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DRUG REGULATORY AFFAIRS AND PHARMACEUTICAL RESEARCH AND DEVELOPMENT IN JAPAN 1960-1985

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ABSTRACT

Japan has become a leading force in pharmaceutical innovation and marketing. This paper examines in detail, the regulatory changes in Japan from 1960 to the present time and the resultant impact upon pharmaceutical research and development. It is apparent that the supportive regulatory environment in Japan has spawned the substantial growth of the country's domestic pharmaceutical industry.

INTRODUCTION

Relatively little has been published concerning Japanese drug regulatory affairs and pharmaceutical research and development for the period 1960-1985. This article is based upon information from the few available sources presently in existence.

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The most definitive sources for information have proven to be private, e.g., the Yakugyo Jiho Company, Ltd., of Tokyo, and Scrip of the United Kingdom. Other documentation for this article came from Pharma, also published by Yakugyo Jiho Company, Ltd., a Japanese pharmaceutical industry newsletter.

The lack of generally available source material probably reflects the provincial nature of pharmaceutical regulatory affairs in Japan. Until 1976, foreign drugs were extremely difficult to register in Japan because the country would not accept foreign data. Even today, domestic Japanese firms are given enormous regulatory advantages for registration of new chemical entities.

It is critical to examine Japanese drug regulatory affairs and their resultant effects upon research and development in Japan if an understanding of present day multinational drug development is to be achieved. Japan is presently the second largest pharmaceutical market in the world. (14:71)

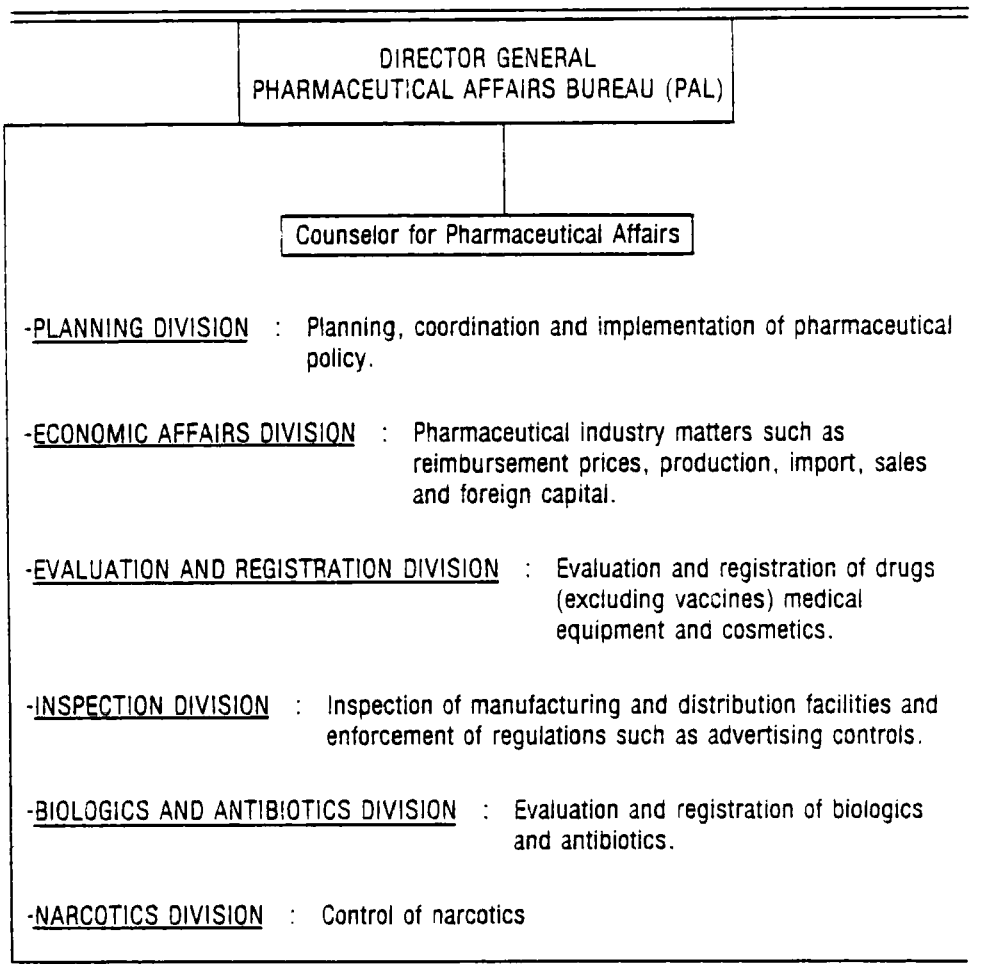
JAPANESE DRUG REGULATORY AFFAIRS 1960-1980

