JKS READING ROOM

The Survey on Actual Conditions Regarding Access to Japan Pharmaceuticals

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Pharmaceuticals

June 1998

Japan External Trade Organization

JETRO

Overall Structure of the Survey

1. The Aim of this Survey

Japan has made particular effort to open its markets through deregulation and other measures to contribute to the well-balanced development of the global economy and enhance the quality of life in our nation. It has also aimed to increase imports through several promotional policies. But we cannot deny the continued presence of discontent and criticism abroad that " There are great barriers to the in-flow of goods from overseas into the Japanese market."

In particular, with trade barriers such as tariffs or quotas becoming lower or less frequent, more attention is being paid to government regulations and business practices within Japan.

If these circumstances are the true reasons for disturbing the in-flow of goods from abroad, the repercussions include not only the preventing of the activities of overseas companies in the Japanese market, but also the limiting of opportunities for Japanese consumers to use foreign goods effectively.

Conversely, we also see some government regulations and business practices which are peculiar to individual countries in Europe and America. Because of this we think it is necessary to compare Japanese government regulations and business practices to those in other countries to evaluate them as objectively as possible.

Regarding the actual conditions of access to the Japanese market, it is important to objectively grasp the characteristics of the government regulations and business practices and the influence they have on market entry. The above should be done to reach an objective understanding, both at the domestic and foreign level of the conditions of access regarding the Japanese market and to advance constructive discussion about how Japanese government regulations and business practices should be.

From these viewpoints, this report, due to the requests of foreign countries and the existence of price gaps, focuses on a particular chosen industry or area every year. We produce concrete international comparisons with US and European countries and

analytical surveys on government regulations, business practices and other market forces relating to certain industries.

The aim of this report is to stimulate a wide range of opinions by providing materials for further discussion on the nature of Japanese government regulations, business practices and other market forces.

2. The Survey Method

The following structure was adopted for the survey.

(1) Establishment of Advisory Council

To implement this survey from an objective and international perspective we have established an “Advisory Council” comprising of nine members who are experts in economics and law and are very active inside and outside of Japan. The Council gave suggestions about concrete implementation of the survey at its opening stage, examined and evaluated the contents from a coordinated viewpoint at the closing stage and participates in the final drafting of the reports.

(2) Survey Method

We have implemented this survey by comparing Japan to some major European countries and the United States. In order to objectively evaluate each regulation and business practice in Japan, we focus on several key points in the surveyed industries, and then investigate the situation overseas for those specific points. The differences have then been highlighted.

In the domestic survey, we performed analyses by first collecting documents and then implementing a wide-ranging interview-based investigation. In the overseas part of the survey, JETRO offices abroad conducted the survey through the collecting of documents and the interviewing of business people in order to identify the actual situation of the surveyed industries in each respective country.

In addition, in the course of the investigation we gathered experts’ opinions about each surveyed field as necessary.

In the implementation of this survey, the members of the Advisory Council agreed to the following common approach. Namely, the aim of the research is to determine which of the following three reasons apply when there are large price differences between foreign goods imported into Japan and the price of these goods in their domestic market:

① Whether this difference might be attributable to high distribution costs within Japan
②Whether the demand in the Japanese market is fairly insensitive to price(pricing to the market)
③ Whether the cost for importing firms of meeting Japanese regulations is high.

In reality these three factors are possibly related. There is also a limitation concerning the quantity of information available when the investigation takes place, so it is difficult to put together a decisive report. Nevertheless, in this survey, considering phenomena appropriate to the surveyed industries, we decided to analyze the problems of market access in each field with this common basic viewpoint in mind.

3. Regarding Contents of the Survey

It is the opinion of the Advisory Council that this survey report does not take up all the problems comprehensively, but rather emphasizes several important points. In addition within each of these important points some issues could not be fully examined due to limitations of the methodology. In the future, because we may receive further suggestions, both domestic and foreign, it may be necessary to continue with the research.

Members of the Advisory Council

	Frans Andriessen	(Utrecht University)
	David Flath	(North Carolina State University)
	Takatoshi Ito	(Hitotsubashi University)
◎	Motoshige Itoh	(Tokyo University)
	Anil K. Kashyap	(University of Chicago)
	Masahiro Murakami	(Yokohama National University)
	Tetsuji Okazaki	(Tokyo University)
	Gary Saxonhouse	(University of Michigan)
	John Sutton	(University of London)

◎ Chairman

Advisors

Masahiro Ohmori	(Josai University)
Yosuke Okada	(Shinshu University)

Contents

Preface

◇ The Japanese pharmaceutical market is said to be the second largest in the world following that of the U.S. and the interest of foreign manufacturers in this market is high. The U.S. and European countries have taken up pharmaceuticals as a topic in individual economic discussions and have requested improvements to the pharmaceutical approval procedures and to the Japanese way of determining pharmaceutical prices under the health insurance system. Moreover, as approximately 25.9% of the national health care expenditure, which has reached as high as ¥28.6 trillion yen (estimated in fiscal 1996), is due to pharmaceutical expenses, there has been an increasing interest in pharmaceuticals even inside Japan, and this figure is pointed out as being higher than that in other countries.

◇ Pharmaceuticals are categorized into two groups: ethical pharmaceuticals, which are used based on doctors' prescriptions, and general pharmaceuticals, which consumers can purchase at pharmacies and drug stores without prescriptions. In Japan, everyone is obliged to be covered by some form of health insurance and pharmaceuticals covered by insurance, namely ethical pharmaceuticals, are priced by the government. The cost of the pharmaceuticals used is reimbursed by health insurance. On the other hand, the cost of general pharmaceuticals is not reimbursed by health insurance, Therefore, official regulations are different for ethical pharmaceuticals and general pharmaceuticals. Since distribution and business practices are also different, it is difficult to discuss ethical pharmaceuticals and general pharmaceuticals together. Moreover, looking at the scale of production, the total value of all domestically produced and imported pharmaceuticals in Japan in 1996 was ¥6,881.8 billion, of which ethical pharmaceuticals represented 85.6% (¥5,881.8 billion).

◇ As a result, ethical pharmaceuticals are the focus of research in this report. The survey clarifies the effect that Japanese regulations, systems, and business practices in the area of pharmaceuticals have on market entry by foreign firms, comparing the situation in Japan to overseas markets. This survey aims thereby to provide information for the study, from an international point of view, on regulations and business practices in Japan's pharmaceuticals market More specifically, three areas were studied in tens of official regulations: 1) regulations governing importation and domestic distribution; 2) approval system for pharmaceuticals; and 3) systems concerning prices. Other areas were studied in tens of distribution and business practices: 4) factors in the selection of pharmaceuticals and sales methods; and 5) business relations in the distribution system. A summary is as follows.

1) In Japan, the Ministry of Health and Welfare regulates the importation and domestic distribution of pharmaceuticals under the "pharmaceutical Affairs Law." As in the U.S. and European countries, before they are marketed, pharmaceuticals must be approved by the government in order to guarantee safety. On the other hand, in regards to the business parties that handle pharmaceuticals, including the importation of pharmaceuticals, their subdivision, and sales to medical institutions, it is necessary to obtain an import and sales business license, a manufacturing license and a wholesale sales business license, respectively. It has been pointed out that this system is complicated and multilayered when compared with the U.S. and European countries.

2) With regard to the approval system for pharmaceuticals, in Japan, the acceptance of foreign clinical trial data is controlled because of the differences of ethnic factors, and so on, between Japanese and foreigners. In the U.S. and European countries, the foreign clinical trial data ate accepted in principle, but in fact the cases of acceptance have not increased so

far. With regard to this issue, an international framework is currently being formed between Japan, the U.S., and European countries in order to promote the harmonization of pharmaceutical approval standards. Moreover, the time required to obtain approval in Japan, either the standard administrative processing period or the actual required period, is longer than in the U.S. and European countries. This has been pointed out as a factor hindering pharmaceuticals manufactured overseas from gaining access to the Japanese market.

3) With regard to systems concerning prices, we compared Japan, the U.S., and European countries from the two viewpoints of regulations governing the pricing of individual pharmaceuticals and those governing the total budget for pharmaceutical expenses. In European countries, there are regulations governing both pricing and the total budget. In Japan there are regulations governing only pricing, and in the U.S., there are systems governing only the total budget. As a result, in European countries, where there are two types of regulations and both pricing and the total budget are controlled, prices themselves are an important factor in the selection of pharmaceuticals. In turn, pharmaceutical prices in European countries are relatively lower than in Japan. On the other hand, in the U.S, where there are only rules governing the total budget, private health insurance is central and in turn the system most reflects market mechanisms. Therefore, the pharmaceuticals which have high therapeutic effects and can be expected to reduce the total medical expenses are said to be highly priced in response to their efficacy and cost effectiveness.

In Japan, in principal there is no total budget regulation for insurance reimbursement, so it is said that the prices of individual pharmaceuticals are controlled from the viewpoint of curbing medical expenditure. In turn it has been pointed out that it is difficult to set insurance reimbursement prices reflecting cost and efficacy. For this reason it has been pointed out that it is hard for new pharmaceuticals with high efficacy and competitiveness to be priced to meet market value and to enter into the market in Japan. At present, introduction of a “Japanese-style reference price system” is under consideration, The system has a potential for individual pharmaceuticals to be priced based upon the market mechanism, so this system deserves praise from the viewpoint of market access. On the other hand, as for “innovative new pharmaceuticals”, which are developed at a high cost, it has been cited that introduction of a system whereby reimbursement by health insurance is at prices which conform to the free market, and which does not discourage pharmaceutical manufacturers from developing new pharmaceuticals, is also necessary from the viewpoint of market access.

4) With regard to factors in the selection of pharmaceuticals and sales methods, it has been pointed out that it is necessary to hire many medical representatives (MRs) in Japan. Since medical practice and the dispensing of pharmaceuticals are as of yet not completely separated, doctors have strong authority in selecting pharmaceuticals. Pharmaceuticals expenses are reimbursed to medical institutions by a “fee-for-services system” in principle. In addition, the price gap between purchasing price and insurance reimbursement price belongs to medical institutions as a “margin”. SO medical institutions have an incentive to use more expensive and greater amounts of pharmaceuticals. Therefore, a highly elaborate marketing system centered around MRs and targeting doctors has a direct influence in boosting sales of pharmaceuticals. Under the present condition, it is necessary for foreign entrants not only to introduce competitive products but also to prepare a highly elaborate marketing system. And it is pointed out that this leads the increase of initial investment costs.

5) With regard to business relations in the distribution system, it has been cited that many

wholesalers exist in the Japanese pharmaceutical distribution system and manufacturers must trade with large numbers of these wholesalers. Moreover, business practices called “gross price for bulk purchases” and “temporary delivery and temporary payment” exist between wholesalers and medical institutions, and these practices have been criticized because they place burdens on manufacturers. Not only are these unique Japanese distribution and business practices hard to understand for foreign corporations, but they also entail substantial initial investment costs. consequently, they have been pointed out as factors which hinder foreign corporations from gaining access to the market.

Major Points of Issue

I. Official Regulations

1. Regulations Governing Importation and Domestic Distribution

Some regulations in Japan governing the importation of pharmaceuticals to their domestic distribution apply to products themselves and others apply to business operators. In addition, one personnel requirement for a license to conduct wholesale business is that a supervisory pharmacist be assigned to each business place. If such a regulatory system is considered to be complex and multiplex when compared with surveys of the United States and European countries (hereinafter, the U.S. and European countries), it could be a factor that hinders market access.

In **Japan**, the Ministry of Health and Welfare (hereinafter, MHW) regulates pharmaceuticals, from their importation to domestic distribution, on the basis of "the Pharmaceutical Affairs Law." The main targets for regulation are products themselves and business operators that handle them. In the case of regulations governing products, imported products like domestically manufactured products must obtain from the Minister of Health and Welfare approval in efficacy and safety according to standards in the Pharmaceutical Affairs Law.[1]

The **U.S.** and **European countries** require approval from respective regulatory authorities[2] before products are put on their markets, regardless of whether the products are imported or manufactured domestically.

<Multiple business licenses are required in Japan>

In the case of **Japan**, business operators who import pharmaceuticals into Japan for business purposes must obtain an import and sales business license from the Minister of Health and Welfare.[3] When imported pharmaceuticals are subdivided,[4] it is necessary to obtain a manufacturing license.[5] If imported pharmaceuticals are sold to medical institutions and so forth, one must obtain not only an import and sales business license, but also a wholesale business license, from the governor of the prefecture.[6]

In the **U.S.** and **European countries**, there is no licensing system for importers of pharmaceuticals. However, if imported pharmaceuticals are subdivided, all surveyed countries require a manufacturing license to be obtained. As to the wholesaling of

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[1] Article 14 of the Pharmaceutical Affairs Law. "Approval" applies to each product and relates entirely to whether the product for which application has been made is suitable or not as a pharmaceutical, etc., that is, whether its quality and characteristics are suitable or not, and whether it is an effective and safe pharmaceutical, etc. or not.

[2] US: Food and Drug Administration (FDA), Britain: Medicines Control Agency (MCA), France: Ministry of Health (Ministère de la Santé), Germany: Federal Pharmaceutical Agency (BfArM).

[3] Article 22 of the Pharmaceutical Affairs Law

[4] "To subdivide" refers to the action to which take out drugs from their original container or wrapper and repackage them with other containers or wrappers without causing to change the quality for the purpose of meeting the public needs.

[5] Article 12 of the Pharmaceutical Affairs Law

[6] Articles 24, 25 and 26 of the Pharmaceutical Affairs Law. The wholesale business is defined as the business to sell or give drugs only to a proprietor of a pharmacy, a manufacturer, a seller, or a proprietor of medical institutions or veterinary clinic, and is described as "wholesale general business" in the Pharmaceutical Affairs Law.

imported pharmaceuticals, in the case of the **U.S.**, a wholesale business license from Federal Drug Enforcement Agency (DEA) is required. As to wholesaling imported pharmaceuticals in the **European Union (E.U.)**, if a business operator who has received marketing approval[7] for pharmaceuticals wholesales them, there is no need to obtain a wholesale sales business license. Thus, as regards regulations governing business operators who subdivide imported pharmaceuticals and wholesale them, in the case of **Japan**, three types of license are needed; these are an import and sales business license, a manufacturing license, and a wholesale sales business license. On the other hand, in the **U.S.**, two types of license are required, namely, a manufacturing license and a wholesales sales business license, whereas only one license, namely a manufacturing license is necessary in **EU member countries**, when business operators subdivide imported pharmaceuticals.

<Assigning supervisory pharmacist is required for wholesale license in Japan>

In **Japan**, there is a personnel requirement for a wholesale business license, in that a supervisory pharmacist[8] with legal qualification[9] must be assigned to take charge of the supervision of pharmaceuticals.[10] In the **U.S.**, there is a personnel requirement that applies to licenses, in that it is necessary to appoint a supervisory pharmacist and register that person's career record. However, supervisory persons are not limited to pharmacists with legal qualification.

《Conclusion》

In **Japan**, as well as in the **U.S.** and **European countries**, the government regulates the importation of pharmaceuticals and their domestic distribution. As far as products are concerned, **Japan** and the **U.S.** and **European countries** require to obtain government approval before putting a product on the market. In the case of business operators, in **Japan**, when one is engaged in the business of importing pharmaceuticals, subdividing them and selling them to medical institutions, it is necessary to obtain licenses for an import and sales business, a manufacturing business and a wholesale business, respectively. In the **U.S.**, there are licenses relating to manufacturing and wholesaling businesses, but there is no business license for importing pharmaceuticals. In **EU member countries**, it is necessary to obtain a manufacturing license for subdividing imported pharmaceuticals, but if one obtains approval to market the pharmaceuticals concerned, it is not necessary to obtain business licenses for the importation and domestic sale of these products. In this way, licensing regarding the sales of imported pharmaceuticals in Japan is different from the situation in the U.S. and European countries, and in turn it is pointed out that burdens on new entrants to the market.

Moreover, in both **Japan** and the **U.S.**, there is a personnel requirement for a wholesale business license whereby one is obliged to appoint a person in charge of supervision. In

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[7] In EU regulation, this approval is specifically called "marketing authorization."

[8] "Supervision" means the technical work relating to the dispensing of medicines and the handling of pharmaceuticals at pharmacies, and that a pharmacist supervise pharmacies to ensure that pharmaceuticals there are handled by a specialist. These provisions concerning pharmacies (Pharmaceutical Affairs Law, Article 8) apply correspondingly to wholesale general sales businesses.

[9] Pharmacist is a person who has a license given from the Minister of Health and Welfare, which is qualified by passing a national pharmacist examination stipulated under the Pharmacist Law.

[10] Since March 31, 1997, deregulation measures have been introduced. For example, a pharmacist is now allowed to work concurrently at different places where only samples are handled.

Japan, one is obliged to assign a pharmacist with legal qualification as the supervisory person at each business place. In the **U.S.**, one is obliged to register the career record of the supervisory person with the regulatory authorities, but there is no regulation that the supervisory person must be a pharmacist. In this way the regulations in Japan governing the import of pharmaceuticals to their domestic distribution are different from those of the U.S. and European countries in comparison with the necessity to obtain an import and sales license and the personnel requirement for a wholesale business license. It tends to be indicated that they could be factors hindering market access.

2. Approval System for Pharmaceuticals

When applications for new drug approvals are submitted in Japan, foreign clinical trial data are accepted as appended documents, but their use is limited. Also, it is said in effect to take two to three years for applications to be examined and approved in Japan. It has been pointed out that the regulations and long examination time related to drug approval applications could be a factor that hinders market access when new drugs are introduced to Japan.

(1) The use of foreign clinical trial data

<The use of foreign clinical trial data is limited in each country surveyed>

When applying for approval for new pharmaceuticals, whether in **Japan** or the **U.S.** and **European countries**, clinical trial[11] data have to be attached in the form of documents which prove the efficacy and safety of the pharmaceuticals.[12] But in regard to the results of foreign clinical trial data, because there are worries that the safety, efficacy, direction and dosage of the pharmaceuticals concerned could be affected by ethnic factors, regulatory authorities in **Japan** and the **U.S.** and **European countries** have prescribed policies concerning the handling of such data. In **Japan,** in the case of absorption, distribution, metabolism and excretion tests, tests to determine dosage levels and comparative clinical trials[13] where there are differences of ethnic factors and others between Japanese and foreigners, it is necessary in principle to use clinical trial data that have been collected in Japan[14].

In the **U.S.**, the Food and Drug Administration (FDA) accepts applications for drug approvals which are based only on foreign clinical data under certain conditions,[15] but it is

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[11] These trials involve the process of verifying the efficacy and safety of drug candidates on human beings, whose effects and toxicity have previously been examined by means of experiments in test tubes and on animals.

[12] Japan: the Pharmaceutical Affairs Law; USA: the Federal Food, Drug, and Cosmetic Act; Britain: the Medicines Act 1968; France: Public Health Law; Germany: Arzneimittelgesetz (Pharmaceutical Affairs Law).

[13] Experiments which apply to part of phase II clinical trials and phase III comparative trials (see Appendix 1).

[14] Notification from the Pharmaceutical Affairs Bureau No. 660 dated June 20, 1985, in the notice by the Director of the Pharmaceutical Affairs Bureau of the MHW; Notification from the Pharmaceutical Affairs Bureau No. 231 dated March 12, 1986, in the notice by the Director of the Pharmaceutical Affairs Bureau of the MHW.

[15] Requirements for accepting this kind of data are: a) the foreign data are applicable to the US population and US medical practice; b) the studies have been performed by clinical investigators of recognized competence; and c) the data must be considered valid without the need for on-site inspections by the FDA,

recommended to have prior consultations with the FDA. In the **U.K.**, clinical data which have been collected abroad are accepted in principle, as long as they are prepared in English. In **France**, in principle the foreign clinical trial data is said to be accepted when the applications for the drug approval is filed, as long as the clinical trials have been conducted complying with the GCP (Good Clinical Practice, which will be discussed later on) and is also submitted along with the designated reporting style.

But in fact, in the case of the **U.S.** and **European countries**, it is claimed little progress has been made in accepting foreign clinical data. According to a survey carried out by a British research company on 35 international pharmaceutical enterprises[16] from 1986, only four products from three European enterprises which applied for drug approvals with foreign clinical trial data could actually receive approval.[17] In addition, there are no cases in which applications for drug approvals based on clinical trial data collected only in **Japan** have been accepted in the **U.S** and **European countries**.

<Efforts to make an international rule have been continued at ICH>

Many pharmaceuticals show similar characteristics of effect and efficacy in each region. Therefore, the view has become established that requiring wide-ranging clinical trials for all pharmaceuticals to be repeated in each country causes a delay in introducing new methods of treatment and wastes pharmaceutical development resources. As a result, the ICH (A Japan-America-Europe conference on the harmonization of the requirements for pharmaceutical registration),[18] has been continually engaged in formulating "guidelines regarding the handling of ethnic factors in clinical trial data" in relation to the acceptance of foreign clinical trial data. However, even the ICH guidelines, which received final agreement between Japan, the U.S., and the European countries in February 1998, failed to provide complete conditions for accepting this kind of data and only stated, with regard to the acceptance of foreign clinical data, that each country should carry out its own independent bridging studies,[19] namely, supplementary trials, as the need arises.

The ICH has also been considering the rules to be followed when conducting clinical trials. "Standards for the operation of clinical trials conducted for the purpose of collecting documents for applications for approval of new drugs" were finally agreed on in May 1996, and **each member nation of the ICH** is proceeding with the standardization of methods for the operation of clinical trials, known as GCP (Good Clinical Practice). In **Japan**,

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or if the FDA considers such an inspection to be necessary, the FDA is able to validate the data through an on-site inspection or other appropriate means. (21 CFR § 314.106).

16 17 European companies, 8 American companies, 10 Japanese companies

17 The survey was carried out by the Center for Medicines Research International. Three of the four products receiving approval were submitted to the FDA in America by European enterprises, and, in the case of the remaining product, a European enterprise applied to the regulatory authorities in another country in Europe.

18 International Conference for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. The Japanese, American and European governments and private sectors are cooperatively promoting the harmonization of standards for pharmaceutical approvals.

19 This refers to trials which are additionally conducted in one country in order to extrapolate the data collected in that country to another country in the form of a foreign clinical data package. This includes trials which produce pharmacodynamic or clinical trial data regarding the efficacy, safety, directions for use and dosage of the pharmaceuticals concerned.

new GCP[20] based on the ICH's final agreement has been in operation since April 1997.

However, since the new GCP has been in effect, clinical trials are said to have been delayed in **Japan** for reasons such as the following: 1) it has been hard to get agreement from patients participating in clinical trials as the concept of providing explanations for and obtaining patients agreement in writing is still new, and 2) operation systems[21] which correspond to the new rules have not been established yet by either the manufacturers that commission clinical trials or the medical institutions that implement them.

(2) Time required to obtain approval

Regarding the time required to obtain approvals, a standard administrative processing period is established in **Japan**, the **U.S.** and **European countries**. In **Japan**, an 18-month standard administrative processing period, based on the "action program framework for improving market access" of the government and ruling party's Headquarters for Promoting Strategies in regards to External Economies, was established in 1985 (see figure 1-2).

<Japan strives to reinforce the review system>

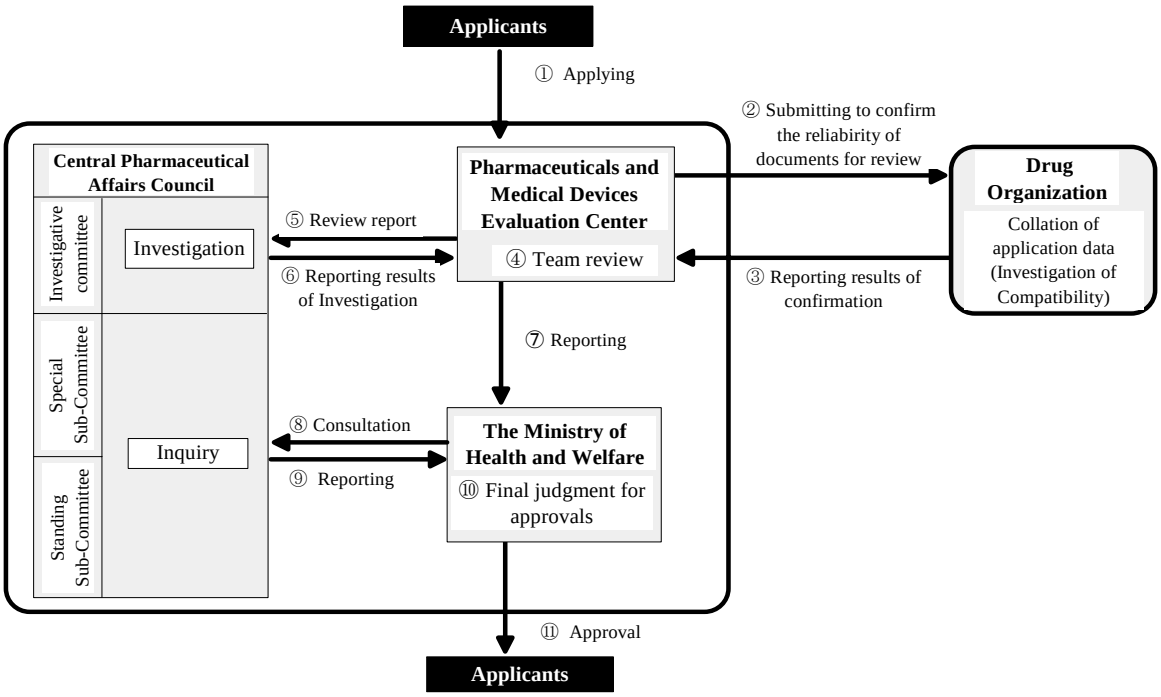
In **Japan**, pharmaceutical approvals are that the Minister of Health and Welfare examines the efficacy, safety and quality of pharmaceuticals based on the findings of the Central Pharmaceuticals Affairs Council (see figure 1-1).[22] The standard administrative processing period is prescribed as 18 months, starting from the date when the application for approval is submitted. However, it has been claimed that, after adding other requirements such as the time required to collect additional data, it will in fact take two and a half to three years. Charting a course to shorten the time to obtain approvals, since July 1997, MHW persuaded the National Institute of Health Sciences and Pharmaceuticals and Medical Devices Evaluation Center, and the Organization for Drug ADR (Adverse Drug Reaction) Relief, R&D Promotion and Product Review (Drug Organization), to share responsibility for drug approval reviews with the main body of MHW in order to increase the number of people who deal with reviews (see figure 1-1). It is unknown to what extent time to obtain approvals has been shortened at this point.

