

## Globalisation and Change in the Japanese Pharmaceutical Industry, 1990-2010

### Introduction

In the 1990s, Japanese pharmaceutical industry faced a crisis caused by the government's decision to open the domestic market to foreign competition. Prior to the 1990s, Japan's imitative and inefficient pharmaceutical firms had been sheltered by protectionist policies. In certain industries, such as automobile or electronics, Japan had managed to develop competitive advantages over its American or European rivals. However, Japan was a second-tier player in the global pharmaceutical industry. Japan's leading pharmaceutical firms were less R&D-oriented and recorded fewer sales compared to leading global firms in the United States, United Kingdom, or Switzerland. Japan was a net importer of pharmaceuticals and launched few global blockbuster drugs.

This paper examines the dramatic transformation of Japan's pharmaceutical industry since the 1990s, and shows how the industry – to a certain extent – came to resemble those of the United States and Europe. During this decade, Japanese firms increased their investments in R&D and pursued an unprecedented number of mergers and acquisitions. The number of Japanese bioventures began to grow, as did a previously absent generics sector. While the Japanese pharmaceutical industry as a whole remained globally uncompetitive, this period saw divergent performance between the domestically-oriented firms who struggled to survive, and the more outward oriented firms – such as Takeda and Astellas – who expanded their international operations to survive in a global economy.

## Literature review

The varieties of capitalism literature has highlighted the difference between the innovative capacities of liberal market economies, such as Britain and the United States, and the more coordinated market economies, such as Germany and Japan.<sup>1</sup> In their influential work, Hall and Soskice argued that economic actors in liberal market economies are coordinated through market institutions, in an environment of competition and formal contracting. By contrast, actors in coordinated market economies depend more on non-market relationships, through relational or incomplete contracting, network monitoring, and collaborative relationships.<sup>2</sup> Scholars have suggested that, with the lack of vertical specialisation, inflexible forms of financing, and illiquid labour markets, coordinated market economies are not suited to the development of sectors build upon radical, product innovations – particularly in an increasingly competitive, globally interconnected economy.<sup>3</sup>

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.<sup>4</sup> Some scholars of Japan have suggested that Japan's economic system posed serious

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<sup>1</sup> Ronald Philip Dore, *Stock Market Capitalism: Welfare Capitalism: Japan and Germany Versus the Anglo-Saxons* (Oxford: Oxford University Press, 2000).

<sup>2</sup> Peter Hall and David Soskice, eds., *Varieties of Capitalism: The Institutional Foundations of Comparative Advantage* (Oxford, 2001), 27.

<sup>3</sup> See for example, Marie Anchooguy, *Reprogramming Japan: The High Tech Crisis Under Communitarian Capitalism* (Ithaca: Cornell University Press, 2005).

<sup>4</sup> 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.

disadvantages, in its inability to respond quickly and flexibly to rapid, discontinuous, and unpredictable advances in science and technology or the increasing pressures of globalisation.<sup>5</sup>

This paper shows how some features of Japanese capitalism, such as *keiretsu* structures and government policies, unravelled in Japan's pharmaceutical industry over the 1990s. For example, while Japanese pharmaceutical manufacturers long maintained *keiretsu* relationships with pharmaceutical wholesalers, these relationships gradually unravelled during this decade. With the internationalisation of business, Japanese firms that had previously responded closely to changes in Japanese government policy, opted to respond more closely to policy shifts in pharmaceutical regimes where the rewards to innovation were greater.

Works on the varieties of capitalism also discuss the tensions between path dependence and convergence in the "new economy." While some have suggested that the pressures of globalisation and deregulation would lead to the erosion of the differences between countries, others have argued that the differences in political and economic institutions would limit convergence.<sup>6</sup> Scholars of Japan have debated

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<sup>5</sup> 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).

<sup>6</sup> 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; Vivien Ann Schmidt, *The Futures of European Capitalism* (Oxford: Oxford University Press, 2002). 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).

whether Japanese capitalism might converge with the Anglo-Saxon model.<sup>7</sup> This paper demonstrates that, with globalisation, Japan's pharmaceutical industry has converged more with those with those of global leaders, such as the United States.

## Overview

Table 1. Leading Pharmaceutical Companies by Sales

	1985	1995	2005
1	Merck	GkaxoWellcome	Pfizer
2	American Home Products	Merck & Co.	Sanofi Aventis
3	Hoechst	Hoechst Marion Roussel	GlaxoSmithKline
4	Ciba-Geigy	Roche	Novartis
5	Bayer	Bristol-Myers Squibb	AstraZeneca
6	Pfizer	American Home Products	Johnson&Johnson
7	Warner-Lambert	Pfizer	Merck
8	Abbott	SmithKline Beecham	Roche
9	Eli Lilly	Johnson&Johnson	Wyeth
10	Bristol-Myers	Lilly	Bristol-Myers Squibb
11	Glaxo	Sandoz	Eli Lilly
12	SmithKline	Pharmacia & Upjohn	Abbott
13	Upjohn	Ciba	Amgen
14	Sandoz	Abbott	Boehringer Ingelheim
15	Roche	Takeda	Takeda
17	Takeda		

Source: Scrip Pharmaceutical Company League Tables, IMS Midas.

Despite its strong performance in industries ranging from machine tools to automobiles, the Japanese pharmaceutical industry did not become a global leader. One of the key reasons lay in its governance by the Ministry of Health and Welfare

<sup>7</sup> Marie Anchooguy, *Reprogramming Japan: The High Tech Crisis Under Communitarian Capitalism* (Ithaca: Cornell University Press, 2005).

(MHW) – rather than the Ministry of International Trade and Industry (MITI). The government long prioritised public health agendas to produce drugs at low cost for its large population.<sup>8</sup> 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 long compromised their ability to compete against Western leaders.

Some of Japan's leading pharmaceutical firms have long histories. For instance, Takeda emerged in the 18<sup>th</sup> century as wholesalers of traditional herbal medicine. As Japan industrialised and modernised after 1868, Japan companies began to deal with Western-style drugs., Between 1915 and 1945, Japan developed a small pharmaceutical industry by expanding into mainland Asia. Japan's defeat in the Second World War had a mixed impact on the country's pharmaceutical industry. During the war, Japan's pharmaceutical industry did not sustain significant damage; in fact, the industry suffered more from the loss of East Asian markets than from Allied bombing.<sup>9</sup> Between 1945 and 1952, Japan was occupied by the Allied powers, who helped rebuild Japan's pharmaceutical industry.<sup>10</sup> In the 1950s and 1960s, the

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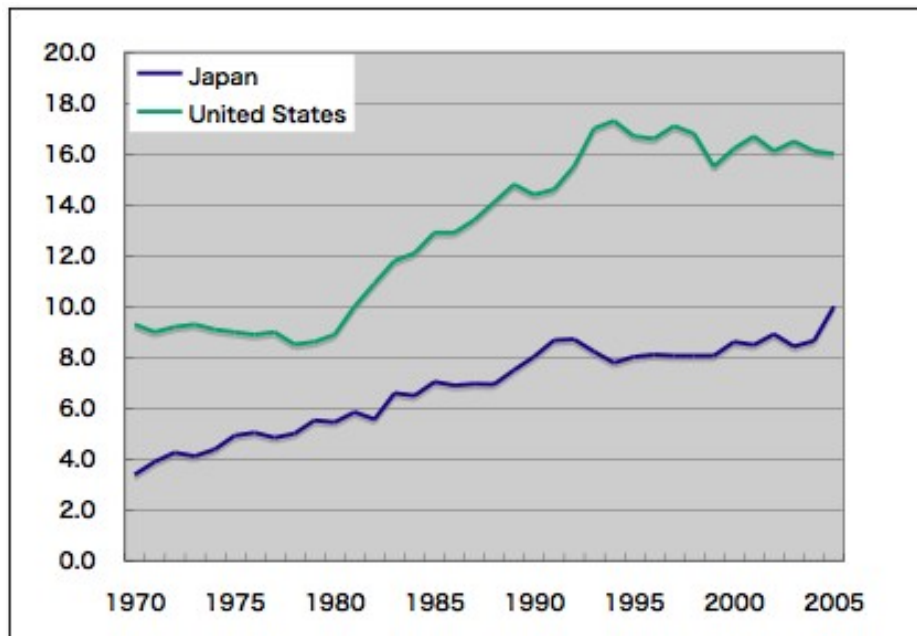
<sup>8</sup> The Ministry of Health and Welfare, established in 1938, became the Ministry of Health, Labour and Welfare (MHLW) in 2001. The Ministry of International Trade and Industry, established in 1949, became the Ministry of Economy, Trade and Industry (METI) in 2001.

<sup>9</sup> This is documented in the security filings of various firms in the late 1940s.

<sup>10</sup> 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. 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

pharmaceutical industry began to prosper by producing foreign-discovered drugs under license. Capital controls and tariffs meant that they were operating in a highly protected environment, The product standards introduced in 1967 also served as a particularly strong non-tariff trade barrier, as did the myriad rules regarding distribution systems. Foreign firms were reluctant to invest in the redevelopment of their drugs for a market where they had few distribution networks.<sup>11</sup>

Figure 1 R&D/Sales US-Japan comparison



Source: Statistical Survey Department, Statistics Bureau, Ministry of Internal Affairs and Communications, Pharmaceutical Research and Manufacturers of America. *Pharmaceutical Industry Profile 2008*, 2008, 53.

Japan's pharmaceutical firms began to shift from manufacturing-based to research-based growth as the government liberalised capital controls and introduced

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personnel stationed in Japan. The Occupation authorities believed that domestic production would enable low-cost provision of essential medicines for both civilian and military purposes whilst adjusting flexibly to fluctuations in demand without the costs and risks of relying on imports.

<sup>11</sup> Basic Policies for Drug Manufacturing Approval" in 1967.

product patents in 1975 and 1976, respectively. The government implemented these changes following Japan's membership to the OECD and World International Patent Organisation, under strong pressure from the United States, and based on its own desire to encourage technological development among Japanese firms. While perhaps limited in comparative perspective, Japanese firms also became more research oriented to compete against both foreign firms and domestic firms from other sectors. Capital liberalisation led to the rapid rise in the number of foreign firms operating in Japan, from 74 in 1970 to 239 by 1980.<sup>12</sup> Unable switch or acquire complex distribution channels, however, new entrants did not pose a serious threat to existing players at the time.

In the 1980s, foreign governments intensified pressures on Japan to improve market access. Among these were the market-oriented and sector-selective (MOSS) talks held between Japanese and American officials in 1986 that aimed to remove barriers to market access.<sup>13</sup> Business organisations such as the Pharmaceutical Manufacturers Association in the United States and the European Business Council in Europe also held talks with Japanese officials and requested Japan to reduce barriers by accepting foreign clinical data; clarifying the criteria for innovation; and improving transparency in the pricing process.<sup>14</sup>

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<sup>12</sup> 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.

<sup>13</sup> 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). See also Maki Umemura, *The Japanese Pharmaceutical Industry: Its Evolution and Current Challenges* (Abingdon: Routledge, 2011).

<sup>14</sup> "Yūsei na Kaihatsuryoku de Kyūseicho o Tsuzukeru Zainichi Gaishi [With Stronger Development Capacities, Foreign Firms in Japan Continue to Grow

Reforms to the regulatory landscape in the 1990s accelerated the globalisation of the Japanese market. In the early 1990s, Japan harmonised its pharmaceutical regulations with 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. Distribution reforms also sparked a wave of consolidation among wholesalers and lowered barriers to entry.

The globalisation of the Japanese pharmaceutical industry was also a two-way street. Just as the number of foreign firms in the Japanese market grew, so did the number of Japanese firms expanding overseas. In fact, leading Japanese firms such as Takeda and Eisai transferred a large part of their operations abroad to take advantage of global R&D capacities, drug pricing regimes, and markets.<sup>15</sup> The new global environment also led to the hollowing out of the leading firms from Japan.

Pressures to change

Reforms in the 1990s

These pressures for reform culminated in the introduction of a number of new measures. The three major measures introduced during this period were: distribution

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Rapidly],” *Detailman*, (May 1992): 28-35.

<sup>15</sup> 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: Okurasho Insatsukyoku, 1955-2000); and Ministry of Health, Labour and Welfare, *Kōsei Rōdō Hakusho* [White Paper on Health, Labour and Welfare](Tokyo: Okurasho Insatsukyoku, 2001-2007).



reforms, the harmonisation of pharmaceutical regulations with Europe and the United States, and a combination of measures that encouraged more entrepreneurship in the Japanese market. These reforms intensified the competitive pressures in the Japanese pharmaceutical industry.

One of the key measures that opened the market came with Japan's participation in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). In 1990, regulatory authorities in the United States, Europe and Japan formed a project to reduce the cost and time involved in duplicating drug development the three regions. The ICH guidelines made it much easier for drugs from each of these regions to be recognised in another region – and avoid the cost of redevelopment in different drug regimes.<sup>16</sup> Given that the product standards established in 1967 had been one of most formidable barriers to the Japanese pharmaceutical market, the adoption of ICH guidelines was an important step in easing foreign access to Japan.

The second major development were the reforms to the distribution sector. In the Japanese pharmaceutical industry, the supply chain linking manufacturers to patients had typically involved two intermediaries: wholesalers and physicians. Since 1951, the government had set the retail price of prescription drugs. As a result, dispensing physicians increased their margins by negotiating down the price paid to wholesalers. Until 1992, pharmaceutical manufacturers usually entered into resale price maintenance agreements with wholesalers. These agreements limited the competitive

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<sup>16</sup> The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, <http://www.ich.org>, (accessed 15 May 2007).

pressure on Japan's many small and inefficient wholesalers and made it difficult for new entrants to sell drugs in Japan.<sup>17</sup> Furthermore, the wholesale sector was highly fragmented. While manufacturers developed a complex web of local and regional wholesale networks to achieve nationwide distribution, physicians used multiple wholesalers to secure drugs from different manufacturers.<sup>18</sup>

As part of the distribution reforms, the government prohibited resale price maintenance in pharmaceuticals in 1991.<sup>19</sup> This measure effectively dissolved the keiretsu relationships between select wholesalers and manufacturers.<sup>20</sup> Wholesalers no longer needed to align themselves with a particular manufacturer because they were free to negotiate the prices of drugs sold to physicians. These reforms sparked a wave of consolidation among wholesalers and lowered barriers to entry.<sup>21</sup>

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<sup>17</sup> Shūmei Tanaka, "Iyakuhin no Ryūtsu o Meguru Mondaiten [Problems in Pharmaceutical Distribution]," in *Shakai Yakugaku Nyūmon* (Tokyo: Nankōdō, 1987), 156-168.

<sup>18</sup> Yakugyō Jihōsha, *Yakuji Handobukku* [Pharmaceutical Affairs Handbook] (Tokyo: Yakugyō Jihōsha, 1968-1999).

<sup>19</sup> The new price settlement system was called "Shin-shikirika-sei." See Ministry of Health and Welfare, "Iyakuhin, Iryōryōgu no Ryūtsu Kindaika [Modernisation of Distribution in Pharmaceuticals and Medical Equipment]," in *Kōsei Hakusho* [White Paper on Health and Welfare] (Tokyo, Ōkurashō Insatsukyoku, 1974); Japan, House of Representatives, Health and Welfare Committee, *Official Report of Debates*, 126<sup>th</sup> Diet, 6<sup>th</sup> Session, 2 April 1993; Japan, House of Councillors, Health and Welfare Committee, *Official Report of Debates*, 126<sup>th</sup> Diet, 7<sup>th</sup> Session, 20 April 1993; Japan, House of Councillors, Health and Welfare Committee, *Official Report of Debates*, 126<sup>th</sup> Diet, 11<sup>th</sup> Session, 30 June 1993.

<sup>20</sup> See Tadashi Inoue, "Iryōryō Iyakuhin 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 Kenjirō Nagasaka spearheaded the industry's reforms in distribution in response to the government's policy reforms.

<sup>21</sup> P. Reed Maurer, "Why Japanese Pharmaceutical Wholesalers Merge," *Pharma Marketletter*, 4 June 1999; 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).

First, local firms merged into regional wholesalers that had sales rights from several manufacturers. These wholesalers then merged into wholesaler groups with nationwide coverage that had sales rights to drugs of most manufacturers – such as Medipal, Alfresa, Suzuken and Toho. While there were 434 wholesalers in Japan in 1987, there were less than 128 by 2007 – many of which were associated with these wholesaler groups through cross shareholdings.<sup>22</sup> The structure of Japan’s pharmaceutical wholesale sector increasingly resembled that of the United States, where a few firms – AmerisourceBergen, Cardinal Health and McKesson – dominated the market.

Table 3 Pharmaceutical Distribution in Japan and the United States, 2007

	Number of companies	Market share of the top three firms	Typical net profit margins
United States	70	96%	1.5-2.5%
Japan	130	70%	1.0-1.5%

Source: KPMG

Another part of the distribution reforms involved a change to the government’s method of reviewing drug prices so that the practice of dispensing drugs became less lucrative. As a result of these changes, many physicians began to abandon the business of dispensing drugs. In 1990, 87.2% of physicians dispensed drugs; by 2009,

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<sup>22</sup> 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 6 July 2011).

only 39.3% of physicians did so.<sup>23</sup>

Pharmaceutical firms altered their marketing strategies as a result of these changes. No longer able to provide generous discounts as a way of inducing physicians to prescribe their drugs, pharmaceutical firms began to invest more in the education of marketing representatives and compete on the basis of quality. The distribution reforms reincentivised manufacturers to develop higher priced drugs with greater innovative value.

The third reform behind the transformation of the 1990s was a combination of measures that encouraged entrepreneurship among pharmaceutical firms. Academic entrepreneurship, through biotechnology firms, has been a particularly important source of pharmaceutical innovation. However, biotechnology entrepreneurship was rather limited in Japan compared to the United States or Europe.

One the strongest barriers to entrepreneurship in Japan remained the limited access to labour and capital.<sup>24</sup> Japanese business practices involving lifetime employment and seniority-based pay, for example, created an illiquid labour market that dissuaded both potential entrepreneurs or employees from establishing or working for small start-up companies. Many Japanese researchers also worked in hierarchical research units under the custom of long-term employment, which incentivized workers to

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<sup>23</sup> 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).

<sup>24</sup> Hiroyuki Odagiri and Yoshiaki Nakamura, “Nihon no Baiobenchā Kigyō: Sono Jittai to Igi [Biotechnology-related Startup Firms in Japan: Lessons from a Survey Study],” National Institute of Science and Technology Policy, Discussion Paper 22, June 2002, 19.

avoid taking risks that might cause mistakes, rather than pursue breakthrough discoveries. Moreover, prior to 1998, scientists working at national universities were not permitted to engage in private sector employment.<sup>25</sup>

In terms of capital markets, venture capital in Japan was scarce compared the United States and Europe, and funding levels were lower. Bankruptcy laws also offered more protection to investors rather than firms; entrepreneurs in Japan could easily face personal bankruptcy in the event of failure. As well, until the Mothers (Market of the high-growth and emerging stocks) section of the Tokyo Stock Exchange was launched in 1999, start-up companies had few opportunities to list their shares in Japan. Furthermore, before 2006, the initial capital requirement for incorporation was ¥10 million.<sup>26</sup>

In the post-bubble period, however, the post-war Japanese business system began to unravel, and the government introduced a number of measures to encourage entrepreneurship Japanese firms' long-term relations that were reflected in features such as lifetime employment or *keiretsu* relationships, had discouraged the creation of new firms. However, the government introduced several laws to facilitate the creation of small to medium sized enterprises at the regional level in the late 1990s.<sup>27</sup> The

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<sup>25</sup> The Law for Promoting University Technology Transfer was introduced in 1998. Samuel Coleman, *Japanese Science: From the Inside*, London: Routledge, 1999.

<sup>26</sup> 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).

<sup>27</sup> This refers to the *Chūsho Kigyō Sōzō Katsudō Sokushin Hō* [Law to Promote Innovation in Small to Medium Size Firms] (1995) and *Shin Jigyō Sōshutu Sokushin Hō* [Law to Promote the Creation of New Business] (1998). See Small and Medium

government also introduced four laws to facilitate technology transfers between academia and industry between 1998 and 2003.<sup>28</sup> In addition to the creation of new markets that listed the shares of emerging companies, and the lowering of capital requirements for incorporation, the government also increased support for biotechnology startups through R&D tax credits and funding.<sup>29</sup>

Change: partial convergence

The post-1990s reforms altered the dynamics of the Japanese pharmaceutical industry. The Japanese industry now faced more foreign firms; it was more research intensive; new biotechnology firms were emerging; and its generics sector was growing. Yet the change in Japan's pharmaceutical industry suggested a rather tempered convergence with those of the advanced industrialised countries.

The number of foreign firms in Japan increased after the 1990s, along with their market share. The reforms to the distribution sector had meant that many no longer had to rely on local partners to distribute their products. Rather, foreign firms could train their much larger sales force to market their drugs directly to Japanese physician from a diverse, global pipeline of drugs.<sup>30</sup>

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Enterprise Agency, *Chūshō Kigyō Hakusho* [White Paper on Small and Medium Enterprise] (Tokyo: Okurasho Insatsukyoku, 1995-1998).

<sup>28</sup> This refers to *Daigaku nado Gijutsu Iten Shokushin Hō* [Law to Promote the Transfer of University Technologies] (1998), *Sangyō Katsuryoku Saisei Tokubetsu Sochi Hō* [Law of Special Measures to Revive Industry] (1999), *Sangyō Gijutsuryoku Kyōka Hō* [Law to Strengthen Industrial Technology] (2000), and the *Kokuritsu Daigaku Hōjin Hō* [University Incorporation Law] (2003). See Robert Kneller, "The Beginning of University Entrepreneurship in Japan: TLOs and Bioventures Lead the Way," *Journal of Technology Transfer* 32 (2007): 435-456.

<sup>29</sup> Cabinet Office, *Dai Sanki Kagaku Gijutsu Kihon Keikaku* [Third Science and Technology Basic Plan], 28 March 2006, <http://www8.cao.go.jp/cstp/kihonkeikaku/kihon3.html> (accessed 14 July 2011).

<sup>30</sup> Jihō, *Yakuji Handobukku*, [Pharmaceutical Affairs Handbook] (Tokyo: Jihō, 2000-

In the meanwhile, Japanese pharmaceutical firms intensified their R&D orientation and expanded abroad. As mentioned earlier, the adoption of ICH strengthened drug standards and encouraged firms to increase their investments in R&D and develop drugs for the global market. As harmonisation made it easier for Japanese firms to access the large markets beyond its borders, more firms ventured abroad.<sup>31</sup> At home, too, Japanese firms competed with a greater number of foreign firms as harmonisation improved access to the Japanese market.<sup>32</sup> In 1990, no foreign firms were among the top ten Japanese pharmaceutical firms.<sup>33</sup> By 2009, half of the top ten firms were non-Japanese.<sup>34</sup>

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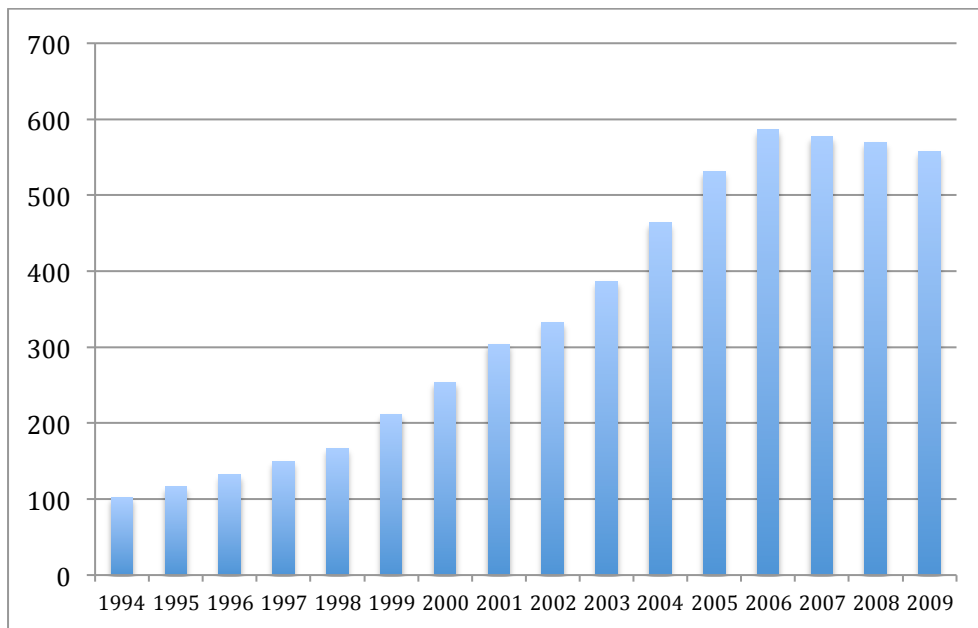
<sup>31</sup> Japan Pharmaceutical Manufacturers Association, *Data Book* (Tokyo: Japan Pharmaceutical Manufacturers Association, 2007).

<sup>32</sup> “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).

<sup>33</sup> PJB Publications, *Scrip: Pharmaceutical Company League Tables 1991* (Richmond: PJB Publications, 1991), 42.

<sup>34</sup> Jihō, *Yakuji Handobukku*, [Pharmaceutical Affairs Handbook] (Tokyo: Jihō, 2010), 53, 55.

Figure 2 Number of bioventures in Japan



Source: Japan Bioindustry Association, *Baiobenchā Tōkei Chōsa Hōkokusho* [Statistical Survey on Bioventures], (Tokyo: Japan Bioindustry Association, 2010).

As Figure 2 shows, Japan's biotechnology sector also grew.<sup>35</sup> The gradual breakdown of entrenched business practices in post 1990s period; the increased liquidity in capital and labour markets; coupled with new incentives created for entrepreneurship fostered the creation of new biotechnology firms. Yet the size of Japan's biotechnology sector paled in comparison with the American and European markets. By 2009, the number of biotechnology firms in the United States and Europe stood at 1,389 and 1,842, respectively, compared to 558 in Japan. The United States and Europe had 314 and 167 public companies respectively, compared to [18] in Japan.<sup>36</sup>

<sup>35</sup> Japan Bioindustry Association, *Baiobenchā Tōkei Chōsa Hōkokusho* [Statistical Survey of the Bioventures] (Tokyo: Japan Bioindustry Association, 2008), 8.

<sup>36</sup> *Ibid.*, Ernst & Young, *Beyond Borders: Global Biotechnology Report* (London: Ernst & Young, 2011), 39, 40, 48.



Table 4 Profile of biotechnology firms in the United States, Europe and Japan, 2009

(in millions of US dollars)

	United States	Europe	Japan
Number of firms	1,703	1,842	558
Number of public firms	314	167	[18]
Average capitalisation	159.4	25.7	0.5
Average number of employees	62.5	37.8	9.0
Average sales	33.0	9.0	0.4

Source: Japan Bioindustry Association, *Heisei 22 nendo Jigyo Hokokusho* [Report on Activities, 2010] (Tokyo: Japan Bioindustry Association, 2010), Ernst & Young, *Beyond Borders: Global Biotechnology Report* (London: Ernst & Young, 2011), 39, 40, 48.

The limited capacities of Japan's biotechnology firms are capacities of Japanese biotechnology firms are reflected in Japanese pharmaceutical firms' acquisitions of American and European rather than domestic biotechnology firms. These acquisitions are driven by the lack of suitable bioventures at home. Some high profile acquisitions include Eisai's takeover of MGI Pharma and Takeda's acquired Millenium Pharmaceuticals in 2008.<sup>37</sup>

While government measures for cost containment did not encourage the development of innovative drugs in Japan, they inadvertently stimulated the growth of Japan's budding generics sector. Before the 1990s, the generic medicines industry was a negligible sector of the Japanese pharmaceutical industry.

There were four main reasons for the low penetration of generics in Japan. First, Japanese physicians and patients were sceptical of the safety and efficacy of non-branded medicines and maintained strong brand loyalty to existing firms. Second,

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<sup>37</sup> Atsuko Fukase and Kana Ishigaki, "Takeda Bid May Fuel Japan Shopping Spree," *Wall Street Journal*, 16 May 2011.

they were also distrustful of generic firms' capacity to produce quality drugs or provide a stable supply of drugs.<sup>38</sup> Third, physicians had few incentives to prescribe low-priced generics, which offered minimal price differentials compared with branded medicine. Moreover, in a hierarchical society, few price-insensitive Japanese patients questioned the drugs doctors prescribed. Fourth, until 2008, Japanese pharmacists did not have generic substitution rights such as those in the United States or Germany, where pharmacists could substitute an equivalent generic product for any brand name drug prescribed.<sup>39</sup> As well, generic producers themselves faced slower, and therefore costly review times in the drug approval process, which deterred new entrants.<sup>40</sup>

However, faced with the task of containing the escalating health care costs, the government has increasingly promoted generics since the millennium – from raising physicians' prescription services fee for generics to slashing the prices of branded drugs where generic versions are available.<sup>41</sup> In line with global trends, branded drug makers in Japan are also incorporating the generics business amid patent expiries, the unexpected decline in R&D productivity, and the growing generics market – which has led to industry-wide restructuring.

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<sup>38</sup> The former perception were not helped when physicians found few medical representatives of generics firms as qualified to engage in in-depth discussions of potential side effects as compared to their branded counterparts. The latter perception stemmed from generics firms tended to face difficulties dealing with pharmaceutical distributors – many of whom were closely tied to established branded manufacturers – but also because many firms were much smaller compared to branded manufacturers.

<sup>39</sup> However, physicians can expressly forbid generic substitution.

<sup>40</sup> For example, Thomson Reuters, *The Japanese Generic Drug Market: Opportunities and Strategies for Success* (London: Thomson Reuters, 2009).

<sup>41</sup> Development Bank of Japan, "Iyakuin Gyōkai no Genjō to Jenerikku Iyakuin Shijō," *Kongetsu no Topikkusu* 145-2 (March 2010); Sumitomo Trust Bank, Kakudai suru Jenerikku Iyakuin Gyōkai no Yukue [The Future of the Expanding Generics Market], *Chōsa Geppō* (January 2006).

Between 1999 and 2009, the share of generics in the Japanese market grew from 10.8% to 23.0% of prescription drugs dispensed in volume terms. The market grew to 396.2 billion yen by 2009.<sup>42</sup> Yet this remained much lower than generic penetration rates in the United States, Britain, or Germany – where generics accounted for over 70% of prescriptions dispensed.<sup>43</sup>

Still, the Japanese generics market has been growing in an increasingly competitive environment, fuelled by foreign entry and M&A activity. Indian firms have made inroads in Japan, such as Zydus Cadila, who acquired Nippon Universal Pharmaceutical in 2007. World leading generics firms such as Teva, for example, formed a joint venture with one of Japan's leading generics firms, Kowa, in 2008, while Sanofi tied up with Nichi-Iko in 2010.<sup>44</sup> Domestic drug makers are also strengthening their generics business through foreign acquisitions. In 2008, for example, Daiichi Sankyo acquired the Indian generics firm Rambaxy.<sup>45</sup>

Change: too little too late?

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<sup>42</sup> Fuji-Keizai, "Jenerikku Iyakuhin, Chōki Shūsai Iyakuhin no Shijō o Chōsa [Investigating the Market for Generic Medicines and Long-listed Medicines]," <https://www.fuji-keizai.co.jp/market/11020.html> (accessed 13 June 2010).

<sup>43</sup> IMS, "Generic Medicines: Essential Contributors to the Long-Term Health of Society," [http://www.imshealth.com/imshealth/Global/Content/Document/Market\\_Measurement\\_TL/Generic\\_Medicines\\_GA.pdf](http://www.imshealth.com/imshealth/Global/Content/Document/Market_Measurement_TL/Generic_Medicines_GA.pdf) (accessed 13 July 2011).

<sup>44</sup> David Harding, "Gaining Market Share in the Generic Drug Industry through Acquisitions and Partnerships," Thomson Reuters, December 2010.

<sup>45</sup> "M&A continues in pharma/biotech, but are mega acquisitions thing of the past?" *Pharma Marketletter* (5 January 2009); "Teva in generics JV with Japan's Kowa," *Pharma Marketletter* (26 September 2008), Sanofi-aventis, "Sanofi-aventis and Generics Leader Nichi-Iko to Establish New Joint Venture for Generics in Japan," Sanofi-aventis. press release, 28 May 2010, on the Sanofi-aventis website [http://en.sanofi.com/binaries/20100528\\_NichiIko\\_en\\_tcm28-28569.pdf](http://en.sanofi.com/binaries/20100528_NichiIko_en_tcm28-28569.pdf) (accessed 14 July 2011).

While the transformations in Japan’s pharmaceutical industry since the 1990s were remarkable from a Japanese standpoint, the changes appeared rather limited in comparative perspective. The Japanese industry did become more R&D intensive, more dynamic and competitive – particularly with the entry of foreign firms. Japanese firms were larger, they merged with other domestic and foreign firms – and they were expanding overseas. But whether it was the level of R&D investment or size of firms, Japanese figures remained smaller than those of global leaders.

Table 5 Top Three Pharmaceutical Firms in Global and Japanese Markets, 2010 (in millions of US dollars)

Global (Market size: 791,449)			Japan (Market size: 109,115)			
Company	Sales	R&D expenditure	Company	Sales	Overseas sales	R&D expenditure
Pfizer Inc.	67,809	9,413	Takeda Pharmaceutical Co.	15,763	8,355	3,187
Novartis International AG	50,624	9,100	Daiichi Sankyo Co.	10,238	5,186	2,116
Merck & Co.	45,987	10,991	Eisai Co. Ltd.	8,636	4,767	1,926

Source: IMS Health, Company Annual Reports.

Several features also made the Japanese market rather unattractive compared to other advanced markets. This included the government’s continued practice of biennial price reductions; an undeveloped infrastructure for drug development; as well as a renewed drug lag following an HIV blood scandal. For many Western firms, Japan presented a rather saturated market with a distant and unfamiliar culture.

By the early 2000s, Japan not only had an ageing population, it had a declining one – placing further pressures on government coffers. The government’s policy of unilaterally reducing drug prices on a regular basis 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 example, where there were no price restrictions on drugs. Moreover, Japanese pharmaceutical firms could not rely on government funding for industrial R&D.<sup>46</sup> This lack of funding was particularly detrimental at a time when R&D processes were becoming increasingly costly and sophisticated.<sup>47</sup> The limited ability to grow also meant that many Japanese firms lacked the capital to acquire foreign firms and expand.

In addition, the infrastructure for drug development and approval remained much more rudimentary in Japan compared to American and European drug regimes. In particular, Japan did not have a structured clinical trial process and had markedly fewer qualified reviewers compared to the United States and Europe. Previously, clinical trials in Japan had been conducted through personal connections, on an ad-hoc basis.<sup>48</sup> Between 2004 and 2009, for example, the number of employees employed in the review office of Japan's Pharmaceutical and Medical Devices Agency more than doubled to 346.<sup>49</sup> Yet the figures still amounted to less than a tenth of the 5,038 employees employed in the equivalent section of the US Food and Drugs

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<sup>46</sup> Government funds for pharmaceutical R&D are provided to universities. Firms are indirectly subsidised through joint projects conducted with universities.

<sup>47</sup> 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.

<sup>48</sup> P. Reed Maurer, interview by author, Tokyo, Japan, 11 July 2007.

<sup>49</sup> Pharmaceutical and Medical Devices Agency, "Current Status of New Drug Reviews and Challenges to Promote Global Drug Development," (presentation, 22<sup>nd</sup> Annual EuroMeeting, Drug Information Association, Monaco, 8-10 March 2010).

Administration.<sup>50</sup> In 2010, the annual budget of the PMDA was about \$120 million, compared to \$3,284 million in the United States.<sup>51</sup> The underdeveloped infrastructure in Japan delayed drug approval times in the country.

An earlier HIV blood scandal had exacerbated this drug lag – or delays in the approval of new drugs. This scandal had come to light in the mid-1980s after Japanese haemophiliacs contracted HIV from the circulation of untreated blood products. The MHW had turned a blind eye to the potential dangers of these products to protect Japan’s leading provider of blood products. Green Cross Corp. had not yet been ready to produce the safer, heat-treated blood products that were available overseas.<sup>52</sup>

Following the scandal, the MHW became much more cautious of approving new drugs. The longer assessment times raised the cost of drug development. By 2000, the average time for drug approval in Japan was 28.5 months compared to 16.5 months in the United States.<sup>53</sup> The drug lag was not just a negative outcome for patients who

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<sup>50</sup> The US figures are combined employee figures for the Center for Biologics Evaluation and Research, Center for Drug Evaluation and Research, and Center for Devices and Radiological Health. US Food And Drug Administration, “FDA Basics,” <http://www.fda.gov/AboutFDA/Transparency/Basics/ucm213161.htm> (accessed 14 July 2011).

<sup>51</sup> Cabinet Office, 2<sup>nd</sup> Meeting on Health Care Innovation, Document 4, 16 June 2011, <http://www.kantei.go.jp/jp/singi/iryuu/dai2/gijisidai.html> (accessed 14 July 2011).

<sup>52</sup> 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.

<sup>53</sup> 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

could only belatedly access much needed drugs. By raising the costs of R&D, firms began to invest in R&D elsewhere. Average drug approval times in Japan did improve over the decade: between 2000 and 2009, evaluation times averaged 22.7 months in Japan compared to 18.7 months and 15.0 months in the United States and Europe, respectively.<sup>54</sup> Yet the comparatively inferior environment in Japan also led to the hollowing out of drug development from the country.

Table 6 Number of Japanese firms expanding overseas

Year	Number of Companies	Manufacturing	Sales	R&D
1985	64	23	37	
1995	146	58	71	
2005	284	102	206	15

Source: Yano Research Institute, reprinted in JPMA, *Databook 2009*, 2009.

Indeed, the globalisation of Japan’s pharmaceutical industry over the past two decades has been accompanied by the hollowing out of Japanese pharmaceutical firms: the domestic leaders have expanded primarily in the United States, while others have done so in Asia.<sup>55</sup> In 1990, still less than a tenth of 1,496 Japanese pharmaceutical firms had expanded overseas. Most Japanese firms neither developed the drugs nor the distribution networks to compete in global markets. By 2007, more

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2006); Federal Drug Administration, CDER Drug and Biological Approval Reports, <http://www.fda.gov/cder/rdmt/default.htm> (accessed 4 May 2008).

<sup>54</sup> Taro Ishihashi, Shinsuke Ono, “Nihon ni okeru Shinyaku no Rinshō Kaihatsu to Shōnin Shinsa no Jisseki [Status of Clinical Trials and Drug Evaluation for New Drugs in Japan],” *Research Paper Series, Office of Pharmaceutical Industry Research, Japan Pharmaceutical Manufacturers Association* 50 (September 2010), 56.

<sup>55</sup> Yano Research Institute *Iyakuhin Kanren Kigyō Kōzō Bunseki 2010-2011* [Structural Analysis of Pharmaceutical and Related Industries 2010-2011] (Tokyo: Yano Research Institute, 2011).

than 285 firms had expanded abroad.<sup>56</sup> Firms such as Takeda, Daiichi Sankyo, Eisai, and Astellas depend on their overseas R&D bases for drug development and expect around half of their sales from overseas markets.

As the barriers to the Japanese market became more porous, the more competitive Japanese firms increasingly converged in form with those of Western leaders, to survive amid globalisation. After all, both the sources and market for their innovations were based overseas. The nationality of these firms were increasingly fluid – perhaps more global than Japanese.

## Conclusion

This paper examined the belated globalisation of the Japanese pharmaceutical industry, and the ways in which the country's institutions accounted for the divergent patterns of industrial development compared to those of the United States and Europe. In the 1990s, Japanese pharmaceutical firms were thrust into global competition. Not only did Japanese firms face a higher level of competition in the domestic and foreign markets, business operations – from R&D, production, to marketing – were increasingly dispersed around the world.

The erosion of national borders since the 1990s, however, exposed a fundamental weakness in the Japanese industry: an underdeveloped infrastructure that disincentivised R&D. The opening of the Japanese market coincided with the rise of the new economy, in which rapid advances in technology fostered an unprecedented level of economic integration in the global economy. While Japan's R&D

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<sup>56</sup> Japan Pharmaceutical Manufacturers Association, *JPMA Databook* (Tokyo: Japan Pharmaceutical Manufacturers Association, 1986-2009).



environment had improved, its inferior environment in relative terms led to the hollowing out of Japanese firms.

Globalisation has encouraged the convergence of the Japanese pharmaceutical industry with those in the United States and Europe. Over the past two decades, Japan's long entrenched business practices began to fade. Japanese firms streamlined their operations, merged across keiretsu loyalties with domestic and foreign rivals, and formed alliances with universities and biotechnology ventures within and beyond Japan. A nascent biotechnology sector emerged alongside a long dormant generics sector that had been suppressed by the proliferation of low cost, branded, me-too drugs. The blurring of national boundaries has diluted the nationality of Japanese firms, who increasingly resemble those of the United States and Europe.

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