Drug regulation in Japan became formalized with the enactment of the Pharmaceutical affairs Law (PAL) on August 10, 1960. (14:143) This law established a Ministry of Health and Welfare (MHW) to oversee pharmaceutical regulatory affairs. Within the Ministry

of Health and Welfare, supervision of the pharmaceutical industry is the responsibility of the Pharmaceutical Affairs Bureau (PAB). Figure 1 below, details the divisions of the Pharmaceutical Affairs Bureau and their functions.

The Pharmaceutical Affairs Law of 1960, empowered the Ministry of Health and Welfare to investigate the safety and effectiveness of drugs based upon an application for an individual manufacturing approval. For the most part, drug manufacturing approvals were based solely upon efficacy, since the principal ingredients were usually compounds listed in the Japanese Pharmacopoeia. (14:109-110) This practice led to the SMON (subacute myelo-optic neuropathy) incident, which brought about the partial revision of the Pharmaceutical Affairs Law in October 1979. The SMON incident, which was based upon an adverse effect of entero-vioform, will be discussed in detail later. The amendments to the original Pharmaceutical Affairs Law (in chronological order) were as follows:

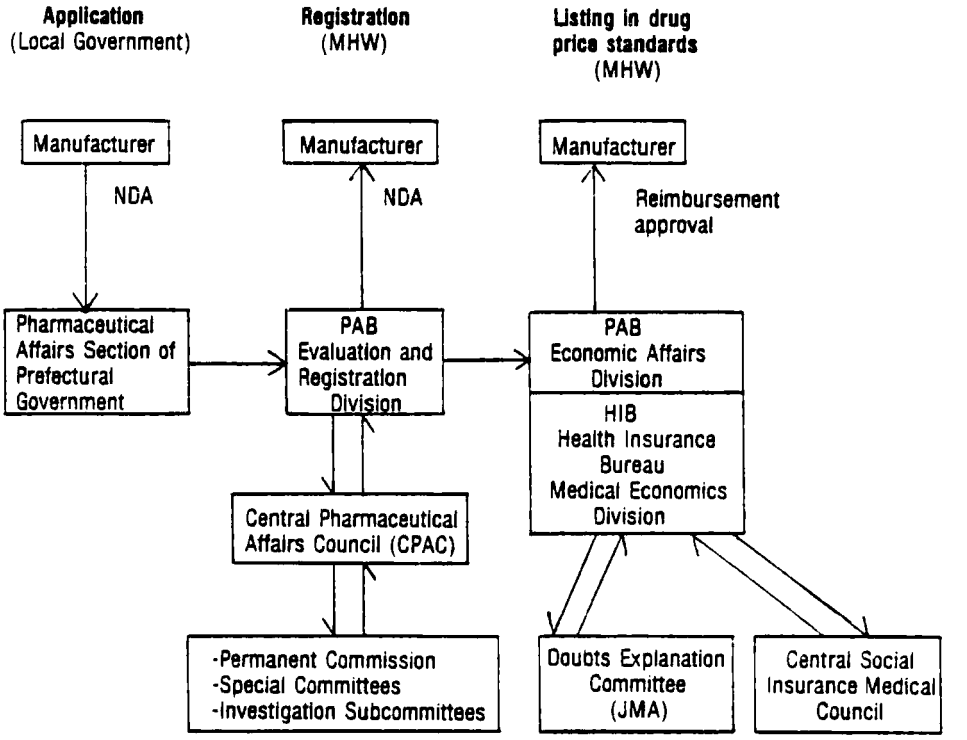
1. MHW Notice 645 (September 13, 1967) *Introduction of new drug approval program.* Defined ethical (by prescription only) and proprietary (over-the-counter) drugs and established registration procedures. (See Figure 2)



SOURCE: "Japanese Pharmaceuticals: A Special Report by Scrip" (Surrey, England: Scrip World Pharmaceutical News, September 1981), p. 95.

FIGURE 1

STRUCTURE AND FUNCTIONS OF THE PHARMACEUTICAL AFFAIRS BUREAU



SOURCE: "Japanese Pharmaceuticals: A Special Report by Scrip" (Surrey, England: Scrip World Pharmaceutical News, September 1981), p. 100.