[20] The former GCP was issued in the form of a notice by the Director of the Pharmaceutical Affairs Bureau in 1989. The new GCP was legally introduced by means of the Revised Pharmaceutical Affairs Law, which was officially proclaimed in 1996, and has been in effect since April 1997.

[21] Problems related to preparation of standard operation procedures (for both manufacturer and medical institution); assignment of clinical research coordinator (for medical institution); and assignment of clinical research monitor (for manufacturer) are some of the examples.

[22] Article 14 of the Pharmaceutical Affairs Law

Figure 1-1: Review System of Approval in Japan



Source : The MHW, "*Iyakuhin Sangyo no Shoraizo wo Kangaeru Kondankai Hokokusho* (Report of the Conference concerning the Future of the Pharmaceuticals Industry)" 1997

<The U.S. and European countries have been in progress to shorten the review time>

In the **U.S.**, the FDA approves new drug applications (NDAs). The FDA conducts a preliminary review to consider whether it will accept the submitted application form in the first 2 months. The FDA formally accepts an application after concluding the applicant deserves a substantive review, and then the FDA takes 6 months, calculated from the day of formal acceptance, to perform a review.[23] During the review period, the FDA decides whether the NDA a) is approved, b) requires additional review, or c) is rejected. In many cases, additional review is required, so in 1996 the FDA's average time required to approve an application, from the date when the FDA formally receives an application to the date when the FDA gives approval, was 17.8 months. In the U.S., the Prescription Drug User Fee Act was enacted in May 1992 with a five-year period of validity,[24] in order to shorten review time. In accordance with this law, review time is said to have been remarkably shortened[25] by increasing the number of FDA staff through the financial support of pharmaceutical manufacturers.

In **E.U. member countries**, manufacturers must receive marketing approval to sell new pharmaceuticals by means of one of the following three methods. In the case of selling products in several E.U. member countries, manufacturers receive approvals in accordance with a "centralized procedure," or through a "mutual recognition procedure."[26] In the

23 21CFR § 314.100

24 A 5-year extension was decided on in 1997

25 In 1992 the average review period was 29.9 months.

26 First approval is received in one of the E.U. member countries. After this first approval has been received, review authorities in other EU member countries confirm the result of the approval made in the initial country.

case of selling products in only one of the E.U. member countries, manufacturers receive approvals in accordance with that member country's system ("independent national assessment"). However, as the "centralized procedure" is currently only stipulated when making applications for approval for biotechnology products and innovative new products, manufacturers that aim to sell their products in the whole E.U. region generally use the "mutual recognition procedure."

Under the "centralized procedure", the aim is to complete administrative processing within 300 days from the date when an application form is received by the EMEA (European Agency for the Evaluation of Medicinal Products). However, it is necessary to submit the purpose for the application and a submission schedule to the EMEA at least 4 months before submitting an application form.

The review periods in the **U.S.** and **European countries** are shown in figure 1-2.

Figure 1-2: Time Required to Review in Surveyed Countries

Country	Standard Administrative Processing Period	Actual Time Required
Japan	18 months	2.5～3 years
U.S.	Document review 2 months＋ Substantive review 6 months = 8 months	17.8 months（1996）
E.U.	300 days	about 1 year
U.K.	120 days（90 days extension is possible）	a little less than 1 year（1994～95）
France	120 days（90 days extension is possible）	200～220 days (1996)
Germany	7 months	2～3 years

Source:：Japan: MHW and interviews with industrial sources,
U.S., E.U., the U.K., France, Germany: Studies by JETRO Centers Overseas

《Conclusion》

Regarding the use in **Japan** of foreign clinical trial data, in principle, data obtained from absorption, distribution, metabolism and excretion tests to determine dosage levels, and comparative clinical trials, where there are differences of ethnic factors and others between Japanese and foreigners, are not accepted. In the **U.S.** and **European countries**, foreign clinical trials are accepted as appended documents under certain conditions, but it is said that there has been little progress in terms of such data actually being accepted. Consequently, it is pointed out that the problem of accepting foreign clinical data does not arise only in the case of entering the Japanese market. Concerning this problem, in order to provide the best pharmaceuticals to patients as quickly as possible, it is necessary to establish common rules, as international as possible, relating to the mutual use of foreign clinical data. It has been pointed out that in situations where part of the clinical trials have to be performed repeatedly in Japan, clinical trials are being delayed and this is a factor that hinders market access when applications for new drug approvals are submitted in **Japan**.

In **Japan**, the time required to obtain approvals is much longer than in the U.S. and European countries, in terms of both the standard administrative processing period and the actual time required. On the other hand, in the **U.S.**, it has been pointed out that the FDA takes a fairly long time for prior consultations with manufacturers. The long review

period in Japan is a problem at home and abroad, but improved access to the Japanese market for foreign pharmaceuticals is expected to be achieved by shortening the approval period. In the "Joint Status Report on the U.S.-Japan Enhanced Initiative on Deregulation and Competition Policy" which was announced in May 1998, following directions are stated: ①Expand acceptance of foreign clinical trial data through the incorporation of ICH guidelines into Japanese domestic regulations by the summer of 1998, and use an acceptance process that is transparent and avoids inappropriate delays; ②Shorten the approval processing period for new drug applications to 12 months by April 2000, and to further speed the introduction of innovative new pharmaceuticals, significantly shorten approval times, particularly for priority drugs.

3. Systems Concerning Prices

In Japan, the MHW determines the reimbursement prices for individual brands of pharmaceuticals used under the health insurance system (the "pharmaceutical tariff" system). It has been pointed out that this system is seen as a factor which impedes manufacturer access to the market. This is because even new innovative pharmaceuticals developed at a high cost cannot be priced sufficiently to meet development outlay, because prices are not allowed to reflect supply and demand conditions in the market, and so on.

(1) Health Insurance Systems and Pricing Mechanisms in Each Country

In **Japan** and **European countries**, a public health insurance system, and in **the U.S.**, private health insurance, cover most of the costs of medical services for citizens. Therefore, the health insurance system of each country participates in the pricing of pharmaceuticals, which form part of medical services. The differences between Japan, European countries, and the U.S. were surveyed mainly on the basis of three factors; the difference in the management body for health insurance in each country, the pricing of individual pharmaceuticals caused by the difference in the health insurance system, and the ways used to curb expanding national health care expenditure, which have recently become a serious problem in advanced countries, and their influence on prices.

<Japan determines insurance reimbursement prices without a total budget restriction>

Japan has adopted a "social insurance system" which obliges every citizen to be insured by some form of public health insurance. There are seven organizations of public health insurance such as the national government, municipal governments, health insurance unions, cooperatives, and so forth. The government pays 13% to 52% of the benefits to these insurance organizations out of its financial resources.

Patients are provided with the necessary pharmaceuticals by medical institutions and, in principle, expenses for these pharmaceuticals are reimbursed to medical institutions out of health insurance at reimbursement prices determined by the MHW for each brand.[27] In

[27] The price list which shows the names of the pharmaceuticals that can be covered by health insurance and their reimbursement prices is called the "pharmaceutical tariff." When pharmaceutical manufacturers want reimbursement prices to be calculated, they have to apply to the MHW. However, if pharmaceuticals which cannot be covered by health insurance are used even in part, all the medical expenses, including not only the pharmaceuticals, but also the medical examination expenses, have to be paid by the patient (health insurance does not apply). Therefore, in practice, if pharmaceuticals are not listed on the "pharmaceutical tariff", they will not be used in the medical treatment covered by health insurance.

the actual market, although medical institutions purchase pharmaceuticals from wholesalers at prices lower than the reimbursement prices, the reimbursement prices are paid back to the medical institutions. The difference between the reimbursement price and the actual purchasing price medical institutions pay is called the "pharmaceutical price profit differential,"[28] which is a source of earnings for those institutions.

In **Japan**, it has been pointed out that due to the method of calculating reimbursement prices, pharmaceuticals are not priced sufficiently to reflect their efficacy and the system inhibits competitive pricing.

For example, looking at the way of calculating prices for "innovative new pharmaceuticals", when such reimbursement prices are calculated, in principle, the "price setting by comparison to similar pharmaceuticals" is used. In this system, first, from among the pharmaceuticals whose reimbursement prices have already been determined, pharmaceuticals having similar efficacy and effects are selected as comparatives. New prices are then determined according to the prices of the selected pharmaceuticals.[29] This system has been criticized both abroad and domestically because, especially in the case of "innovative new pharmaceuticals" with high development costs, the prices calculated by the MHW are too low and the development costs cannot be recovered. Even under the current system, development of new pharmaceuticals is encouraged by a merit premium for "innovative new pharmaceuticals, [30] " and so forth. However, at the present time the merit premium for innovative drugs has been applied to only one ingredient and two items so far. Therefore, it has been pointed out that, since reimbursement prices are not set at levels manufacturers wish, foreign manufacturers who have competitive new pharmaceuticals have to consider postponing the introduction of new pharmaceuticals into the Japanese market.

Moreover, "improved new drugs"[31] are expected to be comparatively highly priced because they are recognized as having effects equal to "innovative new drugs" under the "price setting by comparison to similar pharmaceuticals system," even though their development costs are actually lower than those "innovative new drugs." Therefore, it has been said that manufacturers in Japan are oriented towards developing "improved new drugs." _

Reimbursement prices for so-called "long-time listed pharmaceuticals", those which have

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[28] The pharmaceutical price profit differential is estimated to total about ¥1.3 trillion, which is about 20% of the ¥7 trillion in total pharmaceutical expenses that form a part of total national heath care expenditure in Japan. Medical institutions explain that the costs they incur in providing pharmaceuticals to patients (personnel costs, pharmaceutical management costs, etc.) exceed the pharmaceutical price profit differential. In addition, the fees paid for technical services provided by doctors by medical insurance are held low so that the pharmaceutical price profit differential has become an essential means for management to supplement the fees obtained from technical services.

[29] With regard to pharmaceuticals for which comparative pharmaceuticals cannot be selected, prices are determined by a "cost accounting system" which calculates prices by adding up production costs, selling, general and administrative expenses, business profits, distribution costs, and so forth.

[30] In 1995, according to a proposal by the Central Social Insurance Medical Council, rules were reviewed on applying for the merit premium (for innovativeness, usefulness and marketability).

[31] New pharmaceuticals developed by improving parts of innovative new pharmaceuticals already developed. Also called "*Zoro Shin*," meaning " new imitation."

been listed on the "pharmaceutical tariff" for a long time, are in principle reviewed every two years. The reviewing method is that the MHW researches actual market prices through interviews with wholesalers and medical institutions, and determines the new prices by adding a fixed price balance (reasonable zone)[32] to the weighted averages of the actual market prices. In the actual market, to gain a higher "pharmaceutical price profit differential," medical institutions demand discounts exceeding the reasonable zone, so that every time prices are reviewed, the prices of the "long-time listed pharmaceuticals" tend to decline.[33] Therefore, it has been pointed out that once even pharmaceuticals with high efficacy become old, they are not priced sufficiently to reflect their value any more.

In addition, there are various exceptional rules for price revisions. For example, there is a rule called the re-calculation rule. If certain pharmaceuticals are sold in a far greater quantity than initially estimated,[34] the MHW can reduce their prices by 25% up most at the next round of reviewing. In the current "pharmaceutical tariff" system it has been pointed out to be difficult for the prices to reflect the market supply and demand.

On the other hand, in relation to the way in which to curb pharmaceutical expenses, **Japan** has adopted a "fee-for-services system" in which pharmaceutical expenses are reimbursed to medical institutions in accordance with the amount used. A system which controls the expenses within a total budget, such as a "flat payment system," has not been adopted as in the U.S. and European countries(to be focused on later in this document). Therefore, it has been pointed out that the Japanese system tends to set the reimbursement price of each pharmaceutical[35] rather low.

Under the current system in Japan, it can be seen that medical institutions tend to supplement medical service fees, are said to be lower than those in the U.S. and European countries, by gaining a "pharmaceutical price profit differential" and it is pointed out that this results in increasing the usage of pharmaceuticals. Moreover, it has been pointed out

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[32] Reasonable zone. This has been gradually reduced from 15% in 1992, to 13% in 1994, 11% in 1996, 10% in 1997 (8% applied to the initially marketed products whose later marketed products (generics) have already listed on the pharmaceutical tariff) and 5% in 1998 (2% applies to long-time listed pharmaceuticals). (Refer to footnote 54, for explanations of the initially marketed products and the later marketed products.)

[33] One particular general anesthetic has been sold for more than 45 years in Japan and had a market share of more than 50% among similar types of pharmaceuticals. However, because of pharmaceutical price reductions, this anesthetic has been unprofitable for more than ten years. The manufacturing facilities are becoming old and about one billion yen of investment was required for renovation. Therefore, in autumn 1997, the manufacturer announced that it had decided to stop selling the drug by the end of March 1998. In fact, the company was strongly requested by anesthetists all over the country, to continue selling the anesthetic so it withdrew the announcement.

[34] With regard to the pharmaceuticals whose prices are calculated by the cost accounting system, if the market size expands to double or more than double the estimation made when the pharmaceuticals were initially admitted to the official list, and also exceeds ¥15 billion annually, prices will be re-calculated. With regard to pharmaceuticals whose prices are calculated by the similar effect comparison system, the prices will be re-calculated if the preconditions (e.g. usage, types of patients to which the drug applies, etc.) of pricing change and lose their similarity to those for comparative pharmaceuticals, if the market size grows substantially, or if the efficacy of the pharmaceuticals becomes enhanced after they are admitted to the official list.

[35] In the revision to official pharmaceutical prices for fiscal 1998, the MHW cut prices by an average of 9.7%.

that new pharmaceuticals with high reimbursement prices[36] tend to be selected, as the same discount rate applies when doctors and medical institutions try to maximize the "pharmaceutical price profit differential" (the so-called "shift to new pharmaceuticals")[37]. In the summer of fiscal 1997, however, the MHW and the ruling party's Health Insurance System Reform Council successively presented proposals for radical reforms to the health insurance system and the current method of setting the price of pharmaceuticals was abolished. A proposal was put forward to change to the so-called "Japanese-style reference price system" similar to the **German** reference price (to be mentioned later). In November 1997, the government established the "Health Insurance and Welfare Council," a consultative body under the direction of the Minister of Health and Welfare and made specific inquiries concerning this issue. As of June 1998, the council is still continuing with its inquiries. There is some support for the "Japanese-style reference price system", as it is preventing the increased use of pharmaceuticals and the "shift to new pharmaceuticals" by removing the "pharmaceutical price profit differential." However, the U.S. has requested Japan withdraw the introduction of the "Japanese-style reference price system", in which reference prices actually just become the maximum official price, and has requested that, even should this system be introduced, a rule be made that the price of products with remaining patent periods should be determined by the market .

<France -- determining reimbursement prices and also regulating a total budget>

France has adopted a "social insurance system" as in the case of Japan. As much as 99% of the total population is insured by some form of public health insurance and medical expenses are, in principle, covered by the earnings from the premium income.

With regard to the prices of individual pharmaceuticals used for outpatients, the government determines the reimbursement price for each brand. On the other hand, in the case of the pharmaceuticals used for hospitalized patients (about 13% of the pharmaceutical market), the reimbursement prices are not fixed. In order to have the reimbursement prices of pharmaceuticals used for outpatients calculated, manufacturers apply to the government to have new pharmaceuticals registered on the reimbursement price lists and the National Economic Committee[38] determines the prices in accordance with a report by the Transparency Committee of the Pharmaceutical Affairs Bureau. Price revisions are determined in the same way. The manufacturers apply to raise the prices and the new prices are determined by the National Economic Committee in response to a report by the Transparency Committee of the Pharmaceutical Affairs Bureau. If a proposed increase in the price of pharmaceuticals is not considered beneficial for national medical services, the Economic Committee can reject the price rise. Moreover, manufacturers and the Economic Committee negotiate with each other to lower the price of pharmaceuticals judged to be of less importance. Owing to these factors, the prices of

[36] As the reimbursement price tends to be lowered each time revisions are carried out, new pharmaceuticals whose prices have just been newly calculated are higher-priced than older pharmaceuticals.

[37] For example, supposing there are two new drugs A and B which have the same efficacy, and the reimbursement price of drug A is ¥120 and that of drug B is ¥100 and both of the discount rate is 10%. In this case, the "pharmaceutical price differential" of A is ¥12 and that of B is ¥10. Therefore, if one wishes to maximize the "pharmaceutical price differential," then, drug A will be selected.

[38] This committee consists of representative members of the Department of Economy, the Department of Finance, the Department of Social Security, the Department of Health and the Department of Industry.

pharmaceuticals in France are said to be the lowest in the U.S. and European countries. Because of the separation of dispensing and prescribing functions, the pharmaceutical price profit differential does not occur in medical institutions as it does in Japan[39].

As a means to control pharmaceutical expenses, with regard to those for outpatients, in the"government ordinances related to the curbing of medical expenditure" issued in 1996, the total budget is set by determining the target increase rate for all medical expenditure, such as examination fees for doctors and pharmaceutical expenses for outpatients. If the actual increase in medical expenditure exceeds the target increase, not only is the balance not paid to doctors but it will also be deducted from the examination expenses for doctors. About the pharmaceutical expenses for hospitalized patients, moreover, medical institutions have to cover all the medical expenses including pharmaceutical costs within the annual budget fixed for public hospitals, or the total budget setting daily hospital charge in the case of private hospitals.

<Germany -- determining reference prices and also regulating a total budget>

As is the case in **Japan**, **Germany** has also adopted a "social insurance system." About 90% of the population is insured by the disease depository (*Krankenkasse*[40]) which is an insurance management organization. Medical expenses are in principle covered by the premium income.

With regard to pharmaceuticals for outpatients, the Federal Disease Depository Committee[41] determines the upper price limit (hereafter referred to as "reference prices") reimbursed to pharmacies by health insurance. The government does not actually participate in determining the reference prices of pharmaceuticals.[42] The reference prices are determined by categorizing pharmaceuticals into groups with the same effective ingredients and similar therapeutic effects, and setting the prices reimbursed by health insurance for each group (see figure 1-3). However, reference prices are not set for pharmaceuticals which are still within their patent periods. The prices for these are fully reimbursed. If the actual selling prices exceed the reference prices, the balance is covered by patients. The pharmaceuticals for hospitalized patients are included in hospital treatment expenses and they are not subject to "reference prices." With regard to the pharmaceuticals used for hospitalized patients, there is no "pharmaceutical price profit differential" for medical institutions. Even though it is possible that a"pharmaceutical price profit differential" occurs in the case of outpatients, the system has been adopted to prevent occurrence of such a differential[43].

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[39] The way to reimburse the pharmaceuticals used for outpatient is that once the patients pay for the pharmaceuticals at pharmacies, and then, the patients request the reimbursement to the health insurance.

[40] *Krankenkasse* are responsible for public health insurance and are equivalent to the health insurance unions in Japan.

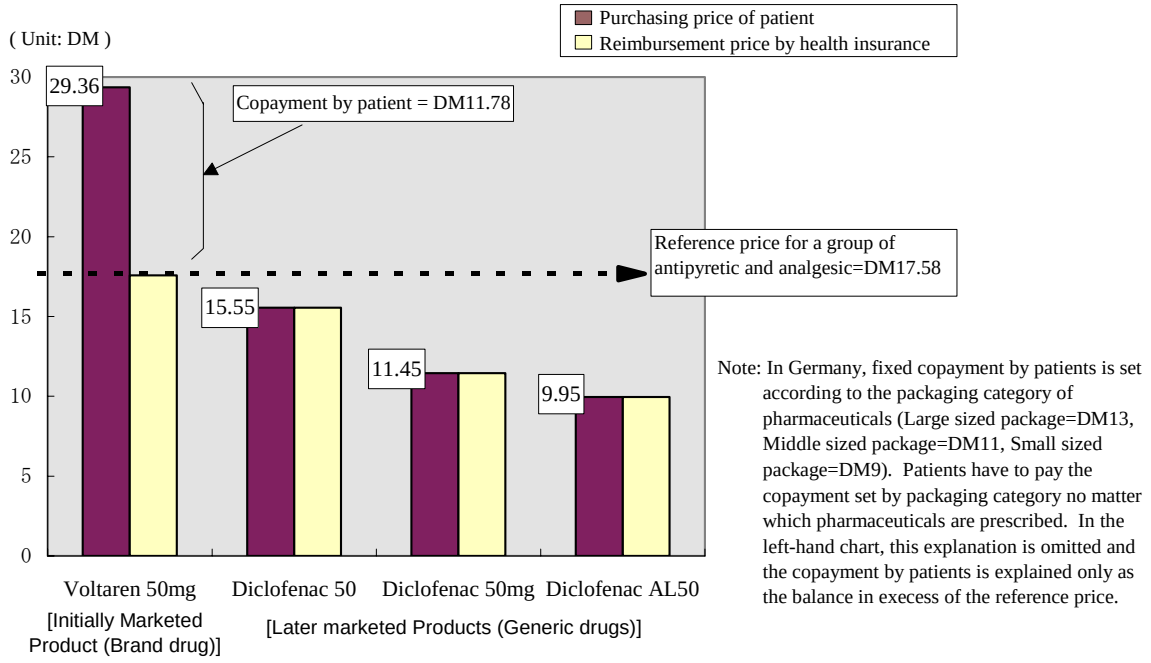
[41] The Federal Disease Depository Committee is an organization at a higher level than the disease depositories, whose total number is approximately 1,100 in Germany.

[42] The reason why the government does not participate in pricing is because the sickness insurance system itself is operated only by private organizations and the financial funds are not provided by the government. In Japan, 30% of the financial source of the health insurance system is provided by the national government and local self-governing bodies.

[43] In the transactions between the wholesalers and the pharmacies, if the wholesalers make discount, all the differential between the purchasing price of the pharmacies and the reimbursement price by the

Pharmaceutical expenses are controlled by setting a total budget. With regard to the pharmaceuticals for outpatients, in January 1998, a "Pharmaceutical Supply Standard Amount" system was introduced, specifying the amount of pharmaceuticals which each doctor can prescribe per patient.[44] Although it is permitted to transfer the benefits for one patient to others, if the total amount of the pharmaceutical benefits exceeds the amount calculated based on the standard amount, the examination fees for doctors are reduced by the excess amount. On the other hand, the cost of pharmaceuticals used by hospitalized patients should be covered by the fixed amount for hospital treatment expenses (including examination fees and pharmaceutical expenses), which are paid to the medical institutions by disease depositories. The fixed amount for hospital treatment expenses is set on the basis of specific diseases.

Figure 1-3: Reference Price System in Germany



Source: Japan Pharmaceutical Wholesalers Association "*Oroshi Yakugyo* (Pharmaceuticals Wholesale)," Vol.21, No.9, 1997

<The U.K. -- controlling the profit rate and adopting total budget regulations>

In **the U.K.**, the "national health care system" whose major part of its cost is covered by general financial sources has been adopted. 90% of the population receive medical services through the National Health Service (NHS).

Although reimbursement prices are not set for the pharmaceuticals covered by health insurance, under a system[45] which determines the upper limit of the manufacturer profit

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disease depositories had become a profit of the pharmacies. However, as the result of the reform done by the Medical Structure Law in 1993 (CSG), it has been determined that the pharmacies are paid by a sum based upon the reimbursement price with a deduction of 5%. It is said that this causes a substantial reduction of revenue of the pharmacies.

[44] Revision of the pharmaceutical benefits budget system introduced in 1993.

[45] A system called the Pharmaceutical Price Regulation System (PPRS), used to determine pharmaceutical prices by means of voluntary agreement between the pharmaceutical industry and the Department of

rate in voluntary negotiations between the Department of Health and manufacturers, the government indirectly participates in determining the manufacturer shipping prices. As a result, this system is actually designed to make pharmaceutical prices fluctuate, not by controlling the prices of individual pharmaceuticals, but by controlling the overall profits. Pharmaceutical prices are determined individually by each manufacturer.

In **the U.K.**, all medical expenses including pharmaceuticals are covered by a budget distributed by the government. Therefore, the government participates in pricing individual pharmaceuticals under the above-mentioned system. Additionally, the medical treatment expenses at medical institutions are controlled by means of the total budget. Moreover, each medical institution makes a list (Hospital Formulary) of the pharmaceuticals which can be used, and medical institutions select pharmaceuticals from this.

<The U.S. -- using free prices and total amount contracts with private insurance organizations>

The U.S. differs from Japan and European countries as most people are covered by private health insurance.[46] People who are not covered by health insurance also represent about 14% of the population (35 million). Private health insurance provides medical services within a budget supported by the premium income paid by the insured.

Manufacturers can freely determine prices of individual pharmaceuticals and the government does not participate in the pricing at all. The actual selling prices are determined in negotiations by the parties related to the distribution of pharmaceuticals, such as manufacturers, wholesalers, medical institutions and pharmacies. However, each manufacturer has its own goal of making efforts to keep the average increase rate for all pharmaceutical prices within the inflation rate, in order to avoid pressure from the public or politicians who think that the manufacturers are making too much money.

Membership system private health maintenance organizations called HMOs,[47] which are one form of private health insurance, cover most of the pharmaceuticals for outpatients. However, only when doctors select pharmaceuticals from a very limited item list (formulary) made by the insurer itself, are they covered by insurance. If patients want to use pharmaceuticals which are not on the item list, they have to pay extra premiums. With regard to the pharmaceuticals used for hospitalized patients, excessive administration is curbed by standardizing treatment methods for each disease as in **the U.K.**, and by including all the expenses in a flat payment scheme. Moreover, medical institutions enter contracts with insurance organizations based on a total amount contract system and are able to make profits within the budget adopted. For example, since HMO contracts with

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Health, was introduced in 1957.

