dimensions* (Honolulu: University of Hawaii Press, 1987), 13. See also, Osamu Tajima, "Mental Health Care in Japan: Recognition and Treatment of Depression and Anxiety Disorders," *Journal of Clinical Psychiatry* 62, Suppl. no. 13 (2001): S39-S44.

⁷⁵⁸ See for example, Douglas Berger, "Antidepressant Clinical Development in Japan: Current Perspectives and Future Horizons," *Clinical Research Focus* 16, no. 7 (September 2005): 32-35.

⁷⁵⁹ Ministry of Health and Welfare, *Yakuji Kogyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Yakugyō Keizai Kenkyūjo, 1953-1967); Ministry of Health and Welfare, *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Yakugyō Keizai Kenkyūjo, 1968-2000).

⁷⁶⁰ See the relevant years of Ministry of Health and Welfare, *Kōsei Hakusho* [White Paper on Health and Welfare] (Tokyo: Ōkurashō Insatsukyoku, 1955-2000).

boundaries of prescription and over-the-counter drugs over the years.

Another potential research project would be to examine the experience of other non-Western countries to add comparative perspective. The emerging economies of India and China are fast developing a modern pharmaceutical industry.⁷⁶¹ A comparative study of Japan's East Asian neighbours, such as South Korea and Taiwan, would provide an invaluable opportunity to investigate how East Asian countries have developed their pharmaceutical industries. A comparative study between these three countries may be particularly useful, as they are more developed and are likely to share more cultural attributes compared to other Asian countries. These comparative approaches would not only help to contextualise the Japanese experience, it would also help to gain a better understanding of how late developing economies acquire competitive strengths in knowledge-intensive industries.

A third possible direction for future research involves archival research at Japanese pharmaceutical firms. An examination of archival data would provide a more complete understanding over the motivations and behaviour of pharmaceutical firms. This thesis consulted an abundant array of sources – from academic, trade, and popular journals, to company security filings – to develop a more comprehensive analysis. Had it been possible, the examination of material from corporate archives would have provided a more intricate understanding of the motivations and behaviour of pharmaceutical firms. However, it remains unclear whether access to corporate

⁷⁶¹ See for example, by PJB Publications, "Asia an Awakening Healthcare Giant," in *Scrip Yearbook 2008*, 14th ed., vol. 2; (Richmond: PJB Publications, 2008), 221-222.

archives will improve in the future.

My next research project will be on the history of Japan's traditional medicines industry, and builds upon the work of this thesis. A study on the business of traditional medicines would be an important project that examines the evolution of modern Japanese business, not in a high-technology sector, but in a very traditional sector. As mentioned in the overview chapter, Western style medicines emerged after the Meiji Restoration, when Japan embraced Western technology, including medicines. This industry has been the subject of this thesis. But the type of traditional medicines used in Japan before the Meiji Restoration continued to be consumed in large quantities. Japanese patients continue to consume a substantial amount of traditional medicines, and it is a significant industry.⁷⁶²

But Japan's traditional medicines industry is very different from its modern pharmaceutical industry. Research on this topic provides an opportunity to further investigate major themes discussed in this thesis, such as state industry relations, industrial structure, and the role of culture in industrial development. The study of a traditional sector in a contemporary setting is also hoped to provide a more intricate understanding the impact of late development and the paradox of Japan's dual economy – of an economy that is both old and modern.

⁷⁶² Ministry of Health and Welfare, *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Yakugyō Keizai Kenkyūjo, 1968-2000); Ministry of Health, Labour and Welfare, *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Jihō, 2001-2006).

Research on the history of Japan's traditional medicines industry would elaborate upon state-industry relations in Japan. After the Meiji Restoration, the Japanese government suppressed the growth of traditional medicines when it endorsed Western medicine over traditional medicine. But after the 1960s, the government reintegrated traditional medicines into the national health care system as prescription drugs, and fostered the growth of the traditional medicines.⁷⁶³ I am interested in understanding why the government reversed its policy.

This project would also illuminate the impact of industrial structure on the development of industry. For example, the market structure of this industry is highly oligopolistic. The two leading firms, Tsumura and Kracie – previously Kanebo – have over 90% of the market.⁷⁶⁴ In addition, there is almost no overlap between the firms engaged in traditional medicines and those engaged in Western style medicines. While the two types of firms coexist in the same pharmaceutical market, they are virtually two separate sectors.

This research would also address the role of culture in the history of Japanese business, particularly in terms of physician dispensing practices or approaches in medical therapy. In many cases, these traditional medicines are also prescribed by the same physicians that prescribe Western style medicines.

⁷⁶³ See "Kanpōyaku no Yukue [The Future of Kampo Medicines]," *Detailman* (February 1995): 40–41. For an overview on the history of traditional medicine in Japan, see for example, Margaret M. Lock, "History of East Asian Medicine in Japan," in *East Asian Medicine in Urban Japan* (Berkeley: University of California Press, 1980), 50–66.

⁷⁶⁴ Tsumura & Co., "Iryōyō Kanpōseizai no Shijō Dōkō [Market Trends in Prescription Kampo Medicines]," Tsumura & Co., <http://www.tsumura.co.jp/zaimu/business/12.html> (accessed 20 July 2008).

This thesis has shown how the history of Japan's pharmaceutical industry has been shaped by a complex interplay of factors. The Japanese pharmaceutical industry would have evolved very differently had the government provided greater rewards for R&D, had Japanese firms been larger, or had Japanese medical culture been more similar to those of the advanced Western markets. Further studies on the history of the Japanese pharmaceutical industry would provide additional insights into Japanese industrial policy, late development, and Japanese capitalism. To some extent, the history of Japan's pharmaceutical industry is a study into the enigma of the Japanese economy. This research has attempted to unravel some of the complexities of an economy that remains caught between imitation and innovation, collectivism and individualism, tradition and modernity.

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Appendix 1. Value of Pharmaceutical Production⁷⁶⁵

Table A1.1 Nominal Value for All Categories of Drugs (in millions of yen)

	All Categories			
	All Drugs	Prescription Drugs		
	Total Production	Total Production	Domestic production	Bulk Imports
1945	335			
1946	1,872			
1947	5,176			
1948	17,092			
1949	31,031			
1950	31,916			
1951	42,376			
1952	58,564			
1953	75,647			
1954	78,468			
1955	89,539			
1956	103,767			
1957	125,147			
1958	134,476			
1959	149,258			
1960	176,012			
1961	218,075			
1962	265,596			
1963	341,141			
1964	423,225			
1965	457,639			

⁷⁶⁵ Compiled from Yakugyō Keizai Kenkyūjo, *Yakuji Nenkan* [Pharmaceutical Annual] (Osaka: Nihon Yakugyō Shimbunsha, 1951, 1957, 1961, 1964); Ministry of Health and Welfare, *Yakuji Kogyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Yakugyō Keizai Kenkyūjo, 1953-1967); Ministry of Health and Welfare, *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Yakugyō Keizai Kenkyūjo, 1968-2000); Ministry of Health, Labour and Welfare, *Yakuji Kōgyō Seisan Dōtai Chōsa Tōkei* [Annual Survey on Production in the Pharmaceutical Industry] (Tokyo: Jihō, 2001-2007). As noted in the anticancer drug chapter, figures for antitumour drugs have been used as proxy for anticancer drugs.

1966	507,108			
1967	563,257			
1968	688,953	488,316	316,152	172,164
1969	842,514	615,800	398,789	217,012
1970	1,025,319	770,451	478,781	291,670
1971	1,060,424	826,173	506,850	319,323
1972	1,091,791	843,531	511,288	332,242
1973	1,367,138	1,081,285	656,800	424,486
1974	1,699,688	1,381,833	856,627	525,207
1975	1,792,406	1,464,030	905,892	558,139
1976	2,162,436	1,799,418	1,079,856	719,562
1977	2,458,294	2,056,991	1,280,655	776,326
1978	2,793,878	2,350,579	1,484,128	866,450
1979	3,042,302	2,562,029	1,665,834	896,194
1980	3,482,177	2,978,437	1,981,278	997,159
1981	3,679,139	3,135,703	2,161,243	974,460
1982	3,980,232	3,406,516	2,339,005	1,067,510
1983	4,032,057	3,438,567	2,382,616	1,055,950
1984	4,027,996	3,429,482	2,450,987	978,495
1985	4,001,807	3,383,710	2,386,022	997,688
1986	4,280,732	3,649,842	2,547,249	1,102,593
1987	4,825,398	4,141,820	2,897,396	1,244,424
1988	5,059,459	4,309,824	2,991,784	1,318,040
1989	5,502,271	4,676,456	3,230,933	1,445,523
1990	5,595,435	4,720,333	3,324,858	1,395,475
1991	5,697,244	4,812,216	3,357,206	1,455,010
1992	5,574,220	4,680,204	3,309,315	1,370,889
1993	5,695,068	4,819,341	3,457,673	1,361,668
1994	5,750,332	4,881,157	3,489,218	1,391,939
1995	6,168,062	5,243,575	3,747,649	1,495,927
1996	6,100,046	5,156,439	3,770,744	1,385,696
1997	6,147,833	5,187,140	3,766,935	1,420,206
1998	5,842,096	4,936,520	3,619,537	1,316,982
1999	6,290,023	5,438,173	4,012,085	1,426,088

2000	6,182,631	5,376,330	3,878,730	1,497,600
2001	6,504,318	5,728,874	4,062,517	1,666,358
2002	6,489,278	5,729,882	4,034,118	1,695,764
2003	6,533,108	5,813,704	4,120,441	1,693,263
2004	6,525,293	5,837,295	4,132,221	1,705,075
2005	6,390,722	5,741,280	4,247,218	1,494,062

Table A1.2 Nominal Value for Antibiotics (in millions of yen)

	Antibiotics			
	All Drugs	Prescription Drugs		
	Total Production	Total Production	Domestic production	Bulk Imports
1950				
1951				
1952	9,288			
1953	12,750			
1954	12,331			
1955	12,511			
1956	12,193			
1957	16,950			
1958	18,399			
1959	14,180			
1960	17,224			
1961	22,010			
1962	28,224			
1963	36,018			
1964	52,247			
1965	58,554			
1966	64,506			
1967	72,992			
1968	95,432			
1969	114,447			
1970	157,020			
1971	176,647			
1972	174,196			
1973	238,916			
1974	331,380			
1975	363,392	363,308	153,062	210,246
1976	522,392	522,313	222,686	299,627
1977	583,908	583,906	275,360	308,546
1978	636,418	636,416	303,817	332,598

1979	658,009	658,008	328,546	329,462
1980	814,320	814,320	425,852	388,467
1981	780,136	780,136	422,796	357,340
1982	865,148	865,148	474,935	390,213
1983	735,888	735,888	417,591	318,296
1984	742,496	742,496	490,469	252,027
1985	690,505	690,505	446,162	244,343
1986	683,361	683,361	431,409	251,953
1987	733,974	733,974	444,721	289,253
1988	702,485	702,485	421,660	280,825
1989	724,523	724,523	438,035	286,488
1990	624,117	624,117	393,867	230,250
1991	589,014	589,244	370,236	219,009
1992	441,097	441,097	287,206	153,891
1993	444,048	444,048	298,683	145,365
1994	386,639	386,639	263,475	123,164
1995	451,477	451,477	314,763	136,714
1996	394,150	394,150	283,377	110,773
1997	433,475	433,475	321,076	112,399
1998	402,483	402,483	305,863	96,620
1999	437,812	437,812	345,470	92,343
2000	373,949	373,949	291,170	82,778
2001	410,413	410,413	304,430	105,983
2002	369,764	369,764	271,224	98,540
2003	386,923	386,923	293,816	93,107
2004	362,813	362,813	276,499	86,314
2005	346,951	346,097	255,367	90,730

Table A1.3 Nominal Value for Anticancer Drugs (in millions of yen)

	Anticancer Drugs			
	All Drugs	Prescription Drugs		
	Total Production	Total Production	Domestic production	Bulk Imports
1955	47			
1956	59			
1957	63			
1958	76			
1959	94			
1960	162			
1961	236			
1962	347			
1963	410			
1964	1,029			
1965	508			
1966	435			
1967	589			
1968	607			
1969	481			
1970	517			
1971	885			
1972	726			
1973	1,602			
1974	4,661			
1975	9,898	9,894	4,929	4,965
1976	32,376	32,376	16,753	15,623
1977	60,236	60,236	37,726	22,510
1978	84,474	84,474	57,325	27,149
1979	93,782	93,782	61,344	32,438
1980	107,351	107,351	72,662	34,689
1981	122,620	122,620	86,937	35,683
1982	124,511	124,511	91,242	33,270

1983	134,725	134,725	98,925	35,800
1984	143,627	143,618	121,344	22,275
1985	138,601	138,591	117,740	20,851
1986	160,822	160,799	137,751	23,047
1987	180,659	180,633	153,687	26,946
1988	193,045	193,031	164,273	28,759
1989	190,927	190,911	144,983	45,927
1990	164,151	164,134	116,044	48,090
1991	166,989	166,987	106,673	60,314
1992	166,810	166,810	98,702	68,108
1993	169,707	169,707	100,568	69,139
1994	169,476	169,476	98,267	71,209
1995	170,149	170,149	99,653	70,496
1996	156,920	156,920	97,364	59,555
1997	151,216	151,216	93,866	57,350
1998	135,378	135,378	83,881	51,497
1999	139,925	139,925	85,782	54,142
2000	146,995	146,995	88,041	58,954
2001	153,155	153,155	90,232	62,924
2002	167,748	167,748	88,581	79,166
2003	144,300	144,300	91,857	52,443
2004	147,811	147,811	101,282	46,528
2005	137,993	137,993	108,436	29,557

Appendix 2 Pharmaceutical R&D⁷⁶⁶

Table A2.1 Nominal Value of R&D Expenditures (in millions of yen)

	R&D Expenditures
1960	3,696
1961	6,794
1962	7,081
1963	9,983
1964	13,214
1965	14,602
1966	15,903
1967	18,068
1968	24,651
1969	20,656
1970	45,410
1971	55,740
1972	55,011
1973	64,406
1974	79,157
1975	95,191
1976	109,537
1977	120,537
1978	134,714
1979	176,905
1980	189,838
1981	218,435
1982	239,817
1983	289,896
1984	295,284

⁷⁶⁶ Compiled from Bureau of Statistics, Office of the Prime Minister, *Kagaku Gijutsu Kenkyū Chōsa Hōkoku* [Report on the Survey of Research and Development] (Tokyo: Office of the Prime Minister, 1961-1984); Statistics Bureau & Statistics Centre of the Management and Coordination Agency, *Kagaku Gijutsu Kenkyū Chōsa Hōkoku* [Report on the Survey of Research and Development], (Tokyo: Management and Coordination Agency, 1985-2000); Statistics Bureau, Ministry of Internal Affairs and Communications, ed., *Kagaku Gijutsu Kenkyū Chōsa Hōkoku* [Report on the Survey of Research and Development] (Tokyo: Ministry of Internal Affairs and Communications, 2001-2006).

1985	341,880
1986	341,978
1987	380,701
1988	416,220
1989	455,950
1990	516,062
1991	590,105
1992	643,415
1993	629,179
1994	632,802
1995	642,190
1996	667,145
1997	643,291
1998	681,118
1999	689,449
2000	746,214
2001	839,400
2002	965,723
2003	883,653
2004	906,749
2005	1,047,747

Table A2.2 R&D Expenditures as a Percentage of Sales

	R&D Expenditures / Sales
1960	2.2
1961	2.0
1962	2.5
1963	2.3
1964	2.9
1965	3.0
1966	3.1
1967	2.8
1968	3.0
1969	3.3
1970	3.4
1971	3.9
1972	4.3
1973	4.1
1974	4.4
1975	4.9
1976	5.1
1977	4.8
1978	5.0
1979	5.5
1980	5.5
1981	5.9
1982	5.6
1983	6.6
1984	6.5
1985	7.0
1986	6.9
1987	7.0
1988	6.9
1989	7.5

1990	8.0
1991	8.7
1992	8.7
1993	8.2
1994	7.8
1995	8.0
1996	8.1
1997	8.1
1998	8.1
1999	8.1
2000	8.6
2001	8.5
2002	8.9
2003	8.4
2004	8.6
2005	10.0

Appendix 3. Value of Pharmaceutical Trade⁷⁶⁷

Table A3.1 Nominal Value for All Categories of Drugs (in millions of yen)

	Imports	Exports
1947	521	7
1948	698	45
1949	934	146
1950	598	514
1951	2,141	1,082
1952	3,352	1,605
1953	4,145	2,165
1954	3,600	3,267
1955	3,522	3,001
1956	3,376	3,882
1957	4,001	5,258
1958	4,026	4,947
1959	5,131	5,539
1960	6,265	6,457
1961	9,690	7,388
1962	9,728	8,996
1963	13,945	9,125
1964	19,425	9,821
1965	21,517	11,911
1966	28,434	12,057
1967	35,292	13,411
1968	45,997	14,440
1969	56,822	18,229
1970	77,873	23,743
1971	81,337	29,989

⁷⁶⁷ Compiled from Yakugyō Keizai Kenkyūjo, *Yakuji Nenkan* [Pharmaceutical Annual] (Osaka: Nihon Yakugyō Shimbunsha, 1951, 1957, 1961, 1964); Ministry of International Trade and Industry, *Tsūshō Hakusho* [White Paper on Trade] (Tokyo: Ōkurashō Insatsukyoku, 1958-1973); Ministry of International Trade and Industry, *Tsūshō Hakusho* [White Paper on Trade] (Tokyo: Gyōsei, 1974-2000). From 2001, this data has been available at Ministry of Economy Trade and Industry, *Bōeki Dōkō Databēsu* [Database on Trends in Trade], http://www.meti.go.jp/policy/trade_policy/trade_db/html/01.html (accessed 12 May 2008).

1972	79,096	25,590
1973	97,938	27,185
1974	133,160	40,122
1975	130,688	36,806
1976	163,200	43,100
1977	164,422	48,401
1978	172,736	47,012
1979	202,471	57,902
1980	243,568	66,826
1981	253,619	72,736
1982	311,107	75,856
1983	288,447	82,709
1984	298,917	84,433
1985	308,166	93,281
1986	290,591	86,500
1987	305,188	85,152
1988	340,586	91,889
1989	366,659	98,923
1990	395,452	111,133
1991	419,134	146,763
1992	464,942	172,941
1993	436,288	163,993
1994	430,939	158,081
1995	461,687	173,359
1996	489,522	205,494
1997	512,668	235,849
1998	490,215	250,585
1999	524,149	274,683
2000	513,377	294,529
2001	611,895	331,628
2002	677,236	351,825
2003	716,502	368,708
2004	769,196	383,028
2005	905,966	367,664

Table A3.1 Nominal Value for Antibiotics (in millions of yen)

	Imports	Exports
1950		3
1951	1,558	280
1952	2,064	321
1953	2,266	499
1954	1,540	741
1955	840	303
1956	572	511
1957	638	908
1958	580	853
1959	648	1,040
1960	1,009	1,027
1961	632	320
1962	1,034	688
1963	1,911	688
1964	2,409	742
1965	2,922	845
1966	4,148	937
1967	5,230	981
1968	7,666	1,170
1969	9,107	1,511
1970	15,319	1,511
1971	17,538	2,437
1972	15,147	2,720
1973	19,813	3,579
1974	35,189	5,044
1975	44,595	5,891
1976	62,937	7,174
1977	54,671	8,680
1978	53,991	8,880
1979	57,725	12,007
1980	69,467	14,530

1981	69,145	15,941
1982	85,916	18,839
1983	71,661	22,153
1984	76,665	25,741
1985	69,889	29,400
1986	62,984	27,273
1987	65,264	29,249
1988	68,435	33,926
1989	73,674	36,523
1990	75,792	46,566
1991	70,826	57,850
1992	67,940	67,218
1993	57,254	58,947
1994	52,202	54,639
1995	63,458	56,255
1996	67,217	63,744
1997	66,874	62,418
1998	64,317	68,464
1999	70,355	60,089
2000	59,887	58,960
2001	62,249	57,704
2002	65,010	68,988
2003	66,592	55,472
2004	59,900	55,472
2005	66,247	59,971

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