FIGURE 2

NEW DRUG REGISTRATION PROCEDURE IN JAPAN

2. MHW Notice 589 (June 29, 1971)
   Introduction of drug re-evaluation program (for drugs on the market prior to PAL). These may be carried out whenever required, to re-evaluate a drug's efficacy.
3. Pharmaceutical Affairs Bureau's Notes for Applications for Manufacturing (or importing)

Approval of new drugs (March 1975)

Emphasized critical aspects of submissions

4. MHW Notice 970 (October 1, 1976)

   Permitted the submission of foreign chronic toxicity trials. In order to gain acceptance, the trials must be done according to Japanese standards.

5. Revised PAL (enacted September 7, 1979, and promulgated October 1, 1979)

   The following elements to the drug regulatory affairs law were added:

   a. New standards for approval of drugs based upon safety, efficacy and quality. Marketed drugs were required to meet the new standards

   b. Pre-approval of clinical trials by the Pharmaceutical Affairs Bureau prior to commencement. Submission of preclinical data must precede any trials of a new drug in humans. Informed consent must be obtained from all prospective subjects. Any subject harmed by an investigational drug must be compensated by the manufacturer

   c. Generic drug manufacturers are required to submit data equivalent to the original

manufacturer's submission in order to gain registration. This includes drugs recognized in the Japanese Pharmacopoeia

d. Re-examination of all new drug approvals will take place four to six years after initial approval based upon regulatory manpower

e. The period of exclusive marketing of a newly approved drug is extended from three to six years for Japanese firms and from zero to three years for foreign firms

f. New drug approvals can be revoked for lack of marketing within two years of approval or for adverse reactions

g. New drugs may be recalled based upon suspected adverse reactions. All adverse reactions must be collected and reported to the Pharmaceutical Affairs Bureau for six years after manufacturing approval. The government will establish a post-marketing surveillance system

h. Labeling must include the date of manufacturing and appropriate storage conditions. Package inserts must address adverse reactions and contraindications

i. A revision of the Japanese Pharmacopoeia (JP) must be produced every ten years in

cooperation with the Central Pharmaceutical Affairs Council (CPAC)

j. All drug sales must be documented in detail, including records of checks for expired products

k. Checks for manufacturers' compliance with Good Manufacturing Practices (GMP) will be carried out (14:101, 109-110, 143-144)

Perhaps the most powerful body within the drug regulatory system in Japan is the Central Pharmaceutical Affairs Council (CPAC). This group provides counsel to the Ministry of Health and Welfare concerning drug regulatory policies and their implementation as well as exercising final approval over all new drug registrations. (14:96)

The Central Pharmaceutical Affairs Council (CPAC) is composed of fifty members representing pharmaceuticals, medicine, law and other disciplines. The members are assigned to committees which meet every three to four months. The committees consist of:

1. Permanent Commission for Evaluation of Totally New Structures or Compositions
2. The Japanese Pharmacopoeia
3. Specialty Areas of Drugs
   a. Biologicals
   b. Antibiotics
   c. Veterinary Compounds

d. Over-the-Counter Drugs

e. Poisons

f. Devices

g. Drug Re-Evaluation

h. Safety

4. New Drug and Other Investigation Subcommittees including:

a. New Drug Advisory Subcommittee

b. Anti-Cancer Therapy Investigation Subcommittee

c. Pharmaceutical Names Investigation Subcommittee

d. Anti-Bacterial Products Investigation Subcommittee

The subcommittees meet twice a month. (3:11)

JAPANESE DRUG REGULATORY AFFAIRS 1981-1985

Over the last five years, Japan has taken further steps toward harmonization, in an effort to reduce trade barriers. Primarily in response to perceived trade inbalances by other industrialized countries, Japan revised the PAL in May, 1983. (2:10-11)

Under the 1983 revision, foreign based pharmaceutical firms can apply directly to the Ministry of Health and Welfare for a manufacturing approval. Once the approval is acquired, a local Japanese importer can be contacted to file an application for an import license.

Another important change associated with the 1983 revision effects the requirements for stability data. Long term stability data can now be submitted during the Ministry's examination of a manufacturing application, as long as mid-term and accelerated stability test data are initially submitted. (2:10-11)

The 1983 revision clearly represents a further movement by Japan towards attracting foreign based multinationals to market their drugs in this far eastern country. The Japanese system still, however, requires an importer, a joint-venture partner or a subsidiary in order to carry out pharmaceutical marketing in Japan.