[46] In the U.S., there is no public health insurance system covering the whole population. In terms of public health insurance, there is Medicaid for low-income earners and Medicare for the elderly, people receiving disability pensions, and so forth. About 25% of the population is covered by public health insurance.

[47] Health Maintenance Organization. A medical service organization with a prepaid fee and membership system. It offers members comprehensive medical services, including hospital expenses when both hospitalized and not hospitalized, fees for examinations by special doctors, clinical examination fees, and so forth. What is different from traditional medical insurance is that the insurer sometimes provides medical services directly to the insured.

doctors by means of the total amount contract system, doctors are obliged to cover all the expenses including pharmaceutical costs related to the examination of HMO members who the doctors contract to examine, within the contracted budget.

(2) Pharmaceutical Prices in Each Country

<Pharmaceutical prices in Japan -- lower than in the U.S., but higher than in European countries>

In order to examine the relationships between the systems and markets in each country, the pharmaceutical prices of **Japan** are compared against **the U.S.** and **European countries** (For details, refer to Appendix 1).

Looking at the pharmaceuticals surveyed this time, although differing by item, in general, prices tend to be the highest in **the U.S.**, followed by **Japan** and with **European countries** the lowest. Moreover, among the **European countries**, most pharmaceutical prices were the lowest in **France**. (Because ① the number of samples was limited, ② the differences in purchasing prices of pharmaceuticals in each country, ③the difference in pharmaceutical distribution from one country to the other, and ④ the appropriateness to the use of foreign exchange rate, etc., (it should be remarked that the results of this survey do not necessarily describe all the circumstances pertaining to the pharmaceutical prices in surveyed countries.)

With regard to the above-mentioned tendency, it has been pointed out that prices in **Japan** are shown to be higher than those in **European countries** because of the respective influence of those countries' systems, which assist in curbing pharmaceutical prices and the total budget for pharmaceutical expenses. As indicated in (1), in **European countries**, there are reimbursement prices in **France**, reference prices in **Germany**, the upper limit of the manufacturer profit rates in **the U.K.**, and so on. These systems function directly or indirectly as the upper limit on prices. Moreover, in **European countries**, each country sets a total budget for treatment expenses or pharmaceutical expenses for each patient or medical institution. Under these circumstances, medical institutions are said to try to reduce pharmaceutical expenses, which encourages competition among pharmaceutical manufacturers. On the other hand, in **Japan**, although reimbursement prices for each pharmaceutical brand function as the upper limit on prices, pharmaceutical expenses are in principle reimbursed by "fee-for-services" and there is no limit on the total budget. Although **Japanese** medical institutions ask for discounts on the purchasing prices in order to gain the "pharmaceutical price profit differential", they tend to purchase expensive pharmaceuticals which provide higher differentials. So competition in the pharmaceutical market is seen to be limited compared with **European countries** where the total budget is subject to regulations.

The reason why the prices in **the U.S.** tend to be the highest is because it may be influenced by the fact that there is no system such as a reimbursement price for each pharmaceutical and, compared to **Japan** and **European countries**, market pricing is more free. On the other hand, medical institutions are required to cover all costs, including pharmaceutical costs, with the budget determined by the total amount contracted with private insurance organizations. Therefore, medical institutions demand pharmaceuticals which have high therapeutic effects and can be expected to reduce the total medical expenses by shortening hospitalization periods. Those pharmaceuticals are said to be

highly priced in response to such demand.

《**Conclusion**》

Japan and **European countries** have public health insurance systems and adopt some regulation on pharmaceutical prices. Moreover, in **European countries**, a total budget is set for pharmaceutical expenses or medical expenses according to patients or medical institutions. On the other hand, in **Japan** pharmaceutical expenses and medical expenses are paid by means of a "fee-for-services" and a total budget is not set. In **the U.S.**, private health insurance plays a major role. Although there is no regulations on pharmaceutical prices, health insurance sets some form of total budget for medical expenses, including pharmaceutical expenses. Therefore, when comparing Japan, European countries, and the U.S. from the two varying viewpoints of systems governing the pricing of individual pharmaceuticals and those governing the total budget for pharmaceuticals, there are differences among them; **European countries** have adopted regulations governing both pricing and the total budget, **Japan** has adopted regulations governing only pricing and **the U.S.** has adopted regulations governing only the total budget.

Comparing **Japan** with **European countries**, even though there are reimbursement prices for individual brands in **Japan**, their purchasing prices of medical institutions are negotiated with wholesalers. If purchasing at a low price, the difference from the reimbursement price called the "pharmaceutical price profit differential" becomes earnings for those institutions. Therefore, the competition in the pharmaceutical market lays emphasis on the amount of "pharmaceutical price profit differential" and the ancillary services rather than the cost versus the performance of the pharmaceuticals. On the contrary, in **European countries**, there are total budget regulations and the systems do not allow a "pharmaceutical price profit differential" in many countries. In turn, prices themselves are an important factor in the selection of pharmaceuticals. These are considered as reasons why prices in **European countries** are relatively lower than in **Japan**.

In **the U.S.**, in comparison with Japan and European countries, private health insurance is central and in turn the system most reflects market mechanisms. In **the U.S.**, consumer choice is the origin of competition in the health insurance system. Insurance organizations contract medical institutions annually based on a total amount contract system and allow the provision of medical services to policyholders. As a result, it is said that medical institutions are highly conscious about cost performance and have motives to purchase expensive pharmaceuticals if the patient hospitalization can be shortened.

In **Japan**, in principal there is no total budget regulation for insurance reimbursement, so it is said that the prices of individual pharmaceuticals are controlled from the viewpoint of curbing medical expenditure. In turn it has been pointed out that it is difficult to set insurance reimbursement prices reflecting cost and efficacy. For example, it is said that according to the "price setting by comparison to similar pharmaceuticals system," it is difficult for "innovative new pharmaceuticals" to be priced sufficiently enough to reflect their efficacy. For this reason it has been pointed out that it is hard for new pharmaceuticals with high efficacy and competitiveness to be priced to meet market value and to enter into the market in **Japan**.

Although their pharmaceutical pricing systems differ, in both Japan and **European countries,** where the national health care services are mostly covered by some forms of public health insurance, the market seems to be limited for highly innovative expensive pharmaceuticals.

At present, introduction of a “Japanese-style reference price system” is under consideration in **Japan**, with the main purpose of curbing total medical expenses. It has been pointed out that, as in Germany which has already implemented a reference price system, this may reduce levels of medical treatment and examination, may not result in the curtailment of pharmaceutical costs without the simultaneous introduction of a total budget ceiling, so on. However, due to the suppression of a “pharmaceutical price profit differential” there is a potential for individual pharmaceuticals to be priced based upon the market mechanism, so this system deserves praise from the viewpoint of market access. On the other hand, as for “innovative new pharmaceuticals”, which are developed at a high cost and whose high therapeutic value have been proven, it has been cited that introduction of a system whereby reimbursement by health insurance is at prices which conform to the free market, and which does not discourage pharmaceutical manufacturers from developing new pharmaceuticals is also necessary from the viewpoint of market access.

II. Distribution and Business Practices

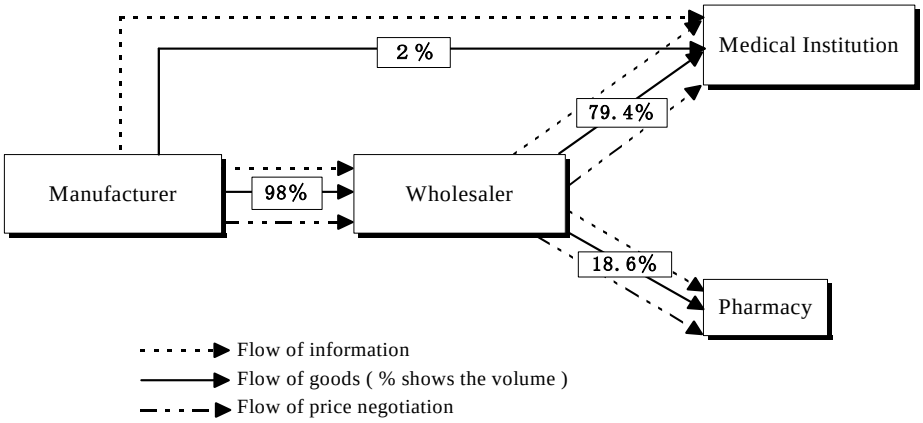
1. Factors in the Selection of Pharmaceuticals and Sales Methods

In Japan, it is necessary for manufacturers to hire many MRs[48], who deal with pharmaceutical information. Also MRs are generally trained at each company, and the use of contract MRs[49] is not increasing. As this kind of practice results in enormous initial investment costs when establishing sales systems in Japan, it has been pointed out that such a practice could be a factor that hinders market access by newcomers from abroad.

＜Japan -- Separation of dispensing and prescribing functions is not developed＞

In **Japan**, ethical pharmaceuticals are mainly sold to medical institutions by manufacturers through wholesalers. On the other hand, in the **U.S.** and **European countries**, since the separation of dispensing and prescribing functions[50] is common practice, separate distribution channels are employed for pharmaceuticals used for outpatients and those used for hospitalized patients. With regard to pharmaceuticals used for hospitalized patients, in the **U.S.** and **U.K.**, pharmaceutical distribution is mainly performed through wholesalers, as in the case of Japan. In **France** and **Germany**, it is said that pharmaceuticals used for hospitalized patients are mainly sold directly from manufacturers to medical institutions. In **Japan**, 80% of the total value of ethical pharmaceuticals sold is to medical institutions (see figure 2-1). In the **U.S.** and **European countries**, pharmaceuticals sold to medical institutions are only used inside hospitals, such as those administered to hospitalized patients. In the **U.K.** and **France**, 13 to 14% of the total value of ethical pharmaceuticals sold is to medical institutions. And in the **U.S.**, that percentage is about 25%.

Figure 2-1: Information, Product, and Cost Negotiation Flow in Distribution for Prescription Drugs in Japan



Source : Prepared based on interviews with industrial sources

Whichever channel is used, in **Japan**, the **U.S.** and **European countries** alike, the demand for pharmaceuticals arises when a doctor consults a patient and writes the name of the pharmaceutical which meets the therapeutic needs in the prescription. Therefore, it is important for manufacturers

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[48] Medical Representatives; Staff of manufacturers in charge of medical information. They provide information on efficacy and side effects of pharmaceuticals to doctors and pharmacists and collect information on them being used.

[49] MRs that have a contract during a certain period with a manufacturer for the sales and sales promotion of pharmaceuticals produced by that manufacturer.

[50] This means that a doctor diagnoses and treats the patient, while a pharmacist dispenses medicines, in accordance with the doctor's prescription, and provides instructions on their use to outpatients. In 1995 only 20.3% of the prescription was prepared by pharmacists outside of medical institutions.

to provide information of their products and make sales promotions to doctors so that doctors will prescribe them. Especially, as pharmaceuticals are products related to life and health, it is essential to provide information relating to the safety of products. So the MR, whose major role is to provide drug information, is regarded as important in **Japan**, the **U.S.** and **European countries** alike.

＜Japan -- Attentive sales promotion system by MRs has been established＞

Figure 2-2 shows the comparison among **Japan**, **the U.S.** and **European countries** in terms of the number of MRs and their frequency of visits to medical institutions. It is hard to compare the number of MRs exactly because of differences in population, and number of hospitals and doctors. However, it has been pointed out that there are too many MRs in **Japan** and their visits to medical institutions are too frequent.

Figure 2-2: Number of MRs and their Frequency of Visit to Medical Institutions in Surveyed Countries

	Total number of MRs	Number of MRs per company	Frequency of visits
Japan	50,000	600～1,000	university hospitals : every day
U.S.	30,000	1,000～3,500	n.a.
U.K.	5,000	100～400	Hospital doctors : once a week General Practitioners: 4 times a year
France	15,000	200～1000	practitioners: 2 ~ 3 times a year
Germany	18,000～25,000	60～200	n.a.

Note: Japanese figure indicates the total number of MRs in the country. Figures for the U.S., the U.K. and Germany, may not include the number of the contract MRs. France's figure indicates the number of MRs employed by manufacturers.

Source: Japan: interviews with industrial sources; U.S.: "*Gekkan MR* (Monthly MR)" October 1997 and JETRO New York center; U.K.: "*Kokusai Iyakuhin Joho* (International Drug Information)" May 12,1997 and JETRO London center; France: JETRO Paris Center; Germany: JETRO Düsseldorf Center.

Moreover, when we look at the system of employing MRs, in **Japan** most companies hire new university graduates, then train them in-house. On the other hand, in the **U.S.** and **European countries** the use of contract MRs is increasing. Especially in the **U.K.**, it is said that contract MRs are common and they constitute about one-third of the total. In **France**, there are several companies that cater to the industry with contract MR services. Most pharmaceutical makers outsource their major promotional activities to such companies whenever they have a newly developed product they want to bring to market. It is said that a merit of using contract MRs is that it is possible to reduce personnel expenses by hiring contract MRs only when needed, rather than keep MRs permanently employed in each company. In **Japan**, it is said a foreign company will start the first contract MR dispatching service here in 1998.[51] There are doubts concerning whether the subcontracting business will spread or not in **Japan** because Japanese MRs are required to provide attentive sales activities.

It is said the reason there are many MRs in **Japan** is mainly because the separation of dispensing and prescribing functions is not developed and the doctor's right to select the pharmaceutical is

[51] According to the reports in *Nikkei-Sangyo-Shinbum* dated March 30, 1998 and *Lâge* (a trade newsletter of pharmaceutical industry) dated February 2, 1998.

rather strong compared to that of in the U.S. and European countries. In **Japan**, pharmacists are regulated by the Law in that they must not alter a prescription unless they have the consent of the issuing doctor[52]. As a practice, doctors write their prescription in specific brand names[53] instead of general names. In that case, pharmacists cannot substitute cheaper generic drugs.[54] Because there is no system to offer opportunities for patients to select pharmaceuticals among the therapeutically equivalent drugs, once doctors write their prescription in specific brand names, it is expected that the specific brand product will be purchased. In addition, unlike the U.S. and European countries, Japan does not regulate the total volume of pharmaceutical cost in principle. So doctors are in the position that they can use pharmaceuticals without cost consciousness. Therefore, for manufacturers, doctors are the most important target for marketing.

＜The U.S. and European countries -- Selection of pharmaceuticals is based upon cost versus effectiveness＞

On the other hand, in the **U.S.** and **European countries**, the cost of pharmaceuticals for in-patients is mainly paid by a so-called "flat payment system." It bears all the costs required for treatment including pharmaceuticals, within the fixed cost which is designated based on the type of illness. This system gives medical institutions an incentive to reduce the cost of pharmaceuticals. In the case of outpatients, pharmaceuticals are dispensed by pharmacies, as separating dispensary from medical practice is standard practice. This means the pharmaceutical price profit differential does not apply to medical institutions, so there is no incentive to use large quantities of pharmaceuticals. In the **U.S.** and **European countries**, on the contrary, as to the selection of pharmaceuticals with the same efficacy, there is an incentive to prescribe cheap pharmaceuticals, however, incentives are also present for high-priced pharmaceuticals due to greater therapeutic value, smaller quantity necessary and reduction of hospitalization days.

In the **U.S.,** even though doctors prescribe brand names, unless stated by doctors, pharmacists can offer choices to patients when cheaper generics exist with the same efficacy. And the private insurance companies give incentives to pharmacies by making contracts with pharmacies if pharmacies dispense cheaper generic drugs to patients, then the insurer pays higher dispensing fees to pharmacies. In the **U.K.**, doctors have been guided by the NHS to prescribe not brand names but general names. In **Germany**, in principle, pharmacists need the consent of the issuing doctor if they alter a prescription. But in practice, pharmacists can recommend and sell the therapeutically equivalent drug as in the prescription upon agreement with the patient. In **France**, however, except in the case where there is a clear prior agreement by the doctor who prescribed the pharmaceuticals concerned, pharmacists are not allowed to change prescriptions. Though the government ordinance "Concerning the Control of Medical Expenditure" enacted in 1996 states a rule which allows doctors to write out prescriptions not with brand names but with indications for specific illness in case of prescribing several pharmaceuticals only. It became possible for pharmacies to sell less-expensive pharmaceuticals for the illnesses indicated on such prescriptions.

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[52] Pharmacist Law, Article 23

[53] Regarding pharmaceuticals names, there are brand names created by each manufacturer, and names showing the substance of pharmaceuticals and which can be used by everyone in common (general names). Chemical names could be listed to show pharmaceutical substance or essence, but in the case of compounds which have complicated structures, chemical names are not suitable to use as general names, because general names tend to become very complicated. As a result, except for some compounds, separate general names have been established besides chemical names. In Japan, pharmaceutical price standards are also based on listing brand names created by manufacturers and doctors are said to use almost only brand names in medical prescriptions.

[54] Generics are called "later marketed products." Generics are pharmaceuticals which have the same active ingredients, administration and dosage, indication or efficacy as the pharmaceuticals which have already been approved ("initially marketed products" which often means a brand name product), or within the range of administration and dosage, indication or efficacy.

《**Conclusion**》

In the pharmaceutical distribution system, pharmaceuticals are sold to medical institutions or pharmacies by manufacturers through wholesalers in **Japan**, the **U.S.** and **European countries** alike. However, in **Japan** the percentage of sales from wholesalers to medical institutions is higher, as the separation of dispensing and prescribing functions is not on the increase, unlike the **U.S.** and **European countries**. Moreover, it has been pointed out that compared with the **U.S.** and **European countries**, there are too many MRs in **Japan** and their visits to medical institutions are too frequent. When we look at the system of employing MRs, MRs are mostly trained in each company, and the use of contract MRs has not become well established in **Japan**, unlike the **U.S.** and **European countries**.

As the background why manufacturers in **Japan** to build such an attentive sales promotion system employing many MRs, it is mentioned that under the current system doctors have a huge say in selecting the brand of pharmaceuticals, and writing the drug names in the prescription. In Japan, separation of dispensing and prescribing functions is not common and dispensing is mostly done in medical institutions, and the reimbursement from health insurance is based on the "fee-for-services system." In addition, if the purchasing price of pharmaceuticals is lower than the reimbursement price by health insurance, the differential will become a profit of medical institutions. Therefore, doctors have less incentive to select pharmaceuticals based upon cost versus effectiveness. Because of these factors, it is seen in Japan that, activities to provide various information to medical institutions utilizing MRs could result in the sales of pharmaceuticals compared to the situation of the U.S. and European countries.

On the other hand, in the **U.S.** and **European countries**, the "flat payment system" is main stream and the practice of the separation of dispensing and prescribing functions is prevalent. Thus the "pharmaceutical price profit differential" is not brought to medical institutions in many countries. Because of these factors, there is no incentive for medical institutions to use more pharmaceuticals than necessary, and the selection of pharmaceuticals is based on cost versus effectiveness. Also, the role of doctors in selecting pharmaceuticals is small in comparison with **Japan**. Consequently, the meaning of promoting pharmaceuticals to doctors is relatively small.

Under the present condition, for those foreign companies to set up sales operations in **Japan**, it is necessary to build a sales promotion system by themselves laying emphasis on MRs. And this has a potential to increase initial investment costs, compared to the U.S. and European countries.

2. Business Relations in the Distribution System

In the pharmaceutical distribution system in Japan, there is an extremely large number of wholesalers, and the number of wholesalers to contract per manufacturer is high. Moreover, it has been pointed out such practices as "provisional supply and provisional payment" which can be seen between wholesalers and medical institutions places a burden on manufacturers. It is not only difficult for new market entrants to understand such business relations, but it has also been pointed out that this practice increases the cost of market entry and acts as a factor that hinders market access.

＜**Japan -- Necessity to do business with many wholesalers**＞

In **Japan**, wholesalers are small in size and the number of business operators with a wholesale business license based upon the Pharmaceutical Affairs Law exceeds over 4,000. Among them the 260 companies that are members of the Japan Pharmaceutical Wholesalers Association handle nearly 90% of the total value of pharmaceuticals sold in Japan. However, there are still no wholesalers that operate on a nationwide basis, nor are there any that have a product line-up consisting of pharmaceuticals produced by all manufacturers. Based on these conditions, in **Japan** even foreign companies, which deal with a more limited number of wholesalers, have agreements with 40 to 50 such firms, and major Japanese manufacturers are said to deal with 100

or more.

Figure 2-3 shows the comparison among **Japan**, **the U.S.** and **European countries** in terms of the number of wholesalers and their share of the market.

Figure 2-3: Number of Wholesalers, Number of Wholesalers with whom One Manufacturer Has Agreement, and Market Share of Wholesalers in Surveyed Countries

	Number of wholesalers	Number of wholesalers with whom one manufacturer has agreement	Market share of wholesalers	
Japan	4,000	40～100 or more	90%	by 260 companies
U.S.	39 (a full product line-up)	n.a.	70～80%	by top 5 companies
U.K.	18 (a full product line-up)	18	60%	by top 2 companies
France	15 (a full product line-up)	5	97%	by 3 major groups
Germany	16 (a full product line-up)	n.a.	79%	by top 3 groups

Source: Japan: MHW "Pharmaceutical Industry Survey" 1994, Japan Pharmaceutical Wholesalers Association, and Interviews with industrial sources; France, Germany, U.K., U.S.: JETRO Centers Overseas

Thus, in **Japan** there are far more wholesalers than in the U.S. and European countries, and an extremely large number of wholesalers per manufacturer to deal with.

＜Japan -- Longer terms of payment＞

It has been pointed out that in **Japan** the reason manufacturers carry out their business via wholesalers is that manufacturers are in need of wholesalers to perform functions of distribution,[55] collection of accounts receivable[56] and credit management.[57] However, in the **U.S.** and **European countries**, wholesalers are expected to specialize mainly in inventory-building a full range of products and distribution.

In **Japan**, manufacturers are said to rely heavily on wholesalers because of the business practices existing between wholesalers and medical institutions called "*souka yamagai"* (lump-sum bulk buying), [58] and "*karinouhin karibarai"* (provisional supply and provisional payment). "Provisional supply" refers to the practice of supplying goods at a provisional price for a certain period until the actual delivery price is determined, when the delivery price of goods supplied by wholesalers to medical institutions is reviewed.[59] Payment during this period takes the form of a "provisional payment" in accordance with the requests of medical institutions. As pharmaceuticals have the special characteristic of life and health related products, even though their

[55] As it would not be efficient for manufacturers to create a distribution system based on shipping only their own products every day to as many as 100,000 users, manufacturers rely on wholesalers to put together and transport products supplied by various manufacturers.

[56] As considerable costs would be incurred if manufacturers were to collect payments for only their own products every month, and because they are unable to do this on their own, they entrust this operation to 50 to 100 wholesalers with whom they have entered contracts.

[57] Wholesalers evaluate management conditions at medical institutions and supervise limits on credit provided to them.

[58] A purchasing method that involves ignoring unit prices of individual pharmaceuticals and determining a discount rate for the total purchase amount when bids are put forward to hospitals

[59] Delivery prices are reviewed on the occasion of revisions to pharmaceutical reimbursement prices by health insurance, which are carried out once every two years, in principle, by the MHW.

price has not been determined, wholesalers cannot suspend delivery to medical institutions. Moreover, if the people in charge of purchasing at medical institutions decide on prices quickly and it then becomes evident they have paid a higher purchase price than other medical institutions, their ability for negotiating prices will be called into question. As a result, price negotiations generally continue over a long period. There are cases where negotiations over the official purchase price remain unresolved for a year or more, and the situation of "provisional supply and provisional payment" continues to exist.

In addition, as regards the collection of accounts receivable, medical institutions are reimbursed by health insurance funds about three months after they have provided medical services. On the other hand, on the average wholesalers receive payment from medical institutions four months after delivery of goods. In longer cases, the terms of payment of some medical institutions are said to be prolonged for more than one year. Even if such payment practices are carried out, they do not infringe any contract, as wholesalers and medical institutions have not established the practice of exchanging written contracts specifying payment conditions. On the other hand, the practice of wholesalers and manufacturers exchanging written contracts is established, and wholesalers are required to make payment to manufacturers about five months later.

In **Japan**, as described above the collection of accounts receivable takes a long time, so to protect their claims manufacturers always need to check the financial position of wholesalers. Manufacturers anticipate hospitals may delay making payment and pay rebates to wholesalers. Especially in the case of small and medium-sized wholesalers, it is said that cases may exist where manufacturers pay large rebates as a form of management support. These practices are considered to place a burden on manufacturers.

＜The U.S. and European countries -- Shorter terms of payment＞

As far as the price of goods sold by wholesalers to pharmacies and medical institutions is concerned, in the **U.S.** and **European countries** it is normal practice to exchange written contracts specifying payment conditions, and there is no evidence of the type of payment practices that exist in Japan. In the **U.S.**, selling prices are determined on the basis of price lists produced in accordance with the monthly purchase value and the term of payment. The greater the monthly purchase value and the shorter the term of payment are, the lower the selling price becomes. In the **U.K.**, **France** and **Germany**, as the wholesaler margin is a rate fixed officially,[60] once the manufacturer invoice price has been decided, the price of goods sold to pharmacies is determined by adding the wholesaler margin on it[61].

Figure 2-4 shows the comparison among **Japan**, **the U.S.** and **European countries** from the viewpoint of the terms of payment from pharmacies and medical institutions to wholesalers, and from wholesalers to manufacturers.

[60] 12.5% in Britain, 10.74% in France, and 15.60% on average in Germany (determined by shipping price of manufacturer).

[61] However, in Britain, France and Germany, it is admitted that wholesalers make discounts for pharmacies in cases such as if pharmacies complete their payment within the term of payment.

Figure 2-4: Terms of Payment in Surveyed Countries

Country	From Medical Institution or Pharmacy to Wholesaler	From Wholesaler to Manufacturer
Japan	4 months ~ 1 year	5 months
France	45 days	60 days
Germany	30 days	n.a.
U.K.	45 days	45 days
U.S.	15 days	30 days

Note: In the case of Japan, it indicates payments from medical institutions to wholesalers, and for U.S. and European countries, it indicates payments from pharmacies to wholesalers

Source: Japan: interviews with industrial sources, U.S., U.K., France, Germany: Studied by JETRO Centers Overseas

Thus, trading conditions in the pharmaceutical distribution system differ considerably between **Japan** and the **U.S.** and **European countries**. Consequently, when setting up business in Japan, foreign manufacturers often consign their sales operations to Japanese manufacturers, who already possess sales networks. In this case, foreign manufacturers receive payment from the Japanese manufacturer consigned to carry out sales for the pharmaceuticals they supply rather than from a wholesaler. With this method, they can collect payment in a shorter time than if they sold their goods to wholesalers, but they have to pay a high rate of commission[62] to the Japanese manufacturer concerned. It has also been pointed out that when foreign manufacturers wish to sell pharmaceuticals themselves, rather than consign their sales operations to Japanese manufacturers, and attempt to deal directly with wholesalers, it is difficult for them to persuade their overseas parent companies to accept longer terms of payment.

The practice in which newcomers consign their sales operations to local manufacturers is also found in **the U.S.** and **European countries**. And it is pointed out that new comers take this option as the method to alleviate the sales administration cost in their early stage of establishing business in a new market. However, in this case, the consignment often consists of a whole package including the promotion activities to doctors and collection of payment. Because in the U.S. and European countries, there does not exist the merit for newcomers that they could collect payment in a shorter time if they consign sales to manufacturers, it is not common to consign the collection of payment only to a local manufacturer as is practiced in **Japan**.

《Conclusion》

There is an extremely large number of wholesalers in the **Japanese** pharmaceutical distribution system, and there are no wholesalers that operate on a nationwide basis, nor are there any that have a product line-up consisting of pharmaceuticals produced by all manufacturers. Therefore, the number of wholesalers per manufacturer to deal with is very large. Moreover, it takes a longer time to fix the content of transactions between wholesalers and medical institutions and the terms of payment is evidently longer than that of the U.S. and European countries. It is pointed out that, these business practices in the Japanese distribution system are complex for newcomers, and increases the costs of bearing the burden of long term payment and others makes it difficult to enter the market.

So far, when first setting up their businesses, foreign manufacturers that have newly entered the **Japanese market** have consigned their sales operations to Japanese manufacturers. Even if

[62] Though the size of the commission itself usually depends on the competitiveness of the foreign maker's pharmaceutical products in the marketplace, it is said to range anywhere from more than 10% to almost half of the sales price.

foreign manufacturers try to sell their products themselves, it is not easy for them to build sales networks that operate in a similar way to those in their own country, and they are said to be forced to follow the trading relationships in the existing Japanese distribution system. Also if they decide to use the existing distribution system, they have to be prepared to bear a degree of burden, which includes paying rebates as a form of management assistance to wholesalers. From the viewpoint of market access, it is pointed out that foreign manufacturers are considered to incur substantial costs in establishing and maintaining business relationships in the Japanese pharmaceutical distribution system.

Details

I. Official Regulations

1. Regulations Governing Importation and Domestic Distribution

(1) Japan

< Content of Regulations >

The Ministry of Health and Welfare (hereinafter MHW) regulates pharmaceuticals from importation to their domestic distribution based upon the Pharmaceutical Affairs Law.[63] Regulations can be broadly divided into those that apply to products themselves and those that apply to business operators that handle these products. In the case of regulations governing products, imported products such as domestically manufactured products must obtain, from the Minister of Health and Welfare, approval in efficacy and safety according to the standards in the Pharmaceutical Affairs Law. The approval system for pharmaceuticals will be discussed in the next section.

If pharmaceuticals are imported "for business purposes,"[64] an import and sales license for each place of business[65] has to be obtained from the Minister of Health and Welfare.

When imported pharmaceuticals are subdivided in Japan, it is necessary to obtain a manufacturing license for each place of manufacture from the Minister of Health and Welfare.

If imported pharmaceuticals are sold domestically to medical institutions and so forth, one must obtain not only an import and sales business license, but also a wholesale business license for each store[66] from the prefectural governors. If pharmaceuticals are shipped directly to a wholesaler from a place of manufacture that has obtained a manufacturing license, a wholesale business license is not required, but if pharmaceuticals are gathered temporarily at a distribution center and then shipped out, the distribution center must obtain a wholesale business license. Furthermore, if stores in various areas distribute samples of pharmaceuticals to doctors as part of their sales activities, each store is regarded as a sample wholesaler and, in turn, required to obtain a wholesale sales business license.

One personnel requirement for the granting of a wholesale business license is that a supervisory pharmacist with legally recognized qualifications be assigned as the person responsible for dealing with pharmaceuticals.

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[63] The Pharmaceutical Affairs Law imposes regulations necessary to guarantee the quality, efficacy and safety of pharmaceuticals and is also aimed at promoting research and development relating to pharmaceuticals and medical equipment which are particularly essential for medical purposes. Below the level of the Pharmaceutical Affairs Law, there are government ordinances consisting of Enforcement Ordinance, Pharmaceutical Affairs Law, as well as Enforcement Regulations, Pharmaceutical Affairs Law and Regulation for Building Structure and Equipment for Pharmacies, etc., and other MHW directives, and notifications such as those given by the Director of the Pharmaceutical Affairs Bureau of MHW (known since July, 1997 as the Director of the Pharmaceutical and Medical Safety Bureau).

[64] This indicates cases where the performance of the same kind of continued behavior by a certain individual can be regarded as the implementation of business in terms of what is commonly accepted in society.

[65] Place of business is widely interpreted to refer to a certain place where business is conducted and this includes head offices, branches and sub-branches.

[66] Store refers to a combination of physical equipment used to sell or give pharmaceuticals; to store them for the purpose of sale or giving; or to exhibit them (Pharmaceutical Affairs Bureau, MHW (ed.), *Chikujo kaisetsu yakujiho* (Interpretation of Pharmaceutical Affairs Law by Article) (Revised Edition), 1995, p. 396).

< Influence of Regulations >
When attempting to import pharmaceuticals and sell them domestically, it is necessary to obtain three licenses: an import and sales license, a manufacturing license, and a wholesale business license. These licenses have to be obtained not by individual companies, but by each place of business, place of manufacture, and store. It has been pointed out that such regulations governing business operators that handle pharmaceuticals both make it complicated for new market entrants to obtain licenses and involve licenses overlapping each other in coverage.

Moreover, it has been pointed out that requiring a supervisory pharmacist to be assigned to each place of business as a condition for the granting of a wholesale sales business license fails to correspond to new situations such as pharmaceuticals which no longer need to be compounded because they are now manufactured and enclosed in packaging. This personnel requirement is pointed out to be a factor that pushes up company costs.

However, in relation to the assignment of supervisory pharmacists, deregulation measures were implemented on March 31, 1997 and these included allowing pharmacists to work concurrently at different places of business that handle only samples.

(2) Overseas

< The United States >
Regardless of whether imported or manufactured domestically, before being put on the market, new drugs must receive approval from the Food and Drug Administration (FDA) through a new drug application (NDA) based on the Federal Food, Drug, and Cosmetics Act and the 21 Code of Federal Regulation (21 CFR).

Furthermore, there is no license that applies mainly to import businesses as in the case of Japan's import and sales business license. However, if imported pharmaceuticals are subdivided, it is necessary to obtain a manufacturing license from the FDA. It is also necessary to obtain a wholesale business license from the Drug Enforcement Administration (DEA) in order to wholesale pharmaceuticals.

One personnel requirement for the granting of a wholesale business license is that a person responsible for supervising pharmaceuticals must be assigned and that person's career record be registered. However, not only pharmacists may act as the person responsible for supervision.

< E.U. Member Countries >
Regardless of whether they are imported or manufactured domestically, new drugs must receive marketing approval (see I-2-2-(2)).

Furthermore, there is no license that applies mainly to import businesses, as in the case of Japan's import and sales business license. However, if imported pharmaceuticals are subdivided, it is necessary to obtain a manufacturing license from the regulatory authorities in each country. Nevertheless, business operators applying for approval to sell pharmaceuticals which have received marketing approval do not have to obtain a wholesales sales business license if they wish to wholesale those pharmaceuticals.

2. Approval System for Pharmaceuticals

2-1. The use of foreign clinical trial data

(1) Japan

< Content of Regulations >

When applying for approval of pharmaceuticals, the MHW requires that clinical trial data be attached in the form of documents which prove the efficacy and safety of the pharmaceuticals.[67] In regard to the foreign clinical trial data, there are worries that the standard of safety, efficacy, direction and dosage of the pharmaceuticals could be affected by ethnic factors and so on. The MHW have prescribed policies since June 1985 such as "Conditions of acceptance and points for attention concerning foreign clinical data" (see figure 1-4), and accepts such data as documents for review when the data conforms with the conditions and points. However, ①when the need arises, it is necessary to submit clinical trial data collected in Japan, and②in the case of absorption, distribution, metabolism and excretion tests, tests to determine dosage levels, and comparative clinical trials where there are differences in ethnic factors and others between Japanese and foreigners, it is necessary in principle to use clinical trial data collected in Japan. Looking at the development stages of new pharmaceuticals, ②indicates an examination applying to part of phase 2 and phase 3 trials.

There are rules which should be followed when collecting clinical trial data. In Japan, since April 1997, clinical trials must be executed in accordance with "ministerial ordinances concerning standards for the execution of clinical trials of pharmaceuticals (commonly termed the new GCP: Good Clinical Practices)."

The new GCP has delivered new rules for each party who is concerned with clinical trials. First, the doctors are obliged to provide an explanation in writing for patients participating in the clinical trials, to give them an opportunity to ask questions, and to obtain their agreement in writing (which is known as informed consent). At the medical institutions, not only the doctors, but also "clinical research coordinators" are recognized as people who are engaged in conducting clinical trials. "Clinical research coordinators" indicate the health care professionals, including pharmacists and nurses who cooperate in clinical trials under a doctor's instructions. Medical institutions are also required to establish internal investigation systems to review the process of clinical trials. And, for manufacturers who are the sponsors of clinical trials, a new system allowing manufacturers to monitor the progress of clinical trials by themselves is established.

The main reason for establishing the new GCP is to ensure that the guidelines on the conducting of clinical trials conform to international standards. The new GCP was established, as a result of efforts to create common standards in each member nation of ICH (International Conference for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) after "Standards for the operation of clinical trials conducted for the purpose of collecting documents for applications for approval of new drugs" were finally agreed on at the ICH of May 1996.

[67] Article 14 of the Pharmaceutical Affairs Law; Article 18, Clause 3 of the Enforcement Ordinance, Pharmaceutical Affairs Law.

Figure 1-4 : Conditions of Acceptance and Points for Attention concerning Foreign Clinical Data

	Conditions of Acceptance	Points for Attention for the Application
1	The methods of clinical tests and appraisals are compliant with Japanese standards and guidelines, and/or are applicable to the actual conditions of medical treatment in Japan.	In the case when methods do not comply with Japan's standard or guidelines, the applicant has an obligation to clarify the characteristics of the medical conditions of the country where the test was executed so that the Ministry could evaluate if the data would be applicable to Japan's medical conditions.
2	The tests must be conducted by the researchers with appropriate experience and ability under credible medical institutions such as public organizations and/or university hospitals.	The applicant should attach the necessary data to certify the credibility of the researchers' ability such as their educational background, certification, records of presentation at academic societies, etc. Those data are also requested for the medical institutions where the test was executed.
3	The tests should be executed under an appropriate procedure and method (Obeying the following standards or the foreign standards which are equally or more strict ones; such as the Helsinki Declaration which was designated by the World Medical Association; Japan's Good Clinical Practice; and Japan's GCP for medical equipment).	The applicant should attach the material to certify the clinical test was executed under an appropriate procedure and method (including the protocol of the clinical test).
4	The clinical data could be traced back to the raw data such as individual case records, records of statistical analysis, etc. if necessary.	The applicant should sort out and care for the necessary data to prepare for the investigation and/or the request of submission of raw data whenever the Ministry requests. The clinical data should require the signature of the researcher to certify that the test was done by the researcher by herself. The applicant should attach a document to explain when an unavoidable event, such as the death of researcher, arises and could not put a signature on the clinical test document.
Other		The applicant should submit the Japanese translation of the material in related to the foreign clinical data in addition to the original material. The document to certify the translator's certification and background is also requested to state.

Source: Notification from Pharmaceutical Affairs Bureau No. 660 dated June 20, 1985
in the notice by the Director of the Pharmaceutical Affairs Bureau of MHW

< Influence of Regulations >

There are said to be two cases of approval in Japan where applications involved only foreign clinical trial data.[68] However, because foreign clinical trial data for part of phase 2 and phase 3 clinical trials is basically not accepted, at present it has been pointed out that some clinical trials have to once again be performed in Japan. It is in turn pointed out that having to repeat clinical trials previously conducted abroad causes an increase in new drug development costs for foreign manufacturers.

In relation to the acceptance of foreign clinical trial data, the ICH has also been continually engaged in formulating "guidelines regarding the handling of ethnic factors in clinical trial data." In regard to the acceptance of foreign clinical data, even ICH guidelines, which received final agreement between Japan, the U.S. and European countries in February 1998, only mentioned that bridging studies should be carried out as the need arises, and did not provide full conditions for accepting this kind of data.

In the "Joint Status Report on the U.S.-Japan Enhanced Initiative on Deregulation and Competition Policy" which was announced in May 1998, the following direction is set for the use of foreign clinical trial data: "Expand acceptance of foreign clinical trial data through the incorporation of ICH guidelines into Japanese domestic regulations by the summer of 1998, and use an acceptance process that is transparent and avoids inappropriate delays."

(2) Overseas

< The United States >

The FDA recognizes the United States cannot force its own regulations on other countries, as regulations for protecting people examined by clinical trials differ in each country. However, the FDA believes that in order to accept foreign clinical trial data which does not conform with the U.S. standards, clinical trials should clear minimum standards to ensure the protection of people examined. Requirements for admitting application with only foreign clinical trial data have been established in the 1985 revised version of rules concerning NDAs (NDA rewrite).[69] Those requirements are as follows:

- Foreign data are applicable to the US population and US medical practice;
- Studies have been performed by clinical investigators of recognized competence; and
- Data must be considered valid without the need for on-site inspections by the FDA, or if the FDA considers such an inspection to be necessary, the FDA is able to validate the data through an on-site inspection or other appropriate means.

The NDA rewrite prescribes that, if there is no report to verify that the data conforms to those requirements, it is not possible to approve applications in accordance with data collected solely from abroad.

According to interviews with Japanese pharmaceutical companies in the U.S., it is said that the FDA has so far never accepted clinical trial data collected in Japan for the NDA.

< The United Kingdom >

Officially, there is no problem in accepting foreign clinical data, as long as the data, written in English, have been properly collected. However, in practice often only partial acceptance of such data occurs. It is said that pharmaceutical manufacturers tend to carry out the most important part

[68] These were cases involving pharmaceuticals to treat illnesses that affect few patients in Japan (orphan drugs), which made it difficult to carry out clinical trials in Japan.

[69] 21 CFR § 314.106

of clinical trials in the U.K., as they do not want applications to be rejected because of a lack of data.

According to a survey carried out by a British research company on 35 international pharmaceutical enterprises from 1986, only four products of three European enterprises which applied for drug approvals with foreign clinical trial data were actually able to receive approval. It is noted that three out of the four products which received approval were submitted to the FDA of the U.S. by European enterprises, and in the case of the other product, a certain European enterprise applied to the regulatory authorities in another country within Europe.

<France>
In principle the foreign clinical trial data is said to be accepted when the applications for the drug approval is filed, as long as the clinical trials have been conducted complying with the GCP and is also submitted along with the reporting style designated by the order of 9th December 1996.

<Germany>
With regard to the acceptance of the foreign clinical trial data, it is said that the clinical trial data collected in Japan has never been accepted until now. In practice the acceptance is limited to the data collected in other European countries and the U.S. Because of this, among 7 Japanese pharmaceutical manufacturers who attempt to sell their products in Germany, 4 companies have been conducting the clinical trials in the U.S. and 3 in European countries. For new drug approval application, it is a common practice that the clinical trial data collected in Germany be required.

2-2. Time required to obtain approval

(1) Japan

< Content of Regulations >
The efficacy, safety and quality of pharmaceuticals is reviewed and, if results meet certain conditions, the Minister of Health and Welfare grants manufacturing (import) "approval." The review is carried out in accordance with the sequence of procedures in Figure 1-1 (previously shown). The approval application documents are submitted to the governor of the prefecture where the applicant is located and after the documents have been checked, they are sent to the MHW. As regards the time required for review, a standard administrative processing period has been established. The standard administrative processing period for drug applications is one year and a half (18 months). The standard administrative processing period starts from the day the application is received by the prefectures and the aim is for the process to be completed within the above-mentioned period. However, this period does not include the time taken for the applicant to reply to points indicated by the Central Pharmaceutical Affairs Council, nor the time required to correct inadequacies in submitted documents (see figure 1-5).

As of the end of fiscal 1997 the number of staff responsible for carrying out reviews was as follows: There were 53 people assigned to this task in MHW Pharmaceutical and Medical Safety Bureau, 66 in the Drug Organization and 45 in the Pharmaceuticals and Medical Devices Evaluation Center, making a total of 164. There are also about 600 people of experience or academic standing appointed as committee members of the Central Pharmaceutical Affairs Council. These committee members are all engaged on a non-full-time basis.

< Influence of Regulations >
The MHW claims it has not taken more than 18 months to deal with approval cases from 1994 to 1996. According to interviews with pharmaceutical manufacturers in Japan (both Japanese and foreign companies), pharmaceutical manufacturers actually expect it to take two and a half to three years from the time of application to obtain approval for pharmaceuticals here. It has been pointed out that this gap is attributable to the fact that (1) the period from the submission of an

application to the time summoned for a first interview of MHW varies from four months to as long as ten months in some cases; and (2) the points indicated by the Central Pharmaceutical Affairs Council include some that cannot be answered without carrying out new trials and reproducing data. As a result, it is said that some foreign manufacturers have experienced cases where, if applications for approval are simultaneously carried out in Japan, the U.S. and the European, countries approval in Japan has not been granted until six months to a year after it has been received.

In July 1997, the MHW took measures to increase the number of people who deal with reviews and to shorten the time to obtain approvals by adding the Pharmaceuticals and Medical Devices Evaluation Center, and the Drug Organization to share responsibility for drug approval reviews with the main body of MHW (see figure 1-1). At this point, it is unknown to what extent time to obtain approvals has been shortened.

In the "Joint Status Report on the U.S.-Japan Enhanced Initiative on Deregulation and Competition Policy" which was announced in May 1998, the following direction is set: "Shorten the approval processing period for new drug applications to 12 months by April 2000, and to further speed up the introduction of innovative new pharmaceuticals, and significantly shorten approval times, particularly for priority drugs."

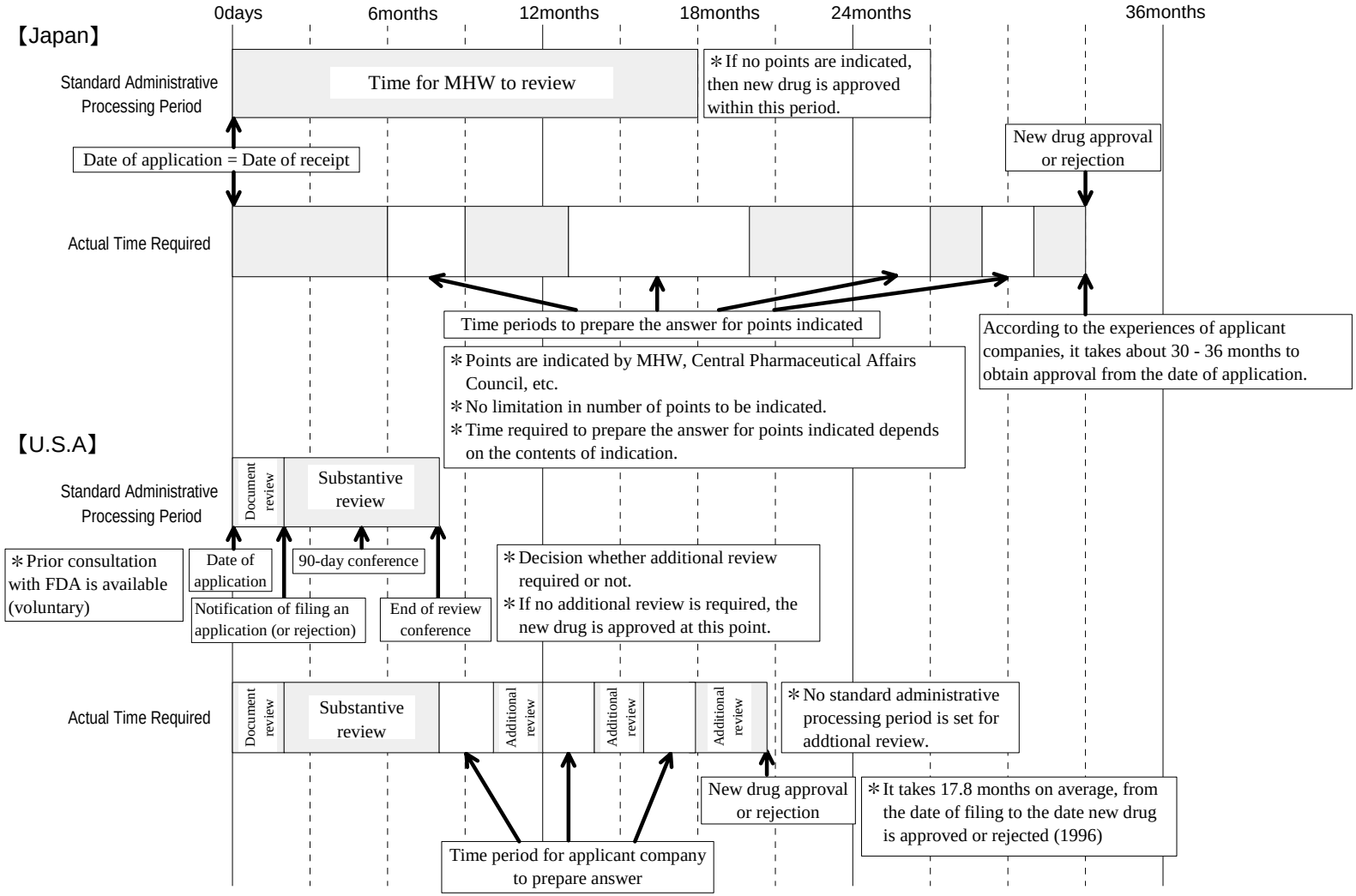
(2) Overseas

< The United States >

New drug applications (NDAs) are approved by the FDA. In the first 2 months the FDA conducts a preliminary review to consider whether or not it will accept the submitted application form. The FDA formally accepts an application after concluding that the application deserves a substantive review, and then the FDA takes 6 months to perform this review. During the review period, the FDA decides whether the NDA a) is approved, b) requires additional review, or c) is rejected. There are many cases where additional review is required, so the FDA's average time required to approve an application, from the date when the FDA formally receives an application to the date when the FDA grants approval, was 17.8 months in 1996 (see figure 1-5).

To shorten the time spent conducting reviews the Prescription Drug User Fee Act was enacted in May 1992 with a five-year period of validity. Based on this law, the number of FDA examination staff was increased, with pharmaceutical manufacturers bearing the expense, and review times are said to have been substantially shortened. At present, there are about 1,600 FDA staff in charge of reviews and around 600 of these are said to be employed using funds provided by this law.

Figure1-5 : Comparison of Review Process between Japan and the U.S.



Source: Japan: Notification from the Pharmaceutical Affairs Bureau No.960 dated Oct. 1, 1985, in the notice by the Director of the Pharmaceuticals Affairs Bureau, MHW, Interviews with industrial sources;
U.S.: 21CFR § 314, JETRO New York center

< EU Member Countries >

To sell pharmaceuticals, marketing approvals must be obtained by one of the following three methods: To sell products in several E.U. member countries, manufacturers receive approvals in accordance with a "centralized procedure" or a "mutual recognition procedure." To sell products in only one of the E.U. member countries, manufacturers receive approvals in accordance with that member country's system ("individual national assessment") (see figure 1-6).

Figure 1-6: The Pharmaceutical Regulatory Authorities and Their Legal Basis in the Surveyed European Countries

Country	Regulatory Authority	Relevant Law
E.U.	European Agency for the Evaluation of Medicinal Products: EMEA	EC Directive 93/39EEC
U. K.	Medicines Control Agency: MCA	Medicines Act 1968
France	Pharmaceutical Affairs Bureau (Direction de la Pharmacie et du Medicament)	Public Health Law (Code de la Sante publique)
Germany	Federal Pharmaceuticals Agency (Bundesamt fur Arzneimittel und Medizinporduct: BfArM)	Pharmaceutical Affairs Law (Arzneimittelgesetz)

Source : Studies by JETRO center overseas

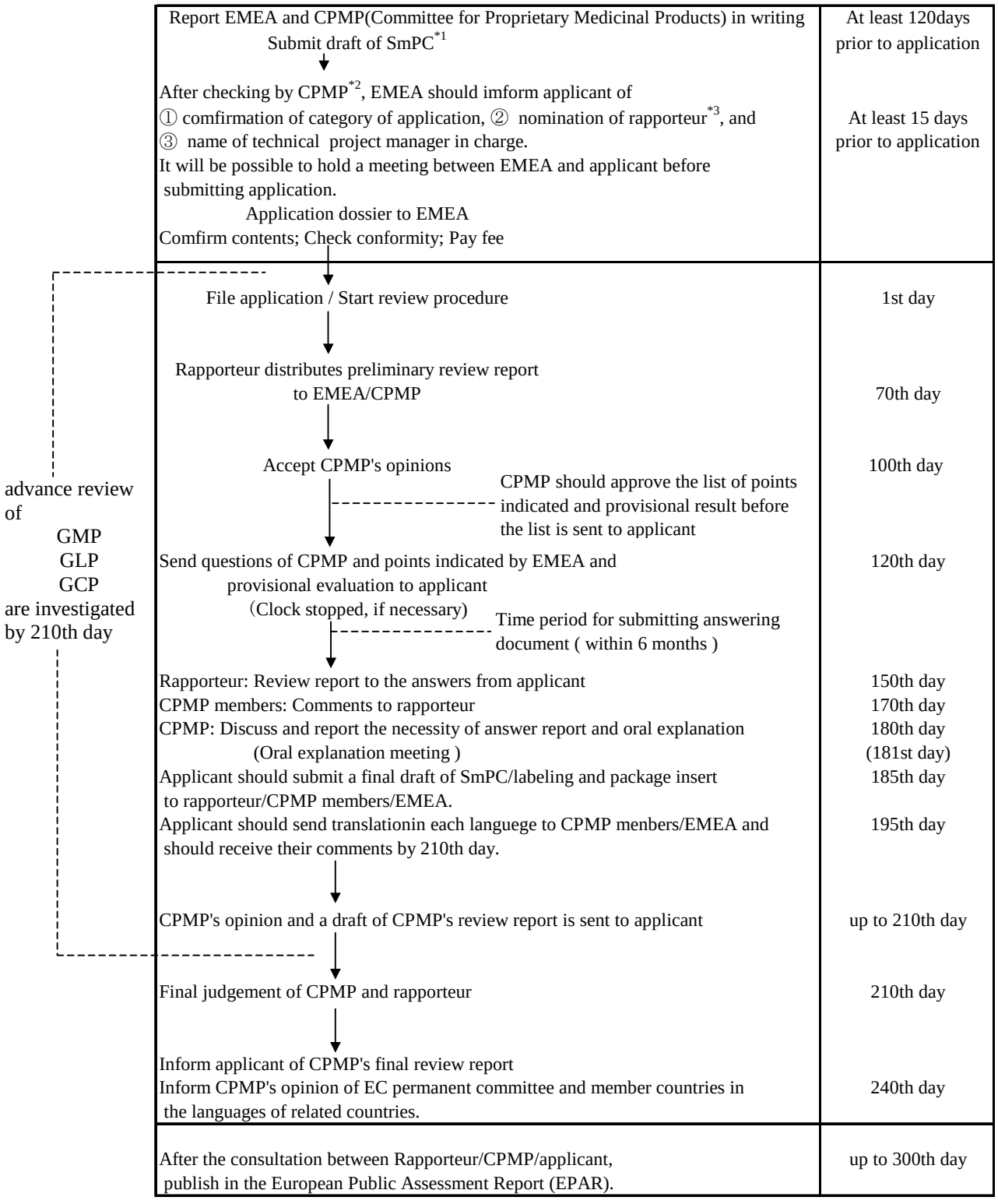
The "centralized procedure" and the "mutual recognition procedure" are new systems that were introduced in 1995. The "centralized procedure" is managed by the EMEA (European Agency for the Evaluation of Medicinal Products) with Regulation 2309/93/EEC as the legal basis. The "mutual recognition procedure" is prescribed by the EC Directive 93/39EEC. As the "centralized procedure" handled by the EMEA currently applies only to applications involving biotechnology products and innovative new products, manufacturers planning to market products in the whole EU region generally use the "mutual recognition procedure."

Under the "centralized procedure", the applicant must attach a Summary of Product Characteristics proposal in a prescribed form and submit application intention and submit this to the EMEA up to four months before making an actual application for approval. During the period before application, it is possible to receive an advance consultation. As the day for submission of the application must coincide with the meeting of the Committee for Proprietary Medicinal Products, the EMEA's advisory body. This day is decided by means of consultation with the EMEA. To determine whether the application complies with GMP[70], GLP[71] and GCP an investigation is performed within 210 days after the submission, and subsequently a European Public Assessment Report is published within 300 days (see figure 1-7). It is said, if the time required for dealings between the manufacturer and the EMEA are included, to actually take about one year for applications to be approved by means of the "centralized procedure."

[70] Good Manufacturing Practice. Standard for production management and quality control of pharmaceuticals.

[71] Good Laboratory Practice. Standard for execution of drug safety tests.

Figure 1-7: Review Process of Centralized Procedure in EU



*1 Summary of Product Characteristics.
*2 Committee for Proprietary Medicinal Products. One of the advisory organizations at the EMEA.
*3 A person who acts as a coordinator going between a review authority and an applicant.

Source: JETRO London Center

3. Systems Concerning Prices

(1) Japan

< Content of Systems >

Japan has adopted a "social insurance system" which obliges every citizen to be insured by some form of public health insurance[72]. There are seven organizations of public health insurance such as the national government, municipal governments, health insurance unions, cooperatives, and so forth. The government pays 13% to 52% of the benefits to these insurance organizations out of its financial resources (for health insurance unions, paid for in the form of a subsidy). Patients are provided with the necessary pharmaceuticals by medical institutions and, in principle, expenses for these pharmaceuticals are reimbursed to medical institutions out of health insurance at reimbursement prices determined by the MHW for each brand.

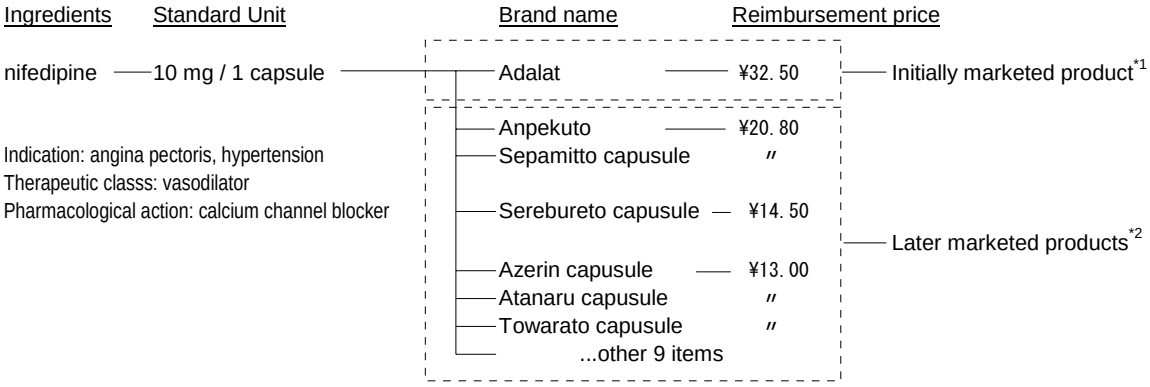
The reimbursement prices by health insurance are, in principle, announced by pharmaceutical brand per standard unit. Listing by brand is a system to set prices by individual commercial names, even though relevant pharmaceuticals have the same ingredients and the same standards.

Manufacturers who want the relevant pharmaceuticals to be used under the health insurance system have to submit application forms with related documents attached to the Federation of Pharmaceutical Manufacturers Association of Japan (FPMAJ). The FPMAJ collects applications from each manufacturer and submits them to the Economic Affairs Division of the Health Policy Bureau of MHW. The Economic Affairs Division of the Health Policy Bureau compiles a list of the applying pharmaceuticals and transfers this to the Medical Economics Division of the Health Insurance Bureau of MHW. The Medical Economics Division of the Health Insurance Bureau is advised by academic institutions whether these pharmaceuticals should be approved for use under the health insurance system. On the other hand, the Health Insurance Bureau calculates the reimbursement prices by health insurance and notifies these preliminarily to the relevant manufacturers. After the aforementioned procedures, reimbursement prices by health insurance are determined and announced in an official gazette.[73]

[72] Japanese health insurance can be broadly divided into 2 types: one is the insurance by occupation which covers people employed by others; and the other is the insurance by regional area which covers self-employed people. In 1961, a health insurance system to cover the whole population was established.

[73] Rules for regular listing were established on the basis of a report on the market-oriented sector-specific (MOSS) negotiations for medical equipment and pharmaceuticals, which were held in January 1986. According to these rules, in principle new pharmaceuticals have to be listed within 60 days, or at the latest no longer than 90 days, after receiving their manufacturing (import) approval at one of four quarterly sessions.

Figure 1-8: Examples of Reimbursement Prices by Health Insurance Calculated based on Brand Name and Standard Unit



*1: Pharmaceutical which was released to the market first,which often means a brand product.
*2: Pharmaceuticals which have the same ingredient,dosage and administration, and indication and efficacy with the initially marketed product. Later marketed products, which are often called as "generics," will be released when the reexamination period or the patent period of initially marketed product expires.

Source: Prepared based on "*Hoken-yaku Jiten* (Directory of Pharmaceuticals used for Medical Services Covered by Health Insurance) April 1997 ed." Yakugyo Jiho-sha

Under the current system, only the health insurance reimbursement prices are determined by the government, and there are no regulations on the shipping price of manufacturers nor the level of margin of wholesalers. If the medical institutions purchase the pharmaceuticals with the price lower than the health insurance reimbursement price, then the differential becomes the earnings of the medical institutions. Therefore, the medical institutions try to purchase the pharmaceuticals as low a price as possible by negotiating with the wholesalers in order to maximize the differential between the actual purchasing price and the health insurance reimbursement price, which works as the upper price limit. The difference between the reimbursement price and the actual purchasing price medical institutions pay is called the “pharmaceutical price profit differential,” which is a source of earnings for those institutions. The pharmaceutical price profit differential is estimated to total about ¥1.3 trillion[74], which is about 20% of the ¥7 trillion in total pharmaceutical expenses that form a part of total national heath care expenditure in Japan. The pharmaceutical expenses are reimbursed based on a “fee-for-services system.” Therefore, medical institutions are paid pharmaceutical expenses in accordance with the amount they used.

Medical institutions explain that the costs they incur in providing pharmaceuticals to patients (personnel costs, pharmaceutical management costs, etc.) exceed the pharmaceutical price profit differential. In addition, the fees paid by health insurance for technical services provided by doctors are held low so that the pharmaceutical price profit differential has become an essential means for management to supplement the fees obtained from technical services.

The reimbursement prices by health insurance are calculated in principle by a “price setting by comparison to similar pharmaceuticals.” With this system, from among the pharmaceuticals listed

[74] According to the material submitted to the “Health Insurance and Welfare Council” by the Japan Medical Association, the way to calculate the total amount of the pharmaceutical price profit differential is as follows: In the national health care expenditure in 1995, the medical costs of hospitals and clinics occupied ¥22,553.6 billion. 31% of the medical costs was spent for the pharmaceuticals, of which the amount was ¥6,991.6 billion. This figure is considered as the annual sales of pharmaceuticals at hospitals and clinics. On the other hand the amount of the pharmaceuticals hospitals and clinics purchased was ¥5,558.1 billion. If the purchasing cost and the consumption tax is subtracted from the sales, the balance is thought to be the amount of the pharmaceutical price profit differential, which comes to ¥1,266.8 billion.

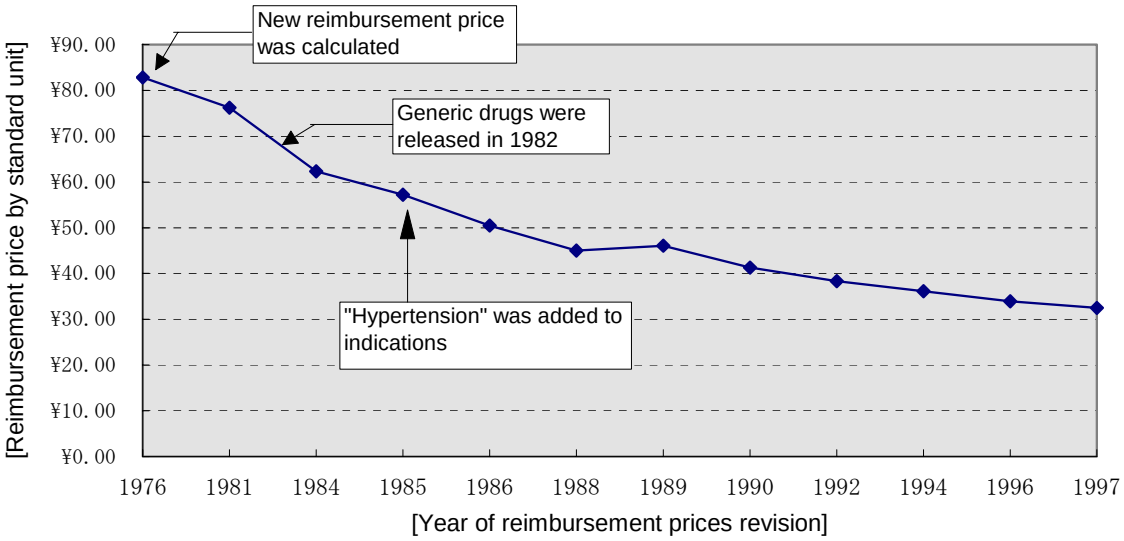
on the pharmaceutical tariff table, pharmaceuticals having similar efficacy and indication are first selected as comparative pharmaceuticals. Then, new prices are determined according to the prices of these comparative pharmaceuticals. In particular, an additional merit premium is applied to pharmaceuticals that are considered to be highly innovative or effective. On the other hand, in the case of pharmaceuticals which are not very new, a price is set which does not exceed the average price of similar pharmaceuticals. With regard to pharmaceuticals for which comparative pharmaceuticals cannot be selected, prices are determined by a “cost accounting system” which calculates prices by adding up production costs, selling, general and administrative expenses, business profits, distribution costs, and so forth.

The reimbursement prices by health insurance are in principle revised every two years. The current method used for this price revision is "the weighted average price plus fixed allowance system" which was established based upon a representation of the Central Social Insurance Medical Council in 1991.[75] This system is to determine new prices by MHW surveying the actual prices that wholesalers charge medical institutions and adding a fixed allowance (Reasonable zone) to the weighted averages of those prices. With this system, as long as the weighted averages of the market prices do not fall below a certain rate, the reimbursement prices by health insurance will theoretically not be lowered at the next review. However, in the actual market, medical institutions demand discounts to gain the highest possible pharmaceutical price profit differential, so that every time prices are reviewed, the reimbursement prices by health insurance tend to decline (see figure 1-9).

In addition to the basic rule previously mentioned, various exceptional rules have been made. For example, a rule called the re-calculation rule says that if certain pharmaceuticals are sold in far greater quantity than initially estimated, at the next revision of prices, MHW reduces the reimbursement prices for these pharmaceuticals by up to a maximum of 25%.

[75] For about 30 years until this system was started, the 90% bulk line system was used to revise the prices of listed pharmaceuticals. The 90% bulk line system involves determining prices using the distribution of market prices by adding up the quantitative ratio of each pharmaceutical against the total quantity, in order of price from the lowest, to 90%. The price of the pharmaceutical on the 90% line was used for the new price. In other words, if one million pharmaceutical tablets were put in order of price from the lowest up, the one on the 90% line, which means the price of the 900,000th pharmaceutical, becomes the new price. The reason why this system was started was that the government tried to accelerate the supply of pharmaceuticals in an era when the nation suffered from a lack of supply and quality of pharmaceuticals after manufacturing facilities were destroyed during World War II. However, since the bulk line system was based on using one price in the market price range to set a new price, if some drugs were sold at high prices, even though others were sold at low prices, new prices would be set at a high level, which was unfair and resulted in widely differing market prices.

Figure 1-9: Changes in the Reimbursement Price of a Vasodilator Drug



Source: A manufacturer of the product

In recent years, in order to curb expanding the national health care expenditure, Japan has been trying to control pharmaceutical expenses. The pharmaceutical expenses can be estimated as the price of an individual pharmaceutical multiplied by the total amount of the pharmaceutical used. The price of an individual pharmaceutical means the reimbursement price determined for each of the above-mentioned brands. A ceiling is not kept for the "total usage" of pharmaceuticals, since the Japanese system is a “fee-for-services system,” which reimburses medical institutions for pharmaceutical expenses largely in accordance with the amount used. It has been thus pointed out that, in order to control pharmaceutical expenses, it tends not to control the amount of usage but to lower the price of each pharmaceutical.

Under the current Japanese system, it can be seen that medical service fees are said to be lower than those in the U.S. and European countries, therefore medical institutions are supplemented by the receipt of a “pharmaceutical price profit differential” and it is pointed out that this results in an increase in the usage of pharmaceuticals. Moreover, it has been pointed out that new pharmaceuticals with high reimbursement prices tend to be selected as the same discount rate applies when doctors and medical institutions try to maximize the “pharmaceutical price profit differential.” In the summer of fiscal 1997, however, MHW and the Ruling Party Health Insurance System Reform Council successively presented proposals for radical reforms to the medical insurance system, and show the plan to abolish the current method of setting the price of pharmaceuticals and change to a system similar to the German reference price system (so called “Japanese Style Reference Price System”). Even though the government set up the “Health Insurance and Welfare Council” in November 1997, a consultative body under the direction of the Minister of Health and Welfare, and made the council specific inquiries concerning this issue, as of June 1998, the council is still continuing with its inquiries. There are opinions to evaluate the “Japanese Style Reference Price System” because it will dissolve the “pharmaceutical price profit differential” and in turn will result in stopping increased pharmaceutical use and shift to high price pharmaceuticals. However, the U.S. has requested that the introduction of the Japanese Style Reference Price System should be withdrawn because actually the reference pricemerely become the maximum official price, and, even if this system is introduced, at least the price of products with remaining patent periods would be determined by the market.

< Influence of Systems >

In recent years, it has been pointed out that, because the government wants to control expanding

national medical expenses[76] for financial reasons, the government has been revising the reimbursement prices (actually reducing prices) in order to curb pharmaceutical expenses forming part of national medical expenses.

It has been said that the pharmaceutical manufacturers who have developed "innovative new pharmaceuticals" are dissatisfied because, under these rules for calculating pharmaceutical prices, those pharmaceuticals cannot be priced high enough in accordance with their marketability, so development costs cannot be recovered. Under the re-calculation rule, if certain pharmaceuticals are sold in great quantity, their prices will be lowered at the next revision. It has been pointed out that the manufacturer efforts will not be rewarded when the re-calculation rule is adopted.

(2) Overseas

In the U.S. and European countries, medical institutions provide the necessary pharmaceuticals for inpatients. However, the pharmaceuticals for outpatients are not administered at medical institutions. The doctors at medical institutions write a prescription and give it to a patient. Then the patient goes to a pharmacy and pays for the pharmaceutical, or receives it as a part of the health care benefit in exchange for the prescription. The pharmacy is reimbursed the cost of the dispensed pharmaceuticals by the health insurance. For the inpatients, the medical institutions are paid the pharmaceutical costs by the "flat sum payment" system. Under the "flat sum payment" system, medical institutions have to cover all the costs for the medical care including the pharmaceuticals within the fixed budget which is designated based on the type of illness. Therefore, for medical institutions, the pharmaceuticals is not a source of earnings as in the Japanese system but a sheer part of the cost.

< France >

France has adopted a "social insurance system" as in the case of Japan. As much as 99% of the total population is insured by some form of public health insurance and medical expenses are, in principle, covered by the earnings from the premium income.

With regard to the prices of individual pharmaceuticals used for outpatients, the government determines the reimbursement price for each brand. On the other hand, in the case of the pharmaceuticals used for hospitalized patients (about 13% of the pharmaceutical market), the reimbursement prices are not fixed. In order to have the reimbursement prices of pharmaceuticals used for outpatients calculated, manufacturers apply to the government to have new pharmaceuticals registered on the reimbursement price lists and the National Economic Committee determines the prices in accordance with a report by the Transparency Committee of the Pharmaceutical Affairs Bureau. Price revisions are determined in the same way. The manufacturers apply to raise the prices and the new prices are determined by the National Economic Committee in response to a report by the Transparency Committee of the Pharmaceutical Affairs Bureau. If a proposed increase in the price of pharmaceuticals is not considered beneficial for national medical services, the Economic Committee can reject the price rise. Moreover, manufacturers and the Economic Committee negotiate with each other to lower the price of pharmaceuticals judged to be of less importance. The price of reimbursable pharmaceuticals is reviewed every three years by renewing the registration of pharmaceuticals subject to reimbursement. In the past pharmaceutical prices have usually been increased, but in 1991 they were lowered. Owing to these factors, the prices of pharmaceuticals in France are said to be lowest in the U.S. and European countries.

As the separation of dispensing and prescribing functions is a common practice, the way to

[76] Under the health insurance system in Japan, expenses which exceed the premiums paid by the insured are covered by government subsidies. The ratio of medical expenses covered by the National Treasury reached 14.9% (¥6.5431 trillion) of the government's general annual expenditure in fiscal 1997.

reimburse the pharmaceuticals used for outpatients is that once the patients pay for the pharmaceuticals at pharmacies, the patients then request the reimbursement to the health insurance. Thus, the pharmaceutical price profit differential does not occur in medical institutions as it does in Japan.

As a means to control pharmaceutical expenses, with regard to those for outpatients, regulations to set a ceiling on medical expenses were introduced in the form of the "government ordinances related to the curbing of medical expenditure" in 1996. By appending provisions every year to Article 17 of government ordinance, the total budget is set by determining the target increase rate for all medical expenditure, such as examination fees for doctors and pharmaceutical expenses for outpatients. If the actual increase in medical expenditure exceeds the target increase, not only is the balance not paid to doctors but it will also be deducted from the examination expenses for doctors. As concerns the pharmaceutical expenses for hospitalized patients, medical institutions have to cover all the medical expenses including pharmaceutical costs within the annual budget fixed for public hospitals, or the total budget setting daily hospital charge in the case of private hospitals.

< Germany >

Germany has also adopted a "social insurance system." About 90% of the population is insured by the disease depository (*Krankenkasse*) which is an insurance management organization.

With regard to pharmaceuticals for outpatients, the Federal Disease Depository Committee determines the upper price limit (hereafter referred to as "reference prices") reimbursed to pharmacies by health insurance. The government does not actually participate in determining the reference prices of pharmaceuticals. The reference prices are determined by categorizing pharmaceuticals into groups with the same effective ingredients and similar therapeutic effects, and setting the prices reimbursed by health insurance for each group (see figure 1-3 in the previous section). However, reference prices are not set for pharmaceuticals which are still within their patent periods. The prices for these are fully reimbursed. If the actual selling prices exceed the reference prices, the balance is covered by patients. The pharmaceuticals for which reference prices are set represent around 60% (in value) of the market for pharmaceuticals used under the health insurance system. The pharmaceuticals for hospitalized patients are included in hospital treatment expenses and they are not subject to "reference prices."

With regard to the pharmaceuticals used for hospitalized patients, there is no "pharmaceutical price profit differential" for medical institutions. Because pharmacies ask some discount from wholesalers, "pharmaceutical price profit differential" occurs in the case of outpatients. However, not the whole amount of difference between the actual purchasing price and the reimbursement price by health insurance becomes the "pharmaceutical price profit differential" as is the case in Japan. The system has been adopted to reduce the amount of such a differential. In the transactions between the wholesalers and the pharmacies, if the wholesalers make a discount, all the differential between the purchasing price of the pharmacies and the reimbursement price by the disease depositories becomes a profit for the pharmacies. However, as a result of reforms under the Medical Structure Law in 1993 (CSG), it was stipulated that the pharmacies are to be paid by a sum based upon the reimbursement price with a deduction of 5%. It is said that this causes a substantial reduction of revenue of the pharmacies.

Pharmaceutical expenses are controlled by setting a total budget. With regard to the pharmaceuticals for outpatients, in January 1998, a "Pharmaceutical Supply Standard Amount" system was introduced, specifying the amount of pharmaceuticals which each doctor can prescribe per patient. Although it is permitted to transfer the benefits for one patient to others, if the total amount of the pharmaceutical benefits exceeds the amount calculated based on the standard amount, the examination fees for doctors are reduced by the excess amount. On the other hand, the cost of pharmaceuticals used by hospitalized patients should be covered by the fixed amount for hospital treatment expenses (including examination fees and pharmaceutical expenses), which are paid to

the medical institutions by disease depositories. The fixed amount for hospital treatment expenses is set on the basis of specific diseases.

< The United Kingdom >

In the U.K., the "national health care system" has been adopted. Ninety percent of the population receives medical services from the National Health Service (NHS). The NHS is mainly funded by taxes.

To set prices of pharmaceuticals used in the NHS, a system called the Pharmaceutical Price Regulation System (PPRS), which is based on agreement between the pharmaceutical industry and the Department of Health, was introduced in1957. The system is that, based upon negotiations between the Department of Health and individual manufacturers, an upper limit is set[77] on the amount of annual earnings from selling pharmaceuticals to the NHS and, in turn, manufacturers set the prices of individual pharmaceuticals freely within the range of their determined profit margin.[78] However, it is not possible to raise the price of a product once it has been put on the market. Companies subject to the PPRS submit a financial report to the Department of Health, and this is used to determine an allowable profit margin in the following fiscal year.

In the U.K., all medical expenses including pharmaceuticals are covered by a budget distributed by the government. Therefore, the government participates in pricing individual pharmaceuticals under the above-mentioned system. Additionally, the medical treatment expenses at medical institutions are controlled by means of the total budget. Moreover, each medical institution makes a list (Hospital Formulary) of the pharmaceuticals which can be used, and medical institutions select pharmaceuticals from this.

< The United States >

In the U.S., there is no public health insurance system that covers the whole population. Most people are covered by private health insurance. In terms of public health insurance, there is Medicaid for low-income earners, Medicare for the elderly, people receiving disability pensions, and so forth.[79] The general public are members of several types of private insurance funds. About 14% of the population (35 million people) are not covered by insurance, as they are not members of any health insurance scheme.

The government is not involved in setting the price of individual pharmaceuticals. Pricing depends on negotiations between those concerned with the distribution of pharmaceuticals, namely, manufacturers, wholesalers, medical institutions or pharmacies. However, in order to avoid pressure from the public or politicians who think that the manufacturers are making too much money, each manufacturer adopts a policy to keep the average increase rate of all pharmaceutical prices within the inflation rate. Moreover, though there are no regulations that govern prices themselves, in the case of pharmaceuticals used by Medicaid, a public insurance, manufacturers are obliged to pay a rebate to state and federal government organizations after they have sold to Medicaid.[80]

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[77] The system currently permits manufacturers to earn a profit margin in the range of 17-21% of their investment capital, after deducting R&D expenditure and sales promotion costs. Companies that make a significant contribution to regional communities by means of exports, R&D and manufacturing and which are regarded as contributing to the British economy are allowed to earn a higher profit margin up to a limit of 25%.

[78] The problem which has been pointed out with the PPRS is that for large scale companies who deal with large number of products , they can develop price strategies for individual products. However, for small and medium-sized companies, because number of products they deal with is small, the options of strategy they can choose is limited.

[79] About 25% of the population is covered by public health insurance.

[80] The rebate is calculated based on the standard price which is the lower of the following: a discount of

Membership system private health maintenance organizations called HMOs, which are one form of private health insurance, cover most of the pharmaceuticals for outpatients. However, only when doctors select pharmaceuticals from a very limited item list (formulary) made by the insurer itself, are they covered by insurance. If patients want to use pharmaceuticals which are not on the item list, they have to pay extra premiums. With regard to the pharmaceuticals used for hospitalized patients, excessive administration is curbed by standardizing treatment methods for each disease as in the U.K., and by including all the expenses in a flat payment scheme.

Moreover, medical institutions enter contracts with insurance organizations based on a total amount contract system and are able to make profits within the budget adopted. For example, since HMO contracts with doctors by means of the total amount contract system, doctors are obliged to cover all the expenses including pharmaceutical costs related to the examination of HMO members who the doctors contract to examine, within the contracted budget.

15.1% off of the average wholesale price or the best price offered by the manufacturer for the drug anywhere in the U.S. An additional rebate may also be called for if the drug's price exceeds a price based on the consumer price index.

II. Distribution and Business Practices

1. Factors in the Selection of Pharmaceutical and Sales Methods

(1) Japan

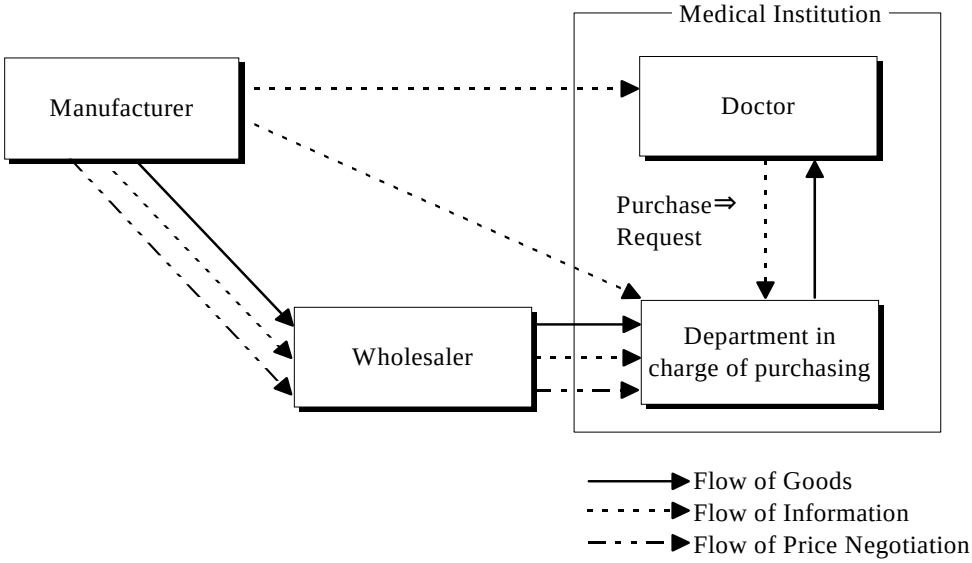
< Content of Business Practices >

The pharmaceuticals cannot be sold alone because they characteristically have a direct influence on human life and health and in turn that they can be used only after they are provided with information on their safety. The information of pharmaceuticals is provided by a person called an MR (Medical Representative) who works for manufacturers, and is in charge of detailing drug information. This kind of activity to supply drug information is performed in the U.S. and European countries alike.

In Japan, the number of MRs is said to be about 50,000 in the country. The number of MRs per manufacturer ranges from 600 to 1000. Looking at the way of employing MRs, in most cases manufacturers recruit college graduates and train them internally. The specialized job of a contract MR, commissioned by pharmaceutical manufacturers to do business and sales promotion of pharmaceuticals during a set contract term, has become wide spread in the U.S. and European countries, but not yet in Japan. A foreign-affiliated company is said to begin offering contract MR dispatching businesses in 1998. The practice to hire and train a large number of MRs by manufacturers themselves has a potential to take a long period of time to establish a sales operation system in Japan and to raise initial investment costs.

It is thought that the reason why Japan is told that there is a relatively large number of MRs is because the distribution system of pharmaceuticals and the factors in the selection of pharmaceuticals at medical institutions, who are the dominant users of pharmaceuticals, are different from those of the U.S. and European countries. First, looking at the distribution system, in Japan's pharmaceutical market, the main channel of merchandise flow is from a manufacturer to a medical institution via wholesalers (see fig. 2-1 in the previous section). In principle, as the separation of dispensing and prescribing functions has made little progress in Japan, the percentage of pharmaceuticals sold by wholesalers to pharmacies is small. 80% of the total value of ethical pharmaceuticals sold is to medical institutions (see fig. 2-5).

Fig. 2-5: Distribution of Pharmaceuticals to Japanese Medical Institutions, as Expressed in Terms of Flow of Goods, Information, and Price Negotiations



Source : Prepared based on interviews with industrial sources

Secondly, looking at the factors in the selection of pharmaceuticals at medical institutions, in Japan there is no ceiling nor fixed amount to regulate the pharmaceutical used under the health insurance system, rather the cost of pharmaceuticals being used under the health insurance system is largely paid back according to a "fee-for-services system[81]" in principle. Therefore, medical institutions are not constrained by the amount of pharmaceuticals they use and can freely select brand-names. Furthermore, in situations where they have a choice of several products, all basically equivalent in terms of active ingredients and efficacy, medical institutions tend to select pharmaceuticals with high health insurance reimbursement prices which maximize their "pharmaceutical price profit differential[82]."

When doctors write the prescription, it is said that it is common practice in Japan for doctors to prescribe pharmaceuticals by brand name because most of the pharmaceuticals that can be used in health insurance are listed by their brand names. If the prescription is written by the brand name, pharmacists can not change it to other therapeutically equivalent drugs because of regulation under the Pharmacist Law. The MHW had advised to write prescriptions in principle using the names of pharmaceuticals listed in the "pharmaceutical tariff system[83]" until the ministry recently changed its policy.[84]

In addition, it is said that doctors neither write generic names nor specify generic brands on their prescriptions even when generic products of equivalent ingredient and efficacy are available. The reason for this is pointed out as doctors and pharmacists are uncertain about whether a generic product actually has the bioequivalence[85] of its brand-name precursor, or whether the manufacturer of a generic product has an adequate framework in place for the supply of information on the product's safety.

Because of these factors, in Japan, medical institutions are weighted more heavily in the pharmaceutical market in comparison with the U.S. and European countries, and the meticulous provision of information to medical institutions is thought to be of great importance in the sales promotion of their own products. With regard to the in-house training of MRs, this practice is not only found in the pharmaceutical industry but also in Japanese corporations as a part of general practice of long term employment, thus it is thought that there is no foundation from which the outsourcing market can grow.

< Influence of Business Practices >

Since the cost of pharmaceuticals being used under the health insurance system is largely paid by a "fee-for-services system," medical institution cost burdens do not increase in spite of the abundant use of pharmaceuticals, but this tends to encourage doctors to earn a pharmaceutical price profit differential by prescribing large quantities of pharmaceuticals.

Even if the place of medication preparation shifts from medical institutions to pharmacies outside of medical institutions as the separation of dispensing and prescribing functions progresses, in most

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81 See the previous section "System concerning prices."

82 See the previous section "System concerning prices."

83 See the previous section "System concerning prices."

84 In 1994, the MHW's Health Insurance Bureau revised its position on prescription entries with a notification by the director of the Health Insurance Bureau's Medical Economics Division, titled "On generic-pharmaceutical listing requirements for non-hospital prescriptions" (Notification of Health Insurance Bureau No.33, Notification of Health and Welfare Bureau for the Elderly No.51, March 29, 1994). That notification stated, in effect, that, while it was considered standard practice to use the names of pharmaceuticals on standard pharmaceutical price lists, generic pharmaceutical names would also be acceptable.

85 Bio-equivalency is a measure of a given generic pharmaceutical's equivalence to a brand-name precursor, as based on measurements of blood density and other pharmacokinetic parameters at a given point in time after it is given to a human subject.

cases doctors list brand-name drugs on the prescriptions they issue and in turn pharmacists cannot recommend generic drugs to patients even if therapeutically equivalent generic alternatives exist. Pharmacists are regulated by the law in that they must not alter a prescription unless they have the consent of the issuing doctor[86]. It could be said that the order for a given drug is made when the doctor writes the brand name on the prescription.

Therefore, the manufacturers can expect that to employ large numbers of MRs, to establish a business system allowing them to visit doctors frequently, and to encourage doctors to prescribe pharmaceuticals of their company, result in increasing product sales.

(2) Overseas

In the U.S. and European countries, the separation of dispensing and prescribing functions is common, and in turn the pharmaceuticals administered to outpatients are sold to pharmacies. Sales to medical institutions comprise only the drugs that are to be administered to inpatients. Therefore, medical institutions do not earn a "pharmaceutical price profit differential" on the pharmaceuticals they prescribe to outpatients. Moreover, it is common that the cost of pharmaceuticals administered to hospitalized patients is usually included in the fixed cost required for treatment including pharmaceuticals, which depends on the type of illness, so that there is no inducement to use large quantities of pharmaceuticals. On the contrary, as to the selection of pharmaceuticals with the same efficacy, there is an incentive to prescribe cheap pharmaceuticals, however, incentives are also present for high-priced pharmaceuticals due to greater therapeutic value, smaller quantity necessary and reduction of hospitalization days.

< The United States >

Looking at the distribution system, though manufacturers sell mostly through wholesalers, they sell about 10 % directly to pharmacies and medical institutions. In terms of the amount of sales, pharmaceuticals sold to medical institutions account for 25% of the market.

In rural areas, the number of MRs is said to be 30,000. Looking at MRs per manufacturer, a medium-size manufacturer has 1,000 MRs and a large manufacturer employs 3,000-3,500 MRs. Each MR has 100-250 clients in his or her assigned territory, and makes the rounds to each on a consecutive basis. In some cases manufacturers contract independent marketing companies with their own sales forces. The reason why manufacturers contract these independent marketing companies is mainly for the promotion of a pharmaceutical product that is nearing the end of its patent life. By doing so, the manufacturers can shift their own sales personnel to new pharmaceuticals with higher earnings potential.

In terms of doctor's prescriptions, both public and private health-insurance have set up frameworks to monitor whether to prescribe excessively and whether the contents of prescriptions are appropriate by using peer reviews[87] doctors report cards, and comparing each doctor's record with accepted prescription practices.

Even if doctors prescribe pharmaceuticals by their brand-names, unless state otherwise, pharmacists can offer patients a choice of less-expensive, therapeutically equivalent generic drugs. In addition, the private insurance companies give incentives to pharmacies by making a contract with pharmacies if pharmacies dispense cheaper generic drugs to patients, then the insurer pays a higher dispensing fee to pharmacies.

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[86] Pharmacist Law, Article 23

[87] Peer review organizations in the U.S. are professional screening bodies with the mission of, among other things, assessing the propriety and medical necessity of health-care services provided through the Medicare and Medicaid programs, and whether the institution providing those services is suited to the task. Their designation as peer review organizations is principled on the view that only doctors are capable of assessing the professional behavior of other doctors.

< The United Kingdom >

Medical institutions purchase about 70 percent of their pharmaceutical supplies through wholesalers. Pharmacies and dispensing doctors[88] also purchase close to 90 percent of their drugs through wholesale sources. In terms of the amount of sales, pharmaceuticals sold to medical institutions account for 14% of the market.

The industry as a whole employs an estimated total of about 5,000 MRs. Mid-sized companies each employ around 100 MRs on average, and large manufacturers each have around 400 MRs. In general, MRs visit GPs about four times per annum, and hospital doctors about once a week. Contract MRs are common in the U.K. and they constitute about one-third of the total. When they have developed a new pharmaceutical for a new market segment, most pharmaceutical companies consider it far more efficient to contract with outside MRs versed in that particular field rather than invest in the training of new MRs.

The pharmaceuticals that medical institutions may use are included on a list termed the Hospital Formulary. Pharmaceuticals listed on the Hospital Formulary are decided upon by the organization called the "Drug and Therapeutic Committee" in which doctors, pharmacists, and the management of medical institutions participate. Pharmacists are in charge of procuring pharmaceuticals. When a pharmaceutical will be newly listed on the Hospital Formulary, pharmacists also play a role of asking for quotations to suppliers and making decisions to procure the pharmaceuticals with the cheapest quotation.

All the pharmaceuticals listed in the Hospital Formulary are listed by generic names. Since most institutions employ computer software to issue prescriptions, the system automatically prescribes a pharmaceutical by generic name even if a doctor happend to input its brand name. Furthermore, the NHS has instructed doctors to write their prescriptions with generic names, not brand names.

< France >

It is rare that medical institutions procure their pharmaceuticals through wholesalers, and in most cases, they purchase directly from the manufacturers by tenders. Pharmacies, on the other hand, purchase mostly from wholesalers. In terms of the amount of sales, pharmaceuticals sold to medical institutions account for 13% of the market.

It is said that in many cases medical institutions consign the price negotiation to a company called "*central d'achat*[89]" which specializes in the negotiation of pharmaceutical prices, and/or several hospitals form a price negotiation group and the group negotiates manufacturers prices. Either way gives a merit to medical institutions that they can gain a lower price than when they negotiate individually, and also the pharmaceutical department of medical institutions can save time. In this case, products are delivered from manufacturers to medical institutions directly.

The French pharmaceutical industry as a whole has an estimated 15,000 MRs. Individual doctors in private practices see MRs from a given maker two to three times a year. Also in France, there are several companies that cater to the industry with contract MR services. Most pharmaceutical makers outsource their major promotional activities to such companies whenever they have a newly developed product they want to bring to market.

It is a common practice for a doctor to prescribe in the specific brand names. Unless pharmacists have the explicit prior consent of the prescribing doctor, they cannot alter a prescription.

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[88] Dispensing doctors are physicians operating in remote districts where no pharmacy is available within a radius of 3 miles. They are licensed to fill prescriptions for patients whose homes are more than a mile away from the nearest pharmacy.

[89] A *central d'achat* is a company who is specialized in negotiating with manufacturers and determining the pharmaceutical price as the representative of several hospitals. It is not engaged in taking order and/or delivering the pharmaceutical.

However, the government ordinance “Concerning the Control of Medical Expenditure” enacted in 1996 states a rule which allows writing prescriptions not with brand names but with indications for specific illnesses in the case of prescribing several pharmaceuticals only. It became possible for pharmacies to sell less-expensive pharmaceuticals for the illnesses indicated on such prescriptions.

< Germany >

Medical institutions purchase about 50 percent of their pharmaceutical inventory directly from pharmaceutical manufacturers, 30 percent via wholesalers, and the remaining 20 percent from special, affiliated pharmacies known as "*bestellapotheke*."

The pharmaceutical industry as a whole employs an estimated total of about 18,000 to 25,000 MRs. Small companies each have about 60 or so MRs, and large manufacturers each employ about 200 MRs.

General hospitals have their own internal pharmaceutical committees, known as *arzneimittelausschuβ*, which monitor and manage the procurement of pharmaceuticals. The members of the committee are pharmacists, administrative managers, doctors (usually medical directors), nursing staff, and management personnel from each medical department. By the committee, the pharmaceutical list is drawn up. According to the list decided here, purchasing officers negotiate manufacturers and purchase pharmaceuticals.

The manner that doctors write the prescription is divided into two cases; one is to prescribe by generic names and the other is by brand names. And for the latter case, as the consideration for the economic conditions of the insured, the generic substitution by the pharmacist is admitted. In principle, pharmacists need the consent of the issuing doctor if they alter a prescription. But in practice, pharmacists can recommend and sell the therapeutically equivalent drug as in the prescription based upon the agreement with a patient. When a doctor prescribes in a generic name, then, a pharmacy must offer the pharmaceutical of which the price is less than 75% of the reference price.

2. Business Relations in the Distribution System

(1) Japan

< Content of Business Practices >

Looking at the number of wholesalers, there are 260 companies affiliated with the Japan Pharmaceutical Wholesalers Association (JPWA), and together they account for close to 90 percent of all domestic pharmaceutical sales revenue. Though the JPWA numbered 486 companies in 1985, that number decreased to 260 mainly by mergers and acquisitions in 1998. But among these wholesalers, there are no nationwide wholesalers to cover a whole nation as their business territory or no full line wholesalers who handle a product line-up consisting of pharmaceuticals produced by all manufacturers. Given these circumstances, it is said that manufacturers like those foreign-affiliated companies who limit the number of wholesalers currently have contract ties with 40 to 50, and large Japanese manufacturers do so with over 100 wholesalers.

Fig. 2-6: The Business Reach of Japan's Larger Pharmaceutical Wholesalers

Company	Location of Headquarters	Number of Prefectures Business Reached
Suzuken	Aichi	26
Kuraya	Tokyo	21
Toho Yakuhin	Tokyo	19
Nihon Shoji	Osaka	17
Fukujin	Tokyo	16

Source: The Industrial Bank of Japan "IBJ" March 1998

In terms of business relations between wholesalers and medical institutions, there exist such traditional practices as "lump-sum bulk buying" and "provisional supply and provisional payments." "Lump-sum bulk buying" refers to the purchase method in which decisions for hospital-tendered bids and so forth are made based upon the discount rate for the total amount of pharmaceuticals purchased, but do not require unit prices for any single pharmaceutical. For example, a wholesaler gets a 20 million yen order for a three-month supply of several different kinds of pharmaceuticals a medical institution regularly uses. The wholesaler later works out unit prices for each item so that the entire order fits within that total bid price. When delivery prices from wholesalers to medical institutions are reexamined, "provisional supply" are deliveries made by the wholesaler to the medical institution at provisional prices until the time delivery prices are determined the two parties can work out a final purchase price. During that interim "provisional payments" are made at the provisional price in keeping with the requests of the medical institution. According to an association survey, looking at whether delivery prices had been settled as of March 1997 for pharmaceutical deliveries made since April 1996, formal delivery prices had yet to be reached with 33 of the 1,802 surveyed hospitals, despite the fact that a year had elapsed since negotiations began.

As to the collection of accounts receivable, medical institutions on average receive payment from health insurance funds about 3.5 months after providing treatments. By contrast, wholesalers reportedly receive payment from medical institutions about four months after their deliveries, on average. In relation to the above mentioned "provisional payments," provisional payments are made for the first time four months after the deliveries and it is said that in some cases medical institutions take up to a year or more to make such payments for the first time. These payment-related practices do not amount to contract violations because the practice of the exchange of written contracts setting explicit terms or conditions between wholesalers and medical institutions has not progressed. Conversely, written contract arrangements have become more common between wholesalers and manufacturers. Wholesalers usually make their payments about five months after deliveries of the pharmaceuticals by manufacturers.

At the beginning of entering into the Japanese market, foreign manufacturers in many cases consign the marketing and sales to domestic manufacturers who already have sales networks. Under such an arrangement, payment for merchandise sold will come not from wholesalers but from the domestic manufacturers that have been consigned for such purposes. Though this arrangement allows foreign manufacturers to collect payment more quickly than would be the case if they went through wholesaler channels, it is said that they typically have to pay the counterpart Japanese manufacturer a high commission.

The main reason manufacturers conduct their business via wholesalers is pointed out that manufacturers require the functions of wholesalers in physical distribution, collection of accounts receivable, credit management, and so on.

Distribution function means to let wholesalers assort and deliver products of manufacturers, since it would not be efficient for makers to build systems for daily deliveries of their own products alone to the 9,606 hospitals, 87,069 clinics, and 39,433 pharmacies now operating nationwide.[90] The function of collection of accounts receivable means to entrust the collection task to the 50-100 wholesalers with whom they have contract ties, since it is costly for manufacturers to collect accounts receivable for their own products every month and in turn impossible for them to do so by themselves. The function of credit management is to monitor financial conditions at specific medical institutions and set ceilings on credit sales.

Until the introduction of the price quotation system in 1992,[91] in Japan, manufacturers wielded de facto control over the pharmaceutical prices wholesalers charged client medical institutions. Most wholesalers were affiliated with domestic pharmaceutical manufacturers so it was difficult for newcomers to set up their own sales channels. So it is said that foreign manufacturers had little choice but to have entrusted their sales operations to Japanese manufacturers. Since the introduction of the quotation system, more and more foreign manufacturers have assumed direct control of the sales and promotional operations for their products in Japan[92] (see fig. 2-7).

[90] Hospitals are defined as medical facilities with beds for 20 patients or more. Clinics are facilities that serve outpatients only, or that have beds for up to 19 inpatients (Medical Service Law, Article 1). Pharmacies are defined as places where pharmacists engage in dispensing activities for the purpose of selling or giving (Pharmaceutical Affairs Law, Article 2). Note, however, that hospital pharmacies are under the jurisdiction of the Medical Services Law, and as such, are not treated as pharmacies under the Pharmaceutical Affairs Law.

[91] In those days, the maker's quotation price (the wholesaler's purchase price) was initially about 5 percent below the reimbursement price by health insurance, a level at which most medical institutions were not prepared to purchase anything (At the time, the margin of the pharmaceutical price differential ran around 30-40 percent of the reimbursement price.). The system worked like this: If a wholesaler contacted a manufacturer about its interest in selling hospital A 1000 units of pharmaceutical B, and asked the manufacturer's quotation price, the manufacturer might instruct wholesaler C to sell to A at a 30 percent discount, which is what C would do. The manufacturer would later compensate the wholesaler for 25 percent of the difference with a rebate. In effect, though the wholesaler is left with a profit margin of zero, it obtains a rebate of 5-10 percent on its 30-percent discounted price. The Fair Trade Commission insisted that this system be revised, however, on grounds that it allowed pharmaceutical manufacturers to control resale prices. That led to the introduction of the price quotation system in 1992. Under this system, manufacturers deliver to wholesalers at a specific quotation price, and wholesalers, in their negotiations with client medical institutions, are free to sell the merchandise at a price that ensures them a suitable margin on top of the manufacturer's quotation price.

[92] There is an exceptional case, as the Pfizer Pharmaceuticals Inc., who started building its own sales network in the previous year of the establishment of the joint venture company with the Taiwan Sugar-manufacturing in 1955.

Fig. 2-7: Recent Examples of Foreign-Affiliated Pharmaceutical Manufacturers that Have Started Selling Their Products by Themselves in Japan

Foreign Affiliated Manufactures	Parent Companies in Overseas	Nationality of Parent Company	Year Established Foothold in Japan	Japanese Companies Sales Consigned	Year Started Sales Independently	Years Taken To Sell Independently
Janssen-Kyowa	Janssen (Johnson & Johnson)	Belgium (U.S.)	1978	Kyowa Hakko	Jan-1999(planned)	21years
Novo Nordisc Pharma	Novo Nordisk A/S	Denmark	1980	Yamanouchi	Apr-1-1998	18years
Astra Japan	AB Astra	Sweden	1975	Fujisawa	in part Oct-1996 completion Apr-1-1998	in part 21years completion 23years
Searle Yakuhin (Monsanto Japan)	Monsano Co.	U.S.	1967	Dai-Nippon Pharmaceutical	in part July-1992 completion Apr-1-1998	in part 25years completion 31years
ZENECA	ZENECA Ltd.	U.K.	1974	Sumitomo Chemical	1995	21years
Nihon Upjohn (Pharmacia&Upjohn)	Pharmacia & Upjohn Inc.	U.S.	1959	Sumitomo Pharmaceutical	1995	36years
Nippon Boehringer Ingelheim	Boehringer Ingelheim International GmbH	Germany	1961	Tanabe,and Dai-Nippon	1993	32years

Source : Prepared from various news reports

< Influence of Business Practices >

Since the collection of payments is prolonged because of such practices as “provisional supply” and “provisional payments” found in the dealings between wholesalers and medical institutions, it is necessary for manufacturers to monitor constantly the financial position of the wholesalers they do business with. In general, manufacturers hold accounts receivable of about a half-year on their transactions with any given wholesaler. That works out to an average 600 million yen in accounts receivable, assuming monthly business with the wholesaler is in the range of 100 million yen. Needless to say, if a wholesaler with that much in liabilities were to fail, the impact on the manufacturer would by no means be small. It has been pointed out that manufacturers anticipate hospitals may delay making payments and pay rebates to wholesalers. Especially in the case of small- and medium-scale wholesalers, it has been pointed out that there may exist cases that manufacturers pay large rebates in the interest of supporting their continued business operations. It can be said that these practices burden manufacturers.

More or less like Japanese pharmaceutical makers, foreign manufacturers who enter into the Japanese market for the first time must be prepared to take on the burden of paying supportive rebates to wholesalers if they intend to utilize the existing distribution system. In many cases, foreign manufacturers at the time of initial entry into the Japanese market entrust their product sales and promotions to Japanese makers who already have the domestic sales channels in place. But once foreign outfits assume control of their product sales in Japan and start doing business directly with wholesalers, no longer will they face the necessity of paying high commissions to Japanese makers for that purpose. On the other hand, they will find that it takes longer to collect payment for their merchandise compared to the days when they received payment from the Japanese makers they initially entrusted their sales operations to. It has been suggested, however, that it will be difficult to persuade many parent companies abroad to accept the prospect of delays in the collection of payments on accounts receivable by subsidiaries who have assumed direct control of product sales and promotions in Japan.

(2) Overseas

In terms of the price at which pharmaceuticals are sold by wholesalers to pharmacies and medical institutions, it is common in the U.S. and European countries to exchange contract agreements explicitly setting forth in writing the terms of payment and "provisional payments" which, in Japan, is not practiced.

The practice which new comers consign their sales operations to local manufacturers is also found

in the U.S. and European countries. And it is pointed out that new comers take this option as the method to alleviate the sales administration cost in their early stage of establishing business in a new market. However, in this case, the consignments often consist of a whole package including the promotion activities to doctors and the collection of payment. Because in the U.S. and European countries, there does not exist a merit for new comers that they could collect payment in a shorter time if they consign sales to manufacturers, it is not common to consign the collection of payment only to manufacturers as in Japan. If only consigning the collection of payment, there is a contractor called a 'distributor' who is specialized in that particular function. It is a common arrangement to consign the collection of payment to the distributor, and the manufacturer focuses on its activity of sales promotion. In that case, the commission to the distributor is said to be less than 10%.

< The United States >

It is estimated that there are 39 full line wholesalers, and the top five are nationwide wholesalers. By doing business with the top five wholesalers, manufacturers could cover 70 to 80% of the entire market.

The prices at which wholesalers sell to pharmacies and medical institutions are set on the basis of price lists that reflect monthly purchase value and length of payment schedules. The more a client buys, and the shorter the payment schedule, the lower the purchase price.

The standard contract schedule for payments by pharmacies or medical institutions to wholesalers is 15 days. The deadline for payment on purchases made between the 1st and 15th of a given month is the 25th of that month. The average payment schedule for transactions between manufacturers and wholesalers is 30 days.

< The United Kingdom >

In the U.K., there are eighteen full line wholesalers. AH Holdings Plc and Unichem Plc each control about 30 percent of the market, or together fully 60 percent. Manufacturers essentially do business with all 18 of the full-line wholesalers.

Wholesaler margins are set by the PPRS.[93] Since they are fixed by the NHS at 12.5 percent of the price after the drug tariff[94], the price a wholesaler charges client pharmacies is set easily once the manufacturer settles on the sales price for a transaction with the wholesaler[95].

Schedules for payment to the wholesaler are often set to accommodate the wholesaler's payment deadline with the maker, and, ordinarily, payments for a given transaction are made by the end of the following the month.

< France >

Manufacturers can have access to 97 percent of the market via wholesalers provided they do business with the three top wholesaling groups: OCP, Alliance Santé, and CERP. In France, however, there exists another class of distribution middlemen called the manufacturer affiliated agents. The manufacturer affiliated agents maintain inventories of their manufacturer's pharmaceutical line, process orders, make deliveries, compile invoices, and occasionally handle imports. The difference that sets them apart from wholesalers is that they have been "commissioned" full-time by pharmaceutical companies to engage in these commercial activities, and in turn they could conceivably be termed distribution subcontractors. The supply of pharmaceuticals via the manufacturer affiliated agents accounts for 8% of the total sales of

[93] See the previous section "System concerning prices."

[94] Official margin regulations do not apply to generic drugs. Margins for those depend on negotiations with the manufacturer, and reportedly average around 20-30 percent.

[95] However, when a pharmacy's purchasing volume is large and/or the pharmacy completes payment within the schedule, the wholesaler gives discount and/or pay rebates to the pharmacy.

manufacturers in 1995.

The wholesaler's margin is officially set at 10.74 percent of the maker's pretax delivery price. Once the manufacturer's delivery price has been settled, the price at which wholesalers make their sales to pharmacies will be easily set[96].

The schedule for payment by pharmacies or medical institutions to wholesalers is basically 45 days. That for payment by wholesalers to manufacturers is 60 days.

< Germany >

In Germany, there are 16 full line wholesalers. If a manufacturer attempts to deal with all the wholesalers carrying a full range of products, a manufacturer only enters into a contract with 16 companies.

Wholesaler margins in terms of percentages or amounts are based on the level of the manufacturer's delivery price.[97] Judging from the size of their markup on the maker's delivery price, wholesalers earn a margin of 15.6 percent, on average. Once settled, the manufacturer's delivery price defines easily the price at which wholesalers make their sales to pharmacies. But heavy competition to date has prompted many wholesalers to cut their official markups by around half and the resulting discounts translate into added profits for the pharmacies. Because of the pressure from the disease depositories who complain that the margin of pharmacies was too high, the system was changed in 1993. The disease depositories now reimburse pharmacies a sum based on the reimbursement price of the health insurance with a deduction of 5%. In other words, in the established system, a certain amount of the discount given to the pharmacy is paid back to the disease depositories.

The schedule for payment by pharmacies or medical institutions to wholesalers is 30 days. That for payment by wholesalers to manufacturers is the same.

[96] However, because of the fierce competition with other wholesalers, there are some cases where the wholesaler gives a discount to the pharmacy.

[97] An absolute-value principle seems to be at work: the lower the drug unit price, the higher the margin, and the higher the unit price, the lower the margin.

Appendix

Appendix 1: Survey on Pharmaceutical Prices

International comparative surveys on pharmaceutical prices have been conducted in several preceding studies.[98] It is not easy to compare pharmaceutical prices internationally as it involves questions about the international comparative survey on pharmaceutical prices such as 1) the appropriate way to select samples for comparison , 2) which comparative unit price, for example, "per single tablet," "per one gram," or "per daily dosage," should be used, 3) and how to evaluate the state of pharmaceutical consumption and frequency of pharmaceutical adoption in countries surveyed, and so on.

Under the present Japanese pharmaceutical tariff system, problems have been pointed out both domestically and from abroad as follows: new innovative pharmaceuticals are not priced at reimbursement prices by health insurance to meet development costs, and also reimbursement prices by health insurance decreases according to the time passed since the pharmaceuticals were put on sale and, in turn, they go through several revisions of reimbursement prices by health insurance. In this study, it has been thus decided to conduct the survey on pharmaceutical prices under the following conditions:

(1) In order to select pharmaceuticals for comparison, they are grouped into three in terms of novelty, that is, "innovative new drugs," "improved new drugs," and "long-time listed drugs." And also into two groups according to the location where pharmaceuticals are to be used, that is, "for hospital use" and "for outpatient use." For each group, three representative drugs are selected based upon advice of industry specialists. In order to examine whether there are price differences between the country where a drug is developed and the country into which it is introduced, at least one item developed in each of Japan, the U.S., and European countries, is selected in the same group.

(2) The prices surveyed are purchasing prices by medical institutions or pharmacies as place to administer medicines to the patients. In order to examine the conditions of competition in the market, this study has surveyed purchasing prices of medical institutions or pharmacies.

(3) Since there are differences in the way drugs are administered to outpatients in Japan, the U.S., and European countries, the survey was conducted in each country as follows: In Japan, those pharmaceutical prices for both hospital use and outpatient use are purchasing prices by medical institutions classified as university hospitals. In Germany, those for hospital use are purchasing prices by medical institutions also classified as university hospitals, while those for outpatient use are purchasing prices of pharmacies. In France, those for hospital use are purchasing prices of private hospitals and those for outpatient use purchasing prices of pharmacies. In the U.S., a part of them are purchasing prices of one of the group purchase organizations,[99] and others are average sales prices of wholesalers if such prices could not be surveyed. In the U.K., those for both hospital use and outpatient use are reimbursement prices[100] by NHS for pharmaceuticals administered by pharmacies,

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[98] Daiwa Research Institute "Solution of price differences between domestic and overseas markets and deregulation -Restructuring of Japanese System and Her Industry," February 1994; Osaka Health Insurance Doctors Association, "International Comparison of Pharmaceutical Prices," 1994 (1st time), 1995 (2nd time); Medical Economics Division, Health Insurance Bureau, Ministry of Health and Welfare "Overseas study report on the evaluation of pharmaceuticals in the health insurance system," 1995; Policy Research Institute for Japan Medical Association "International comparative study on health care cost," 1997; etc.

[99] An organization to purchase pharmaceuticals on behalf of its affiliated hospitals. By utilizing its scale merit, it tries to purchase pharmaceuticals at as low a price as possible.

[100] NHS's reimbursement price is designated based upon the average wholesale price which is investigated

because it proved extremely difficult to survey those of hospitals.

(4) The basic unit for price comparison is, that of the smallest unit (i.e. one tablet, one ample, etc.). For specifications, if the amount of active ingredient specified is the same as that of the Japanese product surveyed, then that specification was sampled. But if not, then specification which is the closest possible to the Japanese one was adopted. Since the amount of active ingredient and the prices are not proportional (i.e. even though the amount of active ingredient is doubled, the prices are not doubled), and the rationale for the amounts of certain active ingredients is considered to be based upon medical practices in surveyed countries, calculation of prices is not based upon the amount of an active ingredient. In order to examine the results of this survey, it is necessary to underscore these points.

(5) Conversions into the Japanese yen are based upon the exchange rate of the period average of inter-banks between Jan-Feb of 1998, when the survey was conducted.

Looking at the results of this price survey, even though there are differences from one group to another, there is a general trend depicting high prices in the U.S., followed by Japan, and the lowest prices in the European countries. Also, among the European countries, prices of many pharmaceuticals are lowest in France.

In terms of "innovative new drugs," purchasing prices of Japanese medical institutions are highest for two out of three items mainly for hospital use. In the case of three items for outpatient use, the prices in the U.S. are highest, followed by Japan. Except for two items of which prices are lowest in Japan, the prices in Japan are two to three times higher than the lowest prices in the surveyed countries[101].

In terms of "improved new drugs," three items developed in Japan are sold at higher prices in the U.S. and European countries than in Japan. Also pharmaceuticals developed in the European countries are sold at the highest prices in Japan.

In terms of "long-time listed drugs," two out of three pharmaceuticals for hospital use are purchased at the highest price in the U.S. and one item in Germany among the surveyed countries. All three items for outpatient use are priced the highest in the U.S. One item in Japan is the second highest to the U.S. price. Two items in Japan are cheaper than the U.S. and two European countries.

It should be noted that the results of this survey do not necessarily represent all the circumstances pertaining to the pharmaceutical prices in each surveyed country, because 1) the number of samples was limited, 2) the widely varying differences in purchasing prices of pharmaceuticals in each country, 3) the differences in domestic pharmaceutical distribution systems of each country, and 4) the difficulty related to the form of exchange rate upon which to base the comparisons.

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from wholesalers those who sold pharmaceuticals to pharmacies.

[101] In France, it is reported that hospitals are provided some of the pharmaceuticals free of charge by manufacturers.

Figure 1: Comparison of Pharmaceutical Prices between Japan, the U.S., and European

No.			Generic name (Country of Origin)		Japan	U.S.	France	U.K.	Germany
1	innovative new drugs	for hospital use	epoetin β stimulates red blood cell production(injection) (1 vial)	Price Active ingredient Brand name	¥12,040.00 6,000IU Epojin-chu	¥6,131.04 4,000IU Epogen	¥7,787.29 5,000IU Recormon	¥9,175.79 5,000IU Recormon	¥8,132.46 5,000IU Recormon
2			leuprorelin acetate hormone (injection) (1 vial)	Price Active ingredient Brand name	¥59,980.00 3.75mg Ryupurin chushayo	¥50,692.21 3.75mg Lupron Depot	¥19,172.27 3.75mg Enantone	¥26,224.90 3.75mg Prostap SR	¥19,926.64 3.75mg Enantone
3			tacrolimus hydrate treatment of diabetes(tablet) (1 tablet)	Price Active ingredient Brand name	¥7,418.00 5mg Prograf chushaeki 5mg	¥23,630.05 5mg Prograf	n.a. Prograf	¥14,151.83 5mg Prograf	¥8,230.42 5mg Prograf
4		for outpatient use	troglitazone treatment of diabetes (tablet) (1 tablet)	Price Active ingredient Brand name	¥100.76 200mg Nosukaru-jo	¥316.77 200mg Rezulin	Not sold	Sales suspended 98/01 Romozin	Not sold
5			prabastatin sodium cholesterol-lowering agent (tablet) (1 tablet)	Price Active ingredient Brand name	¥178.10 10mg Mebarochin-jo 10	¥224.80 10mg Pravacho1	¥123.63 20mg Elisor	¥120.85 10mg Lipostat	¥71.14 10mg Pravasin
6			acarbose treatment of diabetes(tablet) (1 tablet)	Price Active ingredient Brand name	¥64.00 100mg Gurukobai-jo	¥74.08 100mg Precose	¥28.55 100mg Glucor	¥41.13 100mg Glucobay	¥20.40 50mg Glucobay
7	improved new drugs	for hospital use	ondansetron hydrochloride antiemetic (injection) (1 ampule)	Price Active ingredient Brand name	¥8,640.00 4mg Zofuran-chu 4	¥2,875.20 4mg Zofran	¥545.74 4mg Zophren	¥1,411.63 4mg Zofran Injection	¥2,082.36 4mg Zofran
8			iomeprol contrast medium for radiology (injection) (1 vial/100 ml)	Price Active ingredient Brand name	¥19,371.43 71.44% Iomeron 350	n.a. lomeron	n.a. Iomeron	Not sold	¥9,308.71 71.44% Imeron
9			meropenem trihydrate antibiotic (injection) (1 vial)	Price Active ingredient Brand name	¥2,200.00 500mg Meropen tentekiyo 0.5g	¥3,501.08 500mg Merrem	n.a.	¥3,136.95 500mg Meronem	n.a. Meronem
10		for outpatient use	benazepril hydrochloride treatment of hypertension (tablet) (1 tablet)	Price Active ingredient Brand name	¥96.00 5mg Chibasen-jo 5mg	¥80.47 5mg Lotensin	¥44.71 5mg Chibaence	Not sold	¥49.25 5mg Cibacen
11			levofloxacin antibiotic (tablet) (1 tablet)	Price Active ingredient Brand name	¥246.00 100mg Kurabitto-jo	¥670.58 250mg Levaquin	Not sold	Not sold	Not sold
12			famotidine gastro-intestinal (tablet) (1 tablet)	Price Active ingredient Brand name	¥80.96 20mg Gasuta-jo	¥168.60 20mg Pepcid	¥36.31 10mg Pepcidac	¥104.57 20mg Pepcid	¥95.68 20mg Ganor

No.			Generic name (Country of Origin)		Japan	U.S.	France	U.K.	Germany
13	Long-time listed drugs	for hospital use	gentamicin sulfate antibiotic (injection) (1 ampule) (U.S)	Price Active ingredient Brand name	¥442.00 60mg Gentashin-chu	¥531.36 80mg Garamycin	¥20.99 40mg Gentalline	¥329.59 80mg Genticin	¥272.96 40mg Refobacin
14			cefazolin sodium antibiotic (injection) (1 ampule) (Japan)	Price Active ingredient Brand name	¥668.00 1g Sefamejin chushayo	¥590.11 1g Ancef	Not sold	Not sold	¥724.61 1g Gramaxin
15			dopamine hydrochloride cardiotonic drug(injection) (1 anpule) (Sweden)	Price Active ingredient Brand name	¥1,409.52 100mg Inban-chu	¥1,433.13 200mg Dopamine	n.a. Dopamin Nativelle	Sales suspended '96- Intropin	n.a. Dopamin AWD
16		for outpatient use	nifedipine vasodilator (capsule) (1 capsule) (Germany)	Price Active ingredient Brand name	¥28.27 10mg/ capsule Adarato	¥57.48 10mg Adalat	¥13.85 10mg Adalate	¥18.82 10mg Adalat	¥17.59 10mg Adalat
17			diltiazem hydrochloride vasodilator (tablet) (1 tablet) (Japan)	Price Active ingredient Brand name	¥17.62 30mg Herubessa-jo	¥63.87 30mg Cardizem	¥25.61 60mg Tildiem comprime	¥24.05 60mg Tildiem Tablets	¥10.55 60mg Diltiazem
18			nicardipine hydrochloride cardiovascular drug (tablet) (1 tablet) (Japan)	Price Active ingredient Brand name	¥27.62 20mg Perujipin-jo	¥45.98 20mg Cardene	¥20.15 20mg Loxen	¥33.42 20mg Cardene Capsules	¥31.66 20mg Anitagonil

Note: (l) Prices are compared by the smallest unit for use.

(2) For the specifications, if the amount of active ingredient specified is the same as that of the Japanese product surveyed, then the specification was sampled. If not, then specifications, which is the closest possible to the Japanese one was adopted.

(3) Surveyed prices (excluding the value added tax, such as the consumption tax in Japan)

Japan: Purchasing prices of a national university hospital

U.S.:1~2, 5~7, 9~10, 14~15, 17=Average sales prices of wholesalers

3~4, 11~13, 16, 18=Purchasing prices of a group purchase organization: On behalf of its affiliated hospitals, the organization tries to purchase pharmaceuticals at as low a price as possible by utilizing its scale merit.

France: 1~3, 7, 13=Purchasing prices of a private hospital. 5, 6, 10, 12, 16~18=Purchasing prices of a pharmacy.

U.K.: Reimbursement prices of NHS (National Health Service) for the drugs administered by pharmacies.

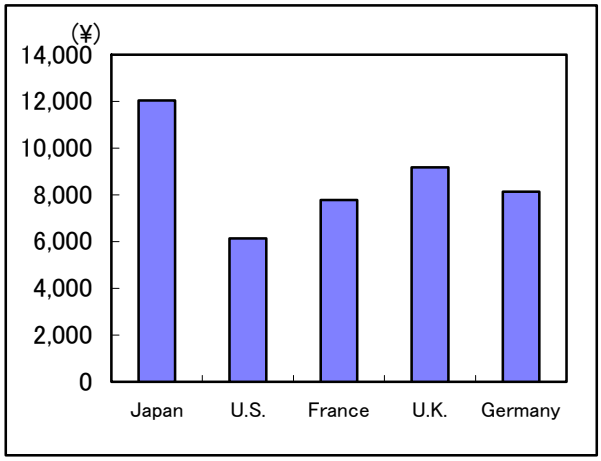
Germany: l~'3, 7~9, 13~14=Purchaslng prices of a pharmacy of university hospital. 6, 10, 12, 16~18=Purchasing prices of a pharmacy 5=Average purchasing price of pharmacies.

(4) The shaded area of the chart indicates the highest price amongst the group of pharmaceutical in the row.

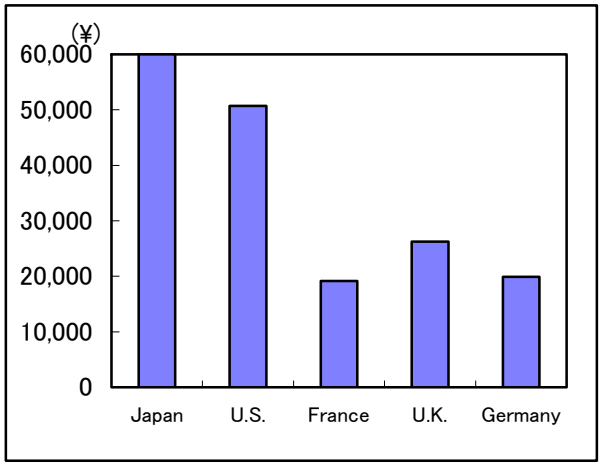
(5) Coversions into Japanese yen are based upon the exchange rate of the period average of inter-banks in Jan-Feb 1998, US$1=¥l27.73, £1=¥209.13, FFl=20.99, DM1=¥70.35

<Innovative new drugs>

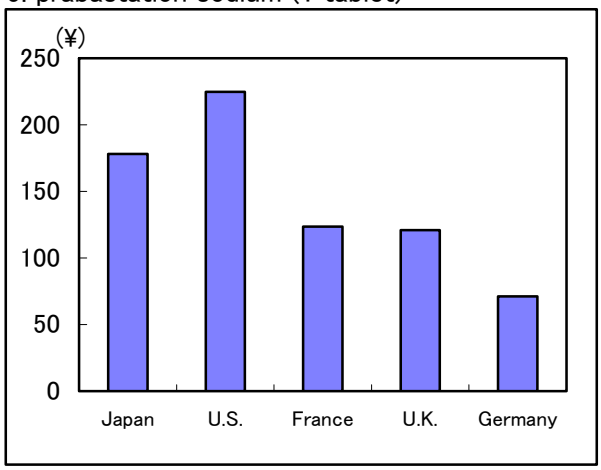
1. epotin β (1 vial)



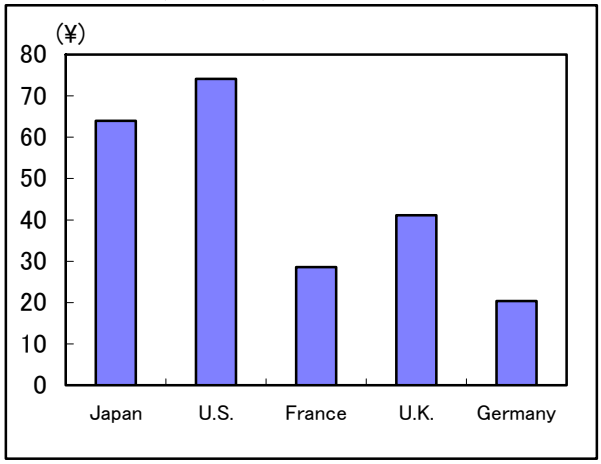
2. leuprorelin acetate (1 vial)



5. prabastation sodium (1 tablet)

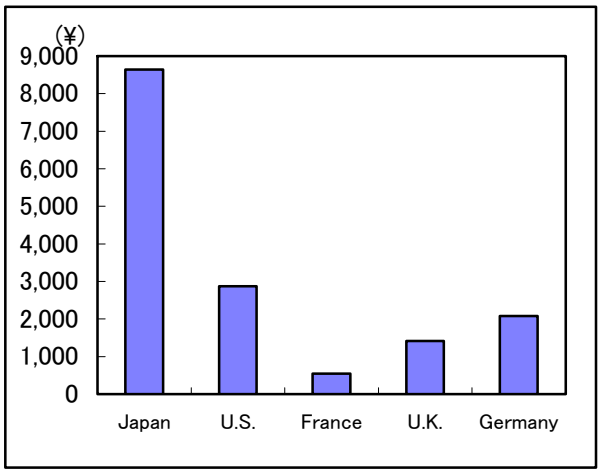


6. acarbose (1 tablet)

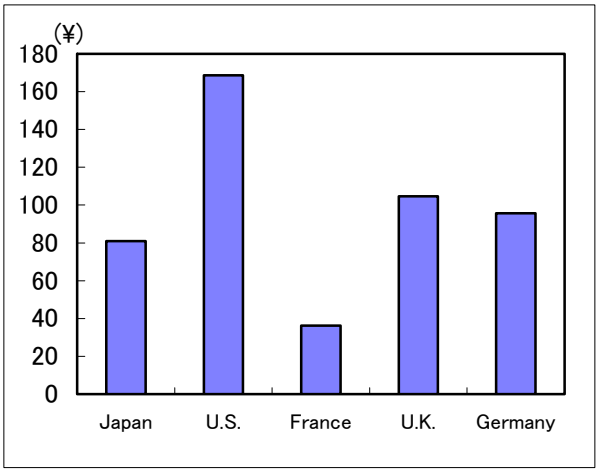


<improved new drugs>

7. ondansetron hydrochlorideantiemetic (1 ampule)

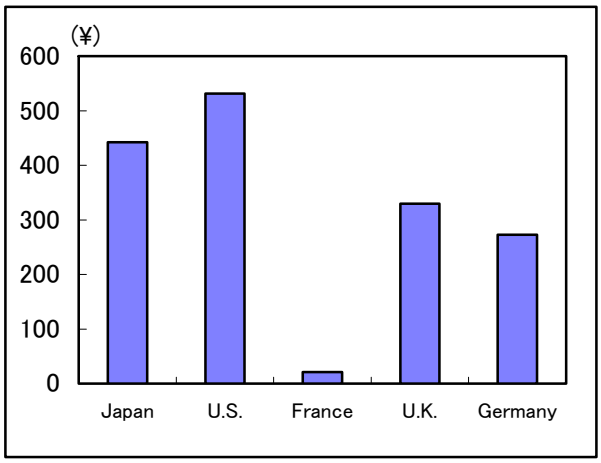


12. famotidinegastro-intestinal (1 tablet)

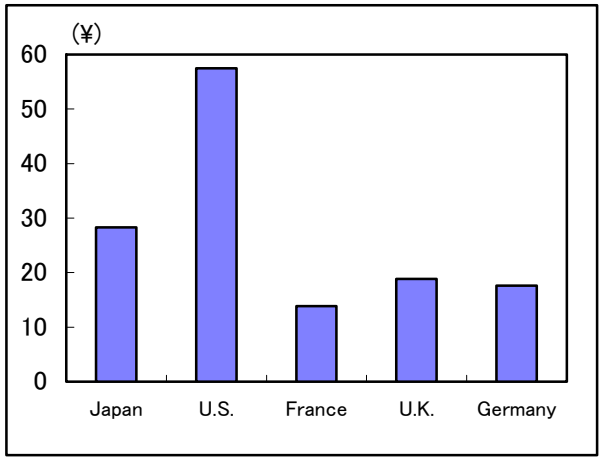


<Long listed drugs>

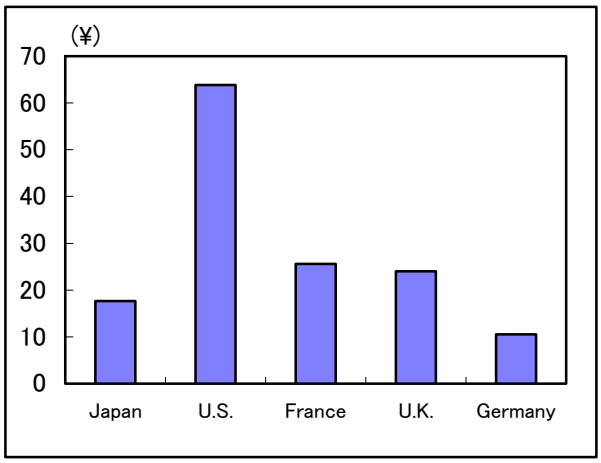
13. gentamicin sulfate (1 ampule)



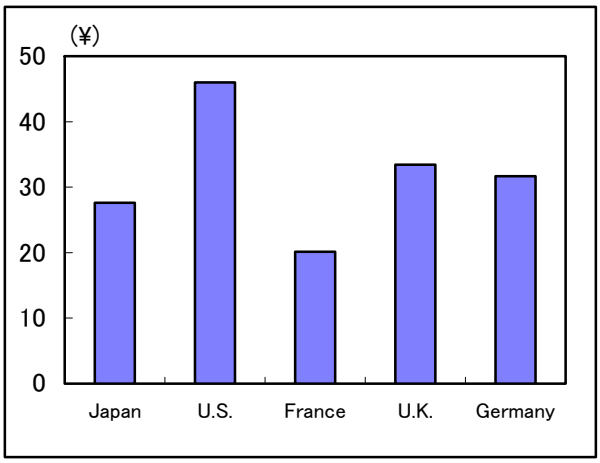
16. nifedipine (1 capsule)



17. diltiazem hydroride (1 tablet)



18. nicardipine (1 tablet)



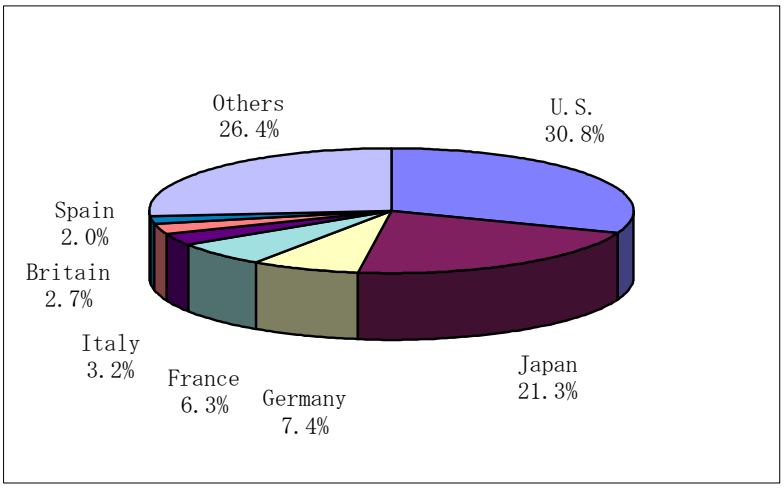
Note: ① Graphs are prepared for the products which can make a comparison of 5 countires only.
② The number shown in the graph title coincides with that of in the chart.

Appendix 2: Statistical Data

Figure 1: Pharmaceutical Market Scale in 1995

Country	Estimated shipments
U.S.	88,380
Japan	60,973
Germany	21,203
France	18,072
Italy	9,119
U.K.	7,628
Spain	5,605
Others	75,520
World total	286,500

($mil.)



Source: Scrip "Yearbook"

Figure 2: Number of Pharmaceutical Manufacturers and Employees of surveyed countries in 1995

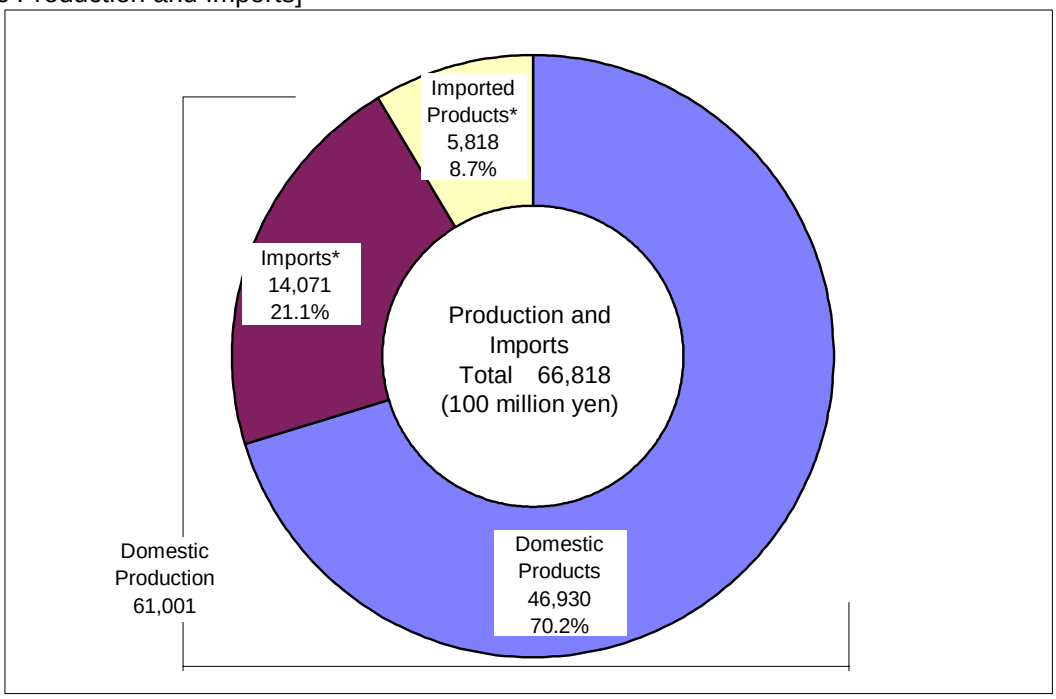
Country	Number of Manufacturers	Number of Employees	
Japan	1,512	244,774	
U.S.	800	203,009	(Number of employees in the U.S. is the data of 1996)
Britain	315	74,000	
France	354	101,000	(Number of employees in France is the data of 1994)
Germany	1,200	122,870	

Note: The number of manufacturers and the number of employees in Japan are the whole sum of the industry.
Whereas the numbers in the U.S. and European countries, they are those who belong to the industry associations only and not the whole sum of the industry.
In Japan, the number of manufacturers who chiefly produce ethical pharmaceuticals is about 500.

Source: Manufacturers Japan: MHW, "Pharmaceutical Industry Survey"
Overseas: Materials of pharmaceutical manufacturers associations in the countries concerned
Employees Japan: MHW, "Pharmaceutical Industry Survey"
European countries: EFPIA
U.S.: PhRMA "Industry Profile 1997"

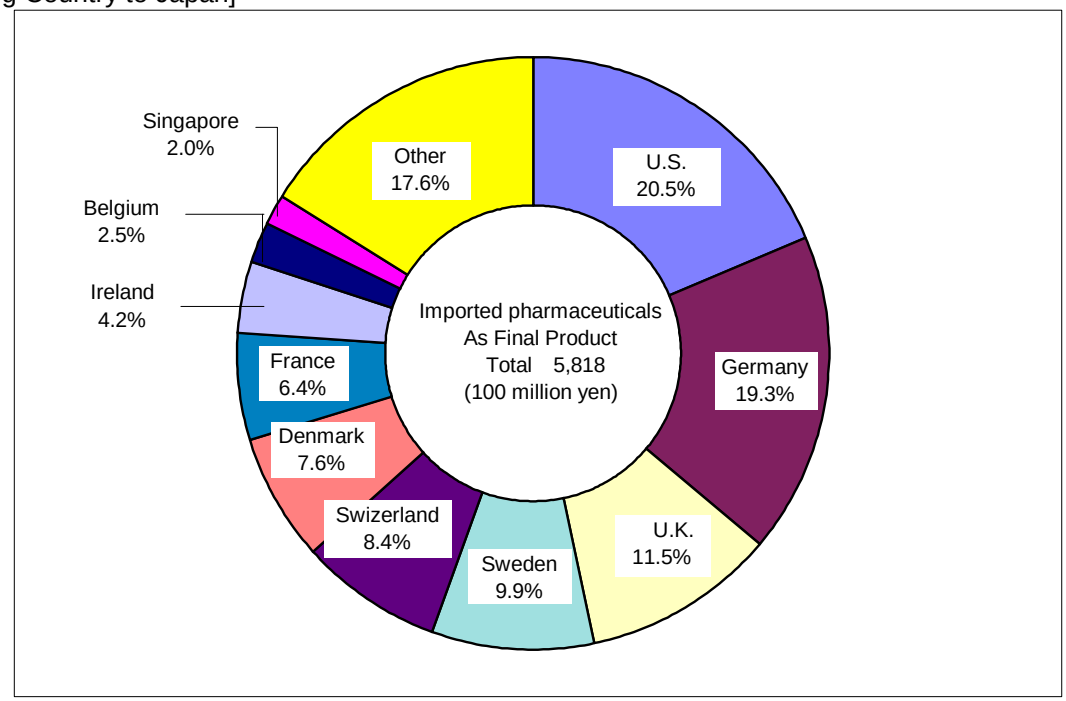
Figure 3: Pharmaceutical Production and Imports in Japan (1996)

[Domestic Production and Imports]



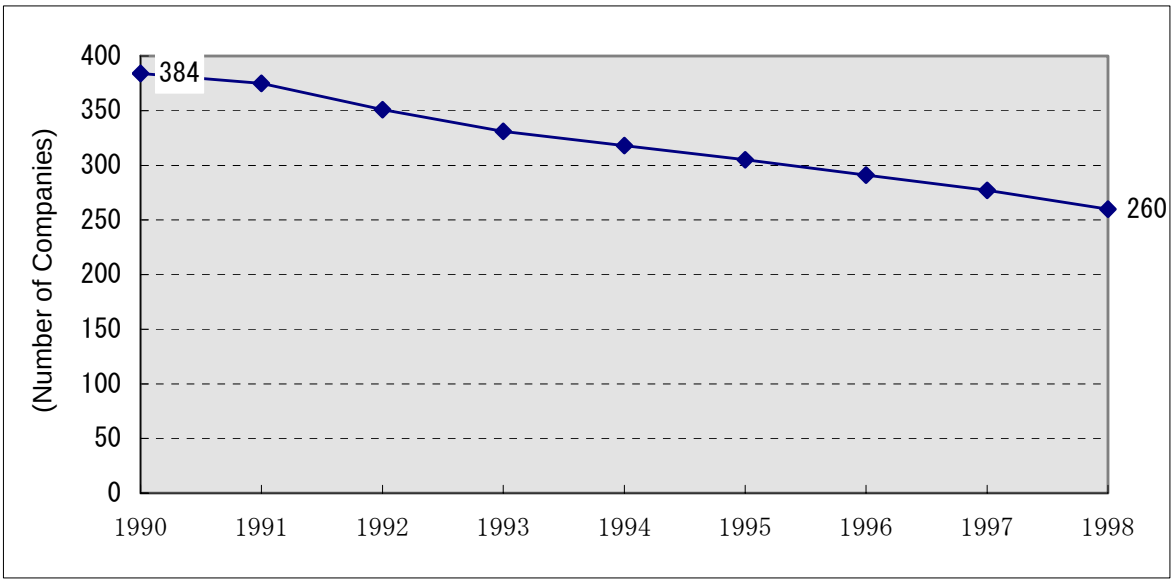
*Notes: Imports refer to the pharmaceuticals which are produced from imported pharmaceuticals (including crude powder, crude liquid, bulk products, and drug raw materials).
"Imported Products" refer to the pharmaceuticals which are imported as a final product.

[Exporting Country to Japan]



Source: Annual Statistics of Pharmaceutical Industry's Production Trends

Figure 4: Changes of Number of Companies Associated with JPWA



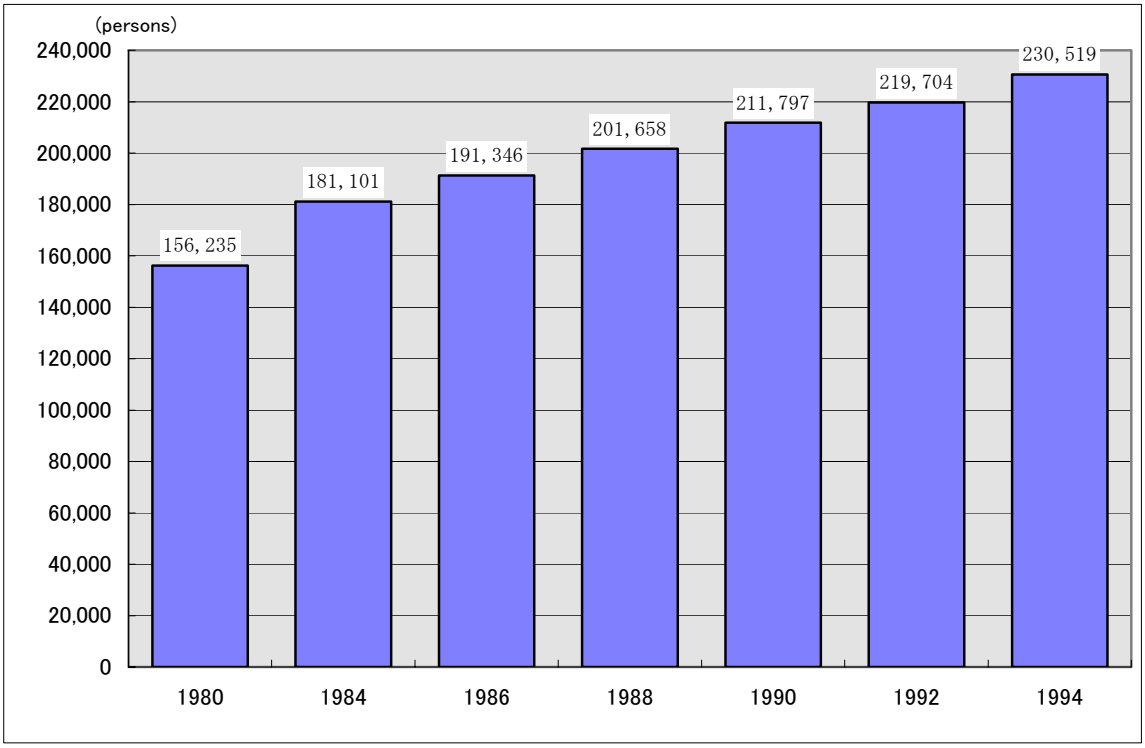
Source: JPWA (Japan Pharmaceutical Wholesalers Association)

Figure 5: Top 129 Japanese Pharmaceutical Wholesalers by Annual Sales and Number of Employees (1996)

No. of Employees / Anuual Sales	1～10	11～50	50～100	100～500	500～1000	More than 1000	Companies Total
less than ¥10 billion	2	7	8	5			22
¥10 to ¥50 billion			1	63	2		66
¥50 to ¥100 billion				1	28		29
more than ¥100 billion					2	10	12
Companies Total	2	7	9	69	32	10	129

Source: "Yakuji Handbook 1997"

Figure 6: Changes in Number of Medical Doctors in Japan



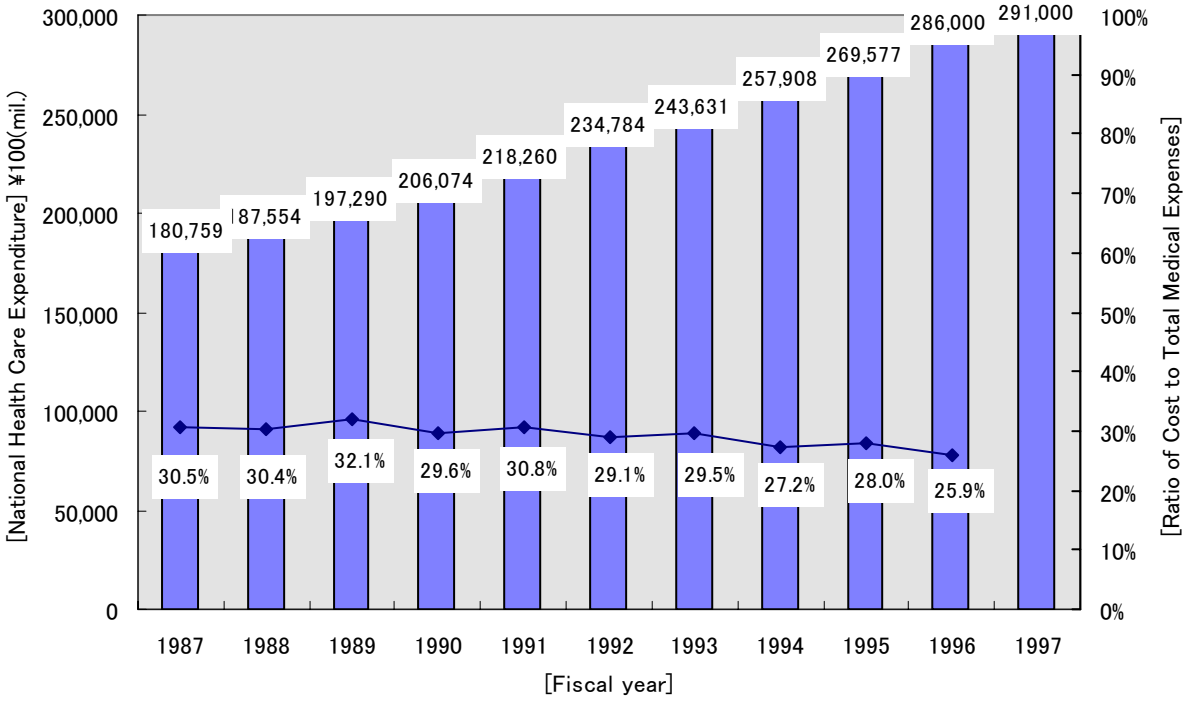
Source: MHW "MHW Whitepaper" 1997

Figure 7: Changes in Numbers of Medical Institutions in Japan

	Hospitals				Clinic
	Total	National	Public	Private	
1950	3,408	383	572	2,453	43,827
1955	5,119	425	1,337	3,357	51,349
1960	6,094	452	1,442	4,200	59,008
1965	7,047	448	1,466	5,133	64,524
1970	7,974	444	1,389	6,141	68,997
1975	8,294	439	1,366	6,489	73,114
1980	9,055	453	1,369	7,233	77,611
1985	9,608	411	1,369	7,828	78,927
1990	10,096	399	1,371	8,326	80,852
1995	9,606	388	1,372	7,846	87,069

Source: MHW "MHW Whitepaper" 1997

Figure 8: Changes in National Health Care Expenditure and Ratio of Drug Cost in Japan



Note: The figures of National Health Care Expenditure in 1996 and 1997 are estimate basis.
Source: MHW, “National Health Care Expenditure”
MHW, “Social Health Care Survey”
MHW, handout material for “Health Insurance and Welfare Council”

Figure 9: Comparison of Ratio of Drug Cost to National Health Care Expenditure

	France (1993)	Germany (1993)	U.K. (1992)	U.S. (1993)	Japan (1993)
Population (100 thousand)	575	584	580	2,580	1,248
Outpatient drug cost in Japanese Yen ¥(billion)	24,941	18,802	9,478	59,536	54,330
Inpatient drug cost (estimated) in Japanese Yen ¥(billion)	4,025	3,555	1,051	31,842	17,541
Total drug cost in Japanese Yen ¥(billion)	28,966	22,357	10,529	91,378	71,871
National health care expenditure in Japanese Yen ¥(billion)	145,866	131,061	64,163	806,908	243,631
Ratio to national health care expenditure					
Outpatient drug cost	17.1%	14.4%	14.8%	7.4%	22.3%
Inpatient drug cost	2.8%	2.7%	1.6%	3.9%	7.2%
Total	19.9%	17.1%	16.4%	11.3%	29.5%
Ratio of drug cost to total outpatient medical expenses	44.6%	44.1%	41.6%	-	47.2%
Ratio of drug cost to total inpatient medical expenses	5.7%	7.9%	2.8%	-	15.0%

Japan: MHW, "National Health Care Expenditure
"Survey on Medical Procedures"
U.S.: HCFA, "Health Care Financing Administration," etc.
France: "Comptes Nationaux de la Sante," etc.
U.K.: Materials of Department of Health
Germany: ABDA Reports, etc.

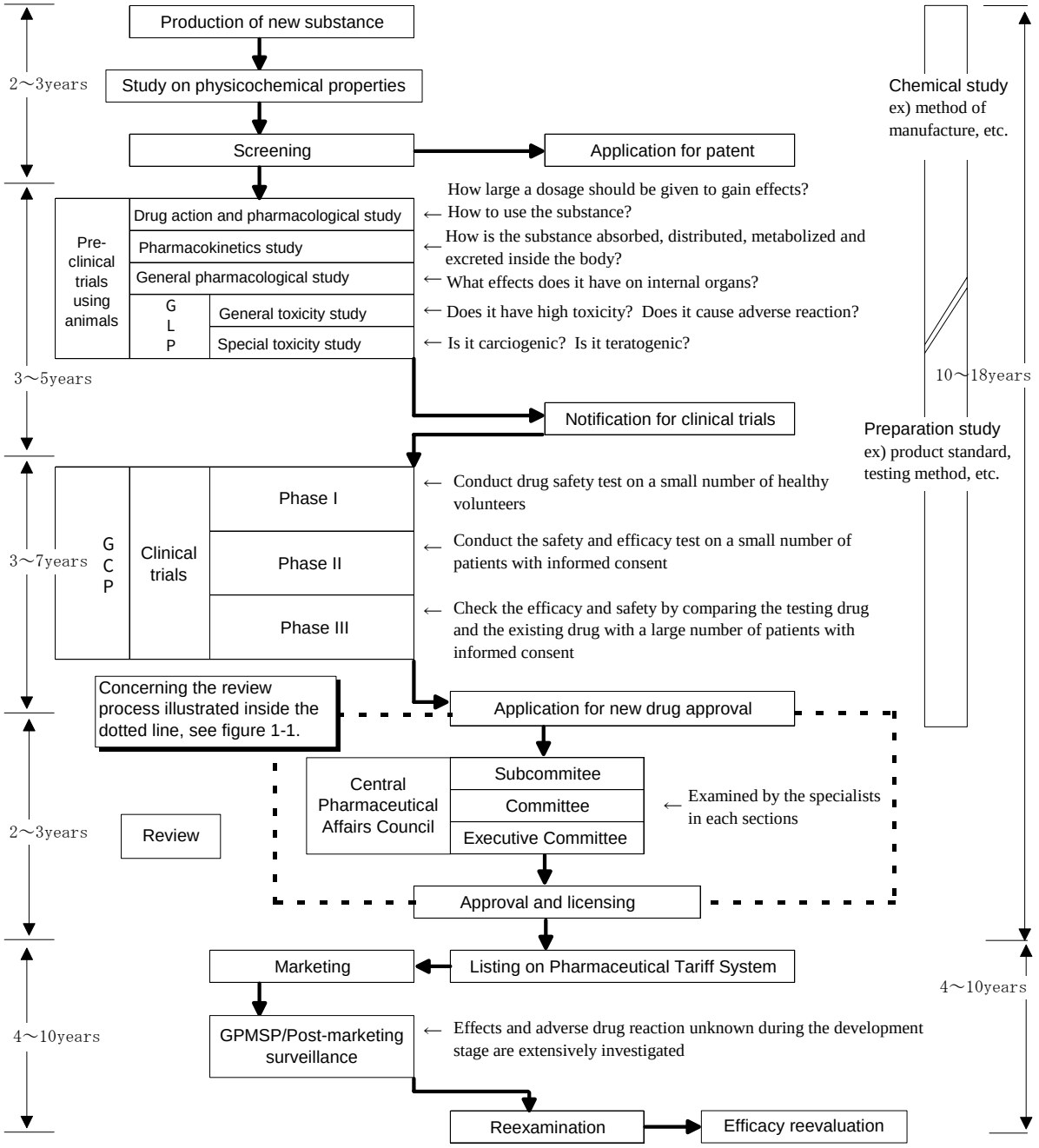
Source: "*Me de miru Iryohoken Hakusho* (Whitepaper of Health Insurance at a Glance),"

Figure 10: Health Insurance System, Pharmaceutical Benefits, Patient's Copayment in Pharmaceutical Cost in Surveyed Countries

	Japan	U.S.A.	U.K.	France	Germany
Health Insurance System	●Public Insurance (compulsory) Contribution to the insurance fund are shared equally by employees and the emplyoer. Health insurance is funded by a quarter of total operational cost by the national treasury and 10% by local authorities.	●Medicare for elderly and handicapped people ●Medicaid for low-income people ●Private plans (HMO, etc.) No public health insurance exists to cover whole U.S. citizen About 4,000 people have not been covered by any health insurance	●NHS(National Health Service) NHS is a public health care service, which is different from a social insurance system. It is covered by general budget and the nation is responsible to provide health care services.	●Public insurance (compulsory) Contribution to the insurance fund are shared by employees and the emplyoer in 2:1 ratio. Health insurance is funded by insurance contripution. No support is made by the national treasury in principle.	●Legal disease insurance (voluntary) Contribution to the insurance fund areshared equally by employees and the emplyoer. Health insurance is funded by insurance contripution. No support is made by the national treasury in principle.
Outpatient Drug					
Separation of Dispensing and Prescription	Ratio=approx. 20%	Dispensing is separated from prescription in principle	Dispensing is separated from prescription in principle (Dispensing doctor is adnitted in the areas where pharmacies are not available)	Dispensing is separated from prescription in principle	Dispensing is separated from prescription in principle
Drugs Covered by Health Insurance	Drugs listed on " *Yakka Kijun* (Pharmaceuticals Tariff Table)"	Depends on the type of health insurance	Except for drugs listed on Limited list (17 categories)	Drugs listed on the reimbursement list	Except for drugs listed on a negative list
Patient's Copayment	1. A portion included in patient's contribution (20%) to total medical cost 2. In addition, there's a separate patient's copayment in pharamaceutical cost	In Medicare, patient to pay in full In Medicaid, patient to share a pharmaceutical cost (% differs by states) In private plans, it depends on the type of insurance	£ 5.65 per prescription Exempt for elderly people, school children, pregnant women, low-income people, etc.	Reimbursement system Patient once pay in full, then health insurance reimburse by % below Important drug=100% General drug=65% Light treatment drug=35% Vitamine preparation=0%	Large package=DM13 Medium package=DM11 Small package=DM9 For drugs which have been set the reference price, patient has to pay an exceeding cost Exempt for younger generation and pregnant women
Inpatient Drug					
Patient's Copayment	No patient's copayment in drug cost. Patient to pay a portion of total medical expense.(Patient's contribution=20%. If the contribution exceeds ¥63,000 per month, then insurance will cover the	No patient's copayment in drug cost. Patient to pay a portion of total medical expense.	No patient's copayment	No patient's copayment in drug cost. Patient to pay a portion of total medical expense.	No patient's copayment in drug cost. Patient to pay a portion of total medical expense.
Payment System of Drug Cost for Medical Institutions	Reimbursed based on piecework payment system (flat payment system has been introduced partially)	All inclusive in hospital payment based on DRG (Diagnosis Related Group) (No specific payment is made for drug cost)	All inclusive in hospital budget (No specific payment is made for drug cost)	Public hospital: Inclusive in budget Private hospital: Inclusive in per diem payment (No specific payment is made for drug cost)	All inclusive in per diem payment (No specific payment is made for drug cost)

Source: Prepared based on the Ministry of Health and Welfare, "Pharmaceuticals and Health Insurance Reform in the U.S. and European Countries" 1995.

Figure 11: Process from Development to Marketing of New Pharmaceuticals in Japan



Source: "DATA BOOK 1996-97," Japan Pharmaceutical Manufacturers Association