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The Japanese vaccine industry's French connection: an exploration of the health policy environment on business development

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I. Introduction

From the end of World War II to the early 1960s, vaccines enjoyed a 'golden age' thanks to the discovery and dissemination of important life-saving products such as the polio vaccine. However, by the late 1970s and early 1980s, public perceptions of vaccines had radically changed due to the rise in vaccine-induced side effects. For manufacturers in the United States, litigation and low earnings made vaccine production an increasing unattractive endeavor. According to David Mowery and Violaine Mitchell, "between 1966 and 1977, one-half of all U.S. commercial vaccine manufacturers stopped producing and distributing vaccines."[1] Consequently, in the 1970s, some American vaccine producers were shifting their research focus towards more promising alternatives such as antibiotics, which they considered to be a less risky and more lucrative investment.[2] Over the same period, however, innovations in the form a new generation of polyvalent or combination vaccines provided promising opportunities for the firms that remained in the market. By the early 1990s, the 'new pediatric vaccines' category had become the market leader in the global vaccine market. [3]

This paper examines the introduction of this new generation of combination vaccines from the French perspective, and compares it with the situation in Japan, where single dose vaccines remained the norm. The paper illustrates the connections between the French and Japanese vaccine industries as well as how entrepreneurship in the French case and the policy environment in the Japanese case impacted the development of the national vaccine industry in the long term.

II. The Rise of the French Vaccine Industry

(II-1) Globalization and Consolidation

The origins of vaccine research and production in France can be traced to the Pasteur Institute in Paris; however, the roots of the country's vaccine *industry* can be found in Lyon. The industry's point of departure was the Mérieux Institute, established by Marcel Mérieux, a former student of Émile Roux at the Pasteur Institute. From the early decades of its operations, Marcel Mérieux emulated the Pasteur Institute's model, although his own activities were small and artisanal. [4] It was not until after his death in 1937, when his second son Charles took the company's reins that the Mérieux Institute would begin its transformation from a regionally-based operation to a multinational enterprise (MNE).

To the extent that Marcel Mérieux remained deeply influenced by the Pasteur Institute, Charles Mérieux paid careful attention to the developments taking

place abroad, particularly in the US vaccine industry. As early as 1945, he left Lyon for the United States to observe the American activities first-hand, and took particular note of the growing use of disposable plastic syringes. Before returning to France, he decided to begin developing an improved pertussis vaccine.[5] In later years, he would continue to cultivate these professional and personal connections in the United States, as witnessed by his close ties with Jonas Salk, best known for his discovery of the polio vaccine.[6]

Given Charles Mérieux's careful observations of the US industry, he was well aware of the mass withdrawals mentioned above. However, unlike his American counterparts, he perceived the situation not as a sign of decline but instead as a golden opportunity for the growth and globalization of the French industry.[7] In 1989, he acquired Connaught Laboratories, Canada's largest and most innovative vaccine manufacturer. This purchase enabled his company to secure 30 percent of the global share of the human vaccine market while also allowing full entry into the North American region.[8] To further consolidate his firm's newly acquired operations, Mérieux instigated a strategic alliance with Merck, another key player in the vaccine industry.

In 1985, after acquiring majority share of the Pasteur Institute's vaccine production division, the company changed its name to Mérieux Serums and Vaccines. In 1994, Rhône Poulenc purchased the remaining shares in Mérieux and changed the name to Pasteur Mérieux Connaught (PMC). Consequently, the firm left the family's hands, although Mériale, France's veterinary vaccine manufacturer still bears the name. A final wave of consolidation in the French vaccine industry occurred in the 2000s after Charles Mérieux's death with Sanofi's hostile takeover of Aventis. In 2004, Sanofi Aventis's vaccine division became Sanofi Pasteur, the world's largest manufacturer of human vaccines.

(II-2) The launch of a new generation of combination vaccines

In the 1980s and 1990s, one of the main technological and marketing drivers for the industry's growth and globalization was combination vaccines.[9] This was made possible through technological innovations. The DTP (diphtheria, tetanus, pertussis) and MR (measles, rubella) vaccines, which had already been developed in the 1960s, were improved upon by thanks to development of a new acellular pertussis vaccine. At the same time, combination products using the polio vaccine, which was previously not been combinable, as well as entirely new vaccines such as Hib (*haemophilus influenzae type B*) were launched. Combination vaccines would become the new standard in most developed nations for several reasons.[10] For governments, they were advantageous from a public health standpoint since they offered wider protection against more diseases in a single dose. For parents, combination vaccines brought convenience by reducing the number of trips to medical institutions. For manufacturers, new-generation combination vaccines added value to their existing products.

Charles Mérieux was especially keen on expanding the use of new combination vaccines, and from an early date, he became directly involved in various technical and licensing issues to ensure their realization. On the technical side, in 1966, Mérieux worked with a syringe manufacturer in the United States, which

he later purchased, to produce special syringes designed to inject multiple vaccines in a single dose.[11] These "double-chambered" syringes were prototypes of the new combination vaccines that would follow. The greatest challenges to the major producers of the new combination vaccines, however, were not technical but legal. [12] Because one firm rarely possessed all the licenses necessary to develop a single new combination vaccine, firms were left with two options: negotiating a licensing agreement for the use of the technology or purchasing the license holder. Mérieux often opted for the latter, making the development of combination vaccines a major driver in the consolidation of the French industry.

In tandem with the development of combination vaccines by MNEs came the opening of national markets. As underlined in one of Galambos's pioneering studies of one of the major players, Merck, national vaccine markets were closed to competition in the late 1970s: "Overseas markets were difficult…to crack. A number of the European companies were looked on by their governments as "national institutions": Pasteur and Mérieux, both in France, and Behringwerke in Germany were the Big Three…Though Merck…was much larger than any of these firms, they had the support of their national governments, as did Sclavo in Italy, RIT in Belgium and Holland, and Burroughs Wellcome and Glaxo in the United Kingdom. As a result, MSDI was making no vaccine sales in France, Germany, Britain, Italy, and Spain".[13] As explored below, this was also the case for the Japanese market.

The situation began to evolve quickly in the 1980s, accelerating into the 1990s, as combination vaccines gradually became the global norm for vaccination. Many of the "national institutions" sold off their production units to MNEs. At the same time MNEs globalized by entering once closed markets via deals with competing firms. PMC formed a formed a strategic alliance with Merck, which later became a joint venture for marketing and co-development in the United States. This enabled Merck to gain entry into European markets, and in exchange, the French could use key components developed by Merck in new combination vaccines.

Over the same period, innovation also became a driver of globalization. The development of a new vaccine, Hib (*haemophilus influenzae type B*) further increased French opportunities for combination vaccine production and global expansion. Hib could be combined with numerous existing vaccines to produce more complex products such as DTaP-IPV/HepB/Hib (diphtheria, tetanus, polio, acellular pertussis, hepatitis B, Hib) launched in the United States in 2003. In the late 1990s, the Hib vaccine provided another opportunity for PMC when its management decided to enter one new Asia-region market, Japan, where neither new combination vaccines nor the Hib vaccine had been approved.

III. Features of the Japanese Vaccine Market

III-A. Features of the Japanese Vaccine Market

The first feature of Japan's vaccine industry is full self-sufficiency for all routine vaccines. According to the Ministry of Health, Labour and Welfare (MHLW), as of 2008, 98.5 percent of all of the vaccines administered in Japan were domestically produced.[14] The government had kept this policy in place since World War II not

only to ensure a stable supply of vaccines but also to guarantee safety and traceability in the event of adverse events. Second, in Japan, MNEs were not suppliers of vaccines; until recently, they have been produced almost exclusively by private institutes, as shown below

(Figure 1) ***Vaccine Manufacturers Operating in Japan in 2008***[15]

Manufacturer (1)	**Legal Status**	**Production Site**	**Vaccines (ratio of total sales, 2003)**[16]
Kitasato Institute	University	Saitama	100%
Biken (1)	Incorporated Foundation	Osaka	96%
Kaketsuken (2)	Incorporated Foundation	Kumamoto	34%
Denka Seiken (3)	Joint-stock Company	Niigata	33%
Japan Poliomyelitis Research Institute	Incorporated Foundation	Tokyo	100%
Japan BCG Laboratory	Joint-stock company	Tokyo (Kiyose)	100%
Takeda Pharmaceutical Co.	Joint-stock Company	Yamaguchi	Less than 2%
Banyu/Merck (MSDI) (2)	Joint-stock Company	*Imported vaccines	Less than 1%
Glaxo SmithKline (GSK)	Joint-stock Company	*Imported vaccines	Less than 1%
Sanofi Pasteur-Daiichi Sankyo	Joint Venture	*Imported vaccines	N/A

(1) Meiji Dairies (Meiji Nyūgyō) also engaged in the small-scale production of the hepatitis B vaccine in 2008 but withdrew from the industry in 2009.
(2) "Ken" is an abbreviation for "institute" or "laboratory" in Japanese. The name of the Kitasato Institute in Japanese is Kitasato *Ken*kyūsho.
(3) Banyu was once a Japanese-owned pharmaceutical company but is now a fully owned subsidiary of Merck (MSDI).

The third feature is that the litigation which took place in many countries in the 1970s and early 1980s had a lasting and profound impact on regulatory policy. In a 1994 supreme court case, the Japanese government accepted full responsibility for all vaccine-related adverse reactions. Following the ruling, the number of new vaccine approvals virtually ceased. Apart from the hepatitis A vaccine, between 1991 and 2006, not a single *new* vaccine was approved.

(Figure 2)
Vaccines Approved for Use in Japan and the United States

Approval year	**Japan**	**United States**
1985	Hepatitis B (1)	
1987	Varicella	HIB IPV (inactivated polio)
1988	Streptococcus (2) Recombinant Hepatitis B MMR (3)	
1991		aP (acellular pertussis)
1992		DTaP-Hib DTaP-IPV

1993		
1994		Plague
1995	Hepatitis A	Varicella
1996		Hib-Hepatitis B Attenuated Hepatitis A
2000		Pneumococcus
2001		Hepatitis A/B
2002		DTaP-IPV/Hep B DTaP-IPV/Hib
2003		Intranasal live influenza DTP (for adults) DTaP-IPV/HepB/Hib
2005	MR (4)	MMRV (PCV13s) Meningococcus
2006		Rotavirus

(1) Approved in the United States in 1981 (recombinant version approved in 1986).
(2) Approved in the United States in 1977.
(3) Approved in the United States in 1971.
(4) MR is the measles rubella vaccine, a modified version of MMR (measles, mumps, rubella).

The fourth feature is a shrinking number of combination vaccines. In 1988, in response to a rise in the number of adverse reactions to the mumps vaccine, MHW approved the MR (measles rubella), a modified version of the MMR (measles, mumps, rubella). [17] Approval of MR and the removal of the mumps vaccine from the routine schedule clearly demonstrates the government's stance toward combination vaccines, a major obstacle for the French when they entered the Japanese vaccine market.[18]

IV. Establishing a Franco-Japanese Joint Venture

The idea for PMC (Pasteur Mérieux Connaught, now Sanofi Pasteur) to enter the Japanese market came by chance. In an article published in 1996 in *Le Monde*, it was reported that a Japanese infant had died of the measles, a rare occurrence in France. Considering its potential, the manager who would head the operation in Japan, Louis Freidel, decided to propose the idea to the company's chairman at the time, Michel Greco.[19]

Finding a joint venture partner was a major challenge, as all the manufacturers he approached showed no interest or were inappropriate in terms of their business model. In 1987, Connaught had founded a joint venture called CD Vac with Daiichi Pharmaceutical Company (which became Daiichi Sankyo Pharmaceutical Company after a 2005 merger with Sankyo) to sell blood derivatives in Japan. CD Vac was closed due to PMC's withdrawal from the blood derivatives business; however, the company was still officially registered for business. With few alternatives, Friedel approached Daiichi. From the French perspective, Daiichi's only real advantage as a partner was that it had marketed a pediatric antibiotic, which meant that it possessed at least some experience in this sector. After lengthy negotiations, a joint venture was established in 1997. Following numerous mergers, the operation would eventually become *Pasteur Mérieux Connaught-Daiichi Vaccine Company Limited*.

Once the joint venture had been established, PMC needed to select a promising candidate from its portfolio. Freidel decided on one of the company's most innovative products, the Hib vaccine, marketed under the trade name, ACTHib. He considered this to be the winning strategy since there were no competitors. Moreover, because there were no new-generation combination vaccines in use in Japan at the time, the Hib vaccine had a strong long-term marketing potential since it could be combined with other vaccines. One added incentive was price. Japan's vaccine prices were the highest in the world followed by the United States. [20] As in many other countries, health authorities in Japan rather than the market determine drug prices. Local governments receive funds from the central government, which are used to cover various public services, including routine vaccination. After the approval of ACTHib, which must be administered three times, the price remained high. In early 2012, patients (parents) paid between 7,000 and 10,000 yen per injection, depending on the medical institution. Howeover, to improve access nationwide, government subsidies were approved in 2010 for the Hib vaccine and others such as HPV.[21]

IV-A. Inventing a "New" Disease

According to a 2005 factsheet issued by WHO, Hib (*haemophilus influenzae type B*) is a bacterial disease that strikes children under the age of five, though infants between four and 18 months are the most susceptible. An estimated three million children worldwide contract the disease annually. The most common symptoms include pneumonia and meningitis, which may result in permanent damage including deafness and mental retardation in 15 to 35 percent of those who contract it. The annual death toll worldwide is approximately 386,000 children.[22]

The first pure polysaccharide Hib vaccine was developed by the National Institute of Infectious Disease and marketed in the United States in 1985. The Haemophilus B Conjugate Vaccine (Tetanus Toxoid Conjugate) or ACTHib, an improved vaccine producing fewer adverse reactions was developed for use in France in 1992 and approved in the United States in 1993. WHO officials recommend that infants be immunized against Hib and promote the use of combination vaccines containing a Hib component. [23] By March 2006, health authorities in some 106 countries had approved it, 90 of which had added it to their routine schedules. The following figure, based on WHO data, shows the immunization ratios for a representative list of 13 developed nations, excluding Japan where the vaccine was not approved until 2007.

(Figure 3)

Ratios (%) of Hib Usage, 2004

Country	Hib Immunization Ratio
Australia	92
Denmark	89
Finland	98
France	97
Germany	94
Luxembourg	99
Netherlands	97

Norway	94
Spain	96
Sweden	98
Switzerland	98
United Kingdom	93
United States	93

Although the Hib vaccine has become routine in many countries, it was relatively unknown to the average Japanese until the late 2000s.[24] Thus in order to successfully market it, French managers had in effect to *create* a new disease. This was no easy task since unlike other diseases such as the measles, the Hib virus cannot be detected through simple observation. Acceptance was further complicated by the strong perception among many Japanese experts including health authorities of a much lower incidence than in other parts of the world. This perception was reinforced by existing medical practices: Japanese pediatricians generally respond to infantile pneumonia or meningitis by administering antibiotics, making the disease more difficult to detect in routine laboratory tests.

In order to verify with absolute certainty whether or not the Hib virus is present, analyses of blood samples (for pneumonia) or spinal fluid (for meningitis) must be performed. The fact that such tests are not routinely carried out in Japanese medical institutions reinforced critics' claim of a lower incidence. However, according to a 1998 study by Kamiya and others conducted at 876 hospitals in six Japanese prefectures, the Hib virus was the most common cause of meningitis.[25] Representatives of PMC collected and submitted data from this study and others in support of their application to health authorities for approval of ACTHib.[26]

Over the same period, the government's position on vaccines had gradually begun to shift. In 2007 MHLW issued the final draft of *Vaccine Industry Vision: Supporting Measures to Prevent Infection while Aiming to Respond to Societal Expectations of Industry*. This voluminous policy statement was the product of two years of regular discussions hosted by ministry officials. It brought together specialists from academia, regulatory and business organizations such as the International Federation of Pharmaceutical Manufacturers and Association and the FDA (Food and Drug Administration), physicians, foreign and domestic industry representatives, etc.[27] *Vaccine Vision* not only clarified the government's new position on vaccines; it also embodied a larger, more fundamental change in policy. By encouraging vaccination, officials had begun to incorporate more preventive measures into a system that had traditionally emphasized curative care, while also addressing larger problems including a growing elderly population and a shrinking birth rate.[28]

IC-B. Clinical trials in Japan

Procedures for obtaining approval for vaccines are similar to other pharmaceuticals. For companies, this stage of the development process is particularly time-consuming and costly, regardless of the market. In the mid 1980s, regulators, experts and industry representatives in the three major world

pharmaceutical markets, the United States, Europe and Japan, began negotiations to harmonize clinical trial procedures, which would become known as ICH (International Conference on Harmonisation of Technical Requirements of Pharmaceuticals from Human Use). The harmonization of clinical trial procedures was designed to accelerate the drug approval process by alleviating the need for duplication in new markets. The implementation of harmonized GCP (Good Clinical Practices) made possible for companies to submit one set of trial data for drug approvals in markets where the same international standards were adopted.[29]Despite the introduction of the ICH-GCP in Japan in 1996; however, the approval process for many types of medicines still takes on the average longer than in other countries. This feature was also a major cause for Japan's slow Covid vaccine rollout.

In support of their request to PDMA (Pharmaceutical and Medical Devices Agency), representatives of the joint venture submitted data collected in countries where the vaccine was already in use. However, because regulators deemed their data insufficient, it could only be submitted as reference.[30] The French did not anticipate the data acceptance problems and lengthy approval process that followed given the wide acceptance of the vaccine worldwide and large pool of data. Data that had been unnecessary in other countries was often required in Japan.[31] To comply, new trials were conducted in over a two-year period on 122 healthy Japanese infants. PDMA granted approval for ACTHib, which was followed by quality inspections by the Japanese National Centre for Infectious Diseases. Though perceived as long, according to an interview with an official at MHLW, the length of time was not excessive by Japanese standards.[32] It should be noted that delays were especially pronounced in the area of vaccines at that time due in part to the much smaller number of examiners in Japan than in other countries, especially United States. As only one new vaccine had been approved since 1989, Japanese examiners with knowledge and experience in vaccine approvals were then particularly scarce. [33]

Of note is that until recently, relatively few MNEs have even considered entering Japan's vaccine market. GlaxoSmithKline began its entry in 2009 with the approval of *Ceravix* for the prevention of cervical cancer. In March 2012, it announced the establishment of a joint venture with Daiichi Sankyo called Japan Vaccine KK to collaborate on new vaccine development, marketing, distribution and research. Merck (MSD), on the other hand, through its fully owned subsidiary Banyu Pharmaceutical Company, endeavored for many years to make inroads into the Japanese vaccine market with mixed results. As mentioned above, the mumps component was removed from the MMR vaccine, making it unfeasible for Merck to contemplate marketing its innovative mumps vaccine in Japan.[34]

IV-C. Post-Approval Problems

PMC's joint venture with Daiichi was officially established in 1997, and 10 years later, in January 2007, ACTHib was approved. The first shipments of the vaccine did not reach most medical institutions however until nearly two years later in December 2008. Even three years after its initial approval, there was still a two-month waiting list for inoculations due to shortages. These delays were not

caused by any reservations on the part of parents or caregivers regarding the vaccine. ACTHib had received a favorable endorsement from the Japan Medical Association,[35] and was already gaining wider recognition among parents.[36] Indeed, some of those most knowledgeable of Hib were eagerly waiting to have their infants vaccinated. According to a 9 March 2009 article in AERA, Japan's equivalent of Newsweek or Time, an infant in Kyoto died from meningitis caused by the Hib virus. The infant's parents, a gynecologist and a pediatrician, were on a waiting list for the vaccine.[37] Such well-publicized cases served as an endorsement for the vaccine and helped to bring about the French representatives' long-awaited change in the public perception of preventive vaccination as the right new direction for Japanese public health policy.[38]

Once launched, recalls occurred, due to mainly to packaging and appearance issues, resulting in delivery delays, and shortages. One problem that Japanese inspectors regularly cited was the quality of the glass vials, which were initially manufactured and imported from France. Health authorities asserted that some contained superficial defects, namely 'black specks.'[39] The French vials were replaced by new ones manufactured by a Japanese subsidiary of the French glass manufacturer, Pechiney. This situation was highly perplexing and frustrating to French managers. Though some saw these delays as a form of non-tariff barrier, one manager offered a different interpretation: To the Japanese, "*quality* is synonymous with *safety;*" thus, products whose outward visual appearance is low in quality are seen as inherently unsafe. In conversations with his Japanese colleagues and officials, he noticed that the terms, *safety* and *quality*, were often used interchangeably.[40] Despite their initial difficulties, PMC prevailed, and eventually succeeded in becoming the first foreign company ever to launch a pediatric vaccine in the Japanese market.

V. Conclusions

By tracing the changes in the French industry from the 1980s, this chapter shed light on two industries: the global French one and its nationally-focused Japanese counterpart. The new-generation combination vaccines in the 1980s became the major technological catalysts for change in the French vaccine industry. In Japan, policy-makers created an institutional environment that fostered a Pasteurian model of production by self-financing institutes. Since the late 1990s and 2000s, however, there have been signs of change, which have been spurred by Japanese policy makers' concerns about the global spread of infectious diseases, such as H1N1 and the need to protect the ageing population.

The institute-based model in Japan is gradually waning in Japan. In 2011, a joint venture was established between Daiichi Sankyo and the vaccine production division of the Kitasato Institute, known as Kitasato Daiichi Sankyo Vaccine. This move is reminiscent of the Pasteur Institute's establishment of Pasteur Production in 1974, which was followed by its acquisition in 1985 by Mérieux. While only one new vaccine, Hepatitis A and only one combination vaccine, MR were approved between 1989 and 2006, since 2007, health authorities have approved four new vaccines as well as new combinations. They are encouraging greater collaboration—both domestic and global—to further strengthen the industry's global competitiveness. Given the government's favorable stance,

Japan's major pharmaceutical manufacturers, which had previously shown little interest in vaccines, have begun increasing their investments in vaccine research. Given the possibility of new global pandemics, the institutional environment and business model for the vaccine industry are likely to continue to evolve in the years to come.

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