THE REGISTRATION PROCESS

As outlined in Figure 2, above, an application for registration of a new drug in Japan begins with submission of the proper documents to the local prefectural government. These applications take the form of approvals to manufacture a drug as opposed to strictly an approval of the drug itself (as is the case in the United States). Ability to manufacture the compound is not considered, because a license to manufacture must also be held prior to marketing. (3:18)

One original and two copies of the application form (see Appendix A) for manufacturing approval must

be submitted to the pharmaceutical affairs section of the local prefectural government along with fees as shown in Table I.

Upon receipt of the application, the pharmaceutical affairs section checks all documents for format and forwards the application to the Pharmaceutical Affairs Bureau.

The Pharmaceutical Affairs Bureau clears the application for format and content through its evaluation and registration division. At this point, the application is passed onto the Central Pharmaceutical Affairs Council. At the Central Pharmaceutical Affairs Council, the application is then reviewed by the specialty subcommittees. Finally, the permanent commission must pass final approval for the drug to be manufactured. (14:98) This process generally takes from one to three years. (14:97) Key points of the application form are found in Table II.

During the final stages of the Central Pharmaceutical Affairs Bureau's approval, the application is forwarded to the Pharmaceutical Affairs Bureau's Economic Affairs Division. This division initiates the process of listing new drugs in the Drug Price Standards by requesting the manufacturer to submit an application for such listing. The application must include the desired standard price as well as the rationale for the price requested. The

TABLE I

APPLICATION FEES FOR APPROVALS TO MANUFACTURE DRUGS

TYPE OF APPROVAL	FEE FOR APPROVAL (yen)
1. Ministry of Health and Welfare	
a. New Drugs	250,00
b. Drugs in the Japanese Pharmacopoeia	12,000
c. Ethical Drugs other than (a) and (b)	72,000
d. Proprietary drugs other than (a) and (b)	20,000 (free if no special investigation needed)
e. Quasi-drugs	12,000
f. Licensed Japanese Pharmacopoeia drugs	1,000
2. Prefectural Government	
g. Drugs manufactured in pharmacies	50
h. Drugs in the Japanese Pharmacopoeia	12,000
i. Other drugs	20,000
j. Licensed drugs	1,000

SOURCE: "Japanese Pharmaceuticals: A Special Report by Scrip" (Surrey, England: Scrip World Pharmaceutical News, September 1981), p. 98.

TABLE II

KEY POINTS FOR JAPANESE REGISTRATION
(Refer to the Manufacturing Approval Application Form-Appendix A)

A. All new chemical entities (NCEs) must be submitted as ethical drugs

"Ethical drugs are those to be used by a physician or a dentist, or drugs used under the direction or through the prescription of a physician or dentist. Proprietary drugs are those drugs which have mild action if used correctly within fixed directions and dose range and are safe enough to be sold directly to the public."

B. All new indications for registered or known compounds must be submitted as new ethical drugs, with dosage and administration information. Clinical trials must be carried out in a minimum of five institutions with thirty patients each, documented by case report forms and reports of adverse effects

C. Stability data on aged samples was required as of July 1, 1971 (notification #589, June 29, 1971)

D. Format for the finished product formula of all dosage forms is as follows:

EXAMPLE: an injection

one ampule (ml) contains:

Active Ingredient	JP XXX.....mg.
Stabilizer	JP XXX.....mg.
Solubilizer	JP XXX.....mg.
Solvent	JP XXX.....mg.

TABLE II-Continued

TABLE II-Continued

E. The manufacturing methods column (see Appendix A) must contain:
   1. A description of the manufacturing steps in detail
   2. All raw material specifications, in-process controls and finished product specifications, citing Japanese Pharmacopoeia (JP) tests if available
   3. A method of manufacturing which does not infringe upon any existent process patents belonging to another company or individual

F. The directions and dose column
   1. Must be clearly express
   2. Must make sense for the indication sought
   3. May include only a single-cross division of tablets (no double-cross tablets will be accepted)
   4. Doses and directions must follow Japanese Pharmacopoeia (JP), even if it differs from a foreign pharmacopoeia

G. Indications and efficacy column
   1. State form of disease and symptom names using medical terminology
   2. No approval will be granted for proprietary drugs (over-the-counter) to be used to treat

infectious diseases or serious diseases such as cancer, glaucoma or mental disorders. The definition of serious diseases, though not entirely clear (no standards exist), at minimum "require the diagnosis of a physician."

3. Include the following limitations due to dosage form
   a. Drinks are limited to nutritional formulas containing vitamins, amino acids and natural drugs in containers of up to 50 ml.
   b. Ampules may not be used for drugs having the following indications: anthelmintics, vertigo, stimulants, cold relief, antipyretic analgesics, antitussives, expectorants, gastro-intestinal analgesics or intestinal bactericide

H. Storage conditions and expiry date column
   1. Is practically optional
   2. Is based upon a determination by the applicant (company) as to whether "ordinary storage" conditions will maintain quality. If ordinary storage will not maintain quality, the applicant must provide results of aging tests (stability)

I. Standards and test methods column

TABLE II-Continued

TABLE II-Continued

1. Reflective of quality assurance
2. Must be consistent with Good Manufacturing Practices (enforced from April 1, 1976)
3. Must state bacterial count limits for finished product (notification #297 of the Pharmaceutical Affairs Bureau)
4. Must absolutely cover the main ingredient(s)
5. Raw materials specifications (or tests) must include:
   a. Name
   b. Structural or empirical formula
   c. Molecular formula and weight
   d. Base material
   e. Content standards
   f. Manufacturing method
   g. Description
   h. Identification
   i. Rational values
   j. Purity
   k. Loss on drying or water content
   l. Loss on ignition
   m. Residue on ignition, total ash or acid insoluble ash
   n. Special tests

o. Pharmaceutical preparation test

p. Assay

6. Finished product specifications take the form of an integration of (5) above, with the following table:

Preparation \ Item No.			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Base material	Drugs with determined structural composition	Organic drugs	o	o	o	Δ	o	x	o	o	o	o	o	x	o	Δ	x	o
		Inorganic drugs	o	Δ	o	Δ	o	x	o	o	o	o	o	Δ	Δ	Δ	x	o
	Drugs with no determined structural composition		o	x	x	o	Δ	Δ	o	o	Δ	o	Δ	Δ	Δ	Δ	x	o
Preparation	Oral administration	Tablets, capsules pills	o	x	x	x	o	Δ	o	o	x	x	x	x	x	Δ	o	o
		Powders, granules	o	x	x	x	o	Δ	o	o	x	x	x	x	x	Δ	o	o
		Liquids	o	x	x	x	o	Δ	o	o	Δ	Δ	x	x	x	Δ	Δ	o
	Natural drugs		o	x	x	Δ	o	Δ	o	o	x	Δ	o	x	Δ	Δ	o	Δ
	Injection	Parenteral injections (in ampules)	o	x	x	x	o	Δ	o	o	Δ	Δ	x	x	Δ	Δ	o	o
		Drugs for injection (in vials or ampules)	o	Δ	Δ	Δ	o	Δ	o	o	Δ	Δ	Δ	x	Δ	Δ	o	o
	External use		o	x	x	x	o	Δ	o	o	x	x	x	x	x	Δ	o	o
Drugs such as natural drugs or animal or plant extracts for which effective ingredients are not clear			o	x	x	o	x	o	o	o	x	x	o	x	o	Δ	o	x

Note: 1. 'o' indicates the item is required, 'Δ' indicates the item is required if the test method is possible, and 'x' indicates the item is not required.
2. The manufacturing method (item 6) is to be entered in the case or preparations for which the active ingredient(s) is not clear when the content standards and assay are technically difficult.

7. Standards and methods must be according to JP where available (entries need only cite the JP) so "persons with only limited pharmacological knowledge can perform the tests."

8. Reference standards and reference equipment must conform to JP

TABLE II-Continued

TABLE II-Continued

9. If assay is impossible, an identification test is mandatory
10. Actual data must support the values stated in the standards and test methods section

J. Remarks column
   1. Must include the following statement for all ethical drugs:
      "For ethical use: (Health Insurance Price List)"
      "Packaging Units: (XX tablets, XXX tablets)"
      This statement insures inclusion of all packages (sizes) on the Health Insurance Price List, once price approval is obtained
   2. If the drug is the same as a marketed or approved preparation, enter: "XXX same as produced by Y company"

K. Attached data must include:
   1. For raw materials:
      a. Data substantiating standards and test methods
      b. Stability over time if raw material is an antibiotic
   2. For finished products:
      a. Data substantiating standards and test methods

b. Stability data over time

c. Pharmacokinetic data (absorption and excretion)

3. If part or all of manufacturing process or product commissioned out to second party, data from (1) and (2) above, must be repeated for the commissioned manufactured material

4. Stability data must include:

a. Three months' stability at room temperature

b. Three lots of product

c. Three stability tests per lot repeated over time

d. Three months' stability under "severe conditions"

e. Opinions and conclusions of the researcher in charge

f. If degradation is or may be significant, one year stability data at room temperature must be provided

5. Pharmacokinetic data must include:

a. Effects of absorption (in organs and in blood)

b. Species and number of animals -- must use rabbits and dogs (or other large animals in groups of five animals/minimum one group)

TABLE II-Continued

TABLE II-Continued

plus a control group of ten animals per drug

c. Tests such as:
   1) Serum concentration vs. time or urinary excretion data (if predictive)
   2) T 1/2 (half-life) for intravenous injections
d. Control drugs used as comparison in the same dosage form
e. Information on the dose specified in the directions and dose column
f. A cross-over design if statistical analyses are to be done

6. Pharmacology data in mice and rats with a minimum of ten animals in drug and control groups
7. Clinical pharmacology (in-vivo) and comparative efficacy data (in-vitro only data will be accepted for bactericidals for external use, antacids not for gastric ulcers and digestive enzymes)
8. Exceptions: If preclinical pharmacokinetics and pharmacology tests cannot be done, double-blind clinical trials with a minimum of sixty patients in two institutions can be

substituted. A technical reason for the ommission must also be submitted.

L. Antibiotics -- special considerations

1. Proprietary name must indicate dosage form
2. Different proprietary names must be used for different salts and esters
3. Active ingredients must meet JP or Japan antibiotic standards. Other specifications must meet Japan antibiotic drug standards (but not JP standards)
4. Stability, if no known problem exists, may be entered as "per the Japan antibiotic drug standards"
5. For IM injections, pH and osmotic pressure ratio at the commonly used concentrations must be specified in the submission
6. Packaging limits have been established as six hundred tablets or capsules or fifty injections
7. For identification tests, actual measured values are not necessary
8. Stability data must include:
   a. Twenty-seven months for solid dosage forms
   b. Ten days for reconstituted liquids
   c. Data in excess of the desired expiration period

TABLE II-Continued

TABLE II-Continued

d. Conditions of light, temperature and humidity consistent with actual marketing conditions

9. Pharmacokinetics data must include consideration of the effects of blood on the drug assay

SOURCE: Drug Approval and Licensing Procedures in Japan 1979 (Tokyo: Yakugyo Jiho Company, Ltd., 1979), pp. 20-83.

rationale must be based upon the merits of the new drug in relation to the marketed drugs of the same class.

The application for listing in the Drug Price Standards is reviewed by the Economic Affairs Division in collaboration with the Health Insurance Bureau. (13:99) The Japanese Medical Association Doubts Explanation Committee may also be consulted regarding technical matters. This committee most closely parallels the Food and Drug Administration's Scientific Advisory panels in the United States. The application is finally forwarded to the Central Insurance Medical Council for approval. This council is made up of representatives of the Japanese Medical Association and the Health Insurance Fund (a group which represents major corporations). (14:99) The Central Insurance Medical Council is responsible for setting the final

price of each new drug and informing its manufacturer of that price.

The new drug and its reimbursement price must be listed in the Drug Price Standards before marketing can take place. The Drug Price Standards are revised only once or twice yearly. The infrequent revisions delay the marketing of many drugs. Once listed in the Drug Price Standards, a new drug must be marketed within three months. (14:99)

MANUFACTURING LICENSES

The second step in the regulatory process is the application for a license to manufacture a new drug. This license has two basic prerequisites, specifically:

1. The drug (active ingredients) which will be manufactured or imported must be recognized in the Japanese Pharmacopoeia or approved by the Minister of Health and Welfare
2. The equipment used to manufacture the drug (finished product) must conform to "the construction and equipment regulation for pharmacy." (Ordinance #2 of the Ministry of Health and Welfare.) The personnel involved must meet the requirements established in the Pharmaceutical Affairs Law. The manufacturing establishment must meet Good Manufacturing Practices requirements. (3:363)

The manufacturer is responsible for the quality of all raw materials and finished products. Tests for quality of these products may be carried out by the manufacturer or an outside agency (such as the Public Drug Consultation Office). (3:363) Equipment and utensils used to carry out tests of raw materials and finished products must be those specified in the Japanese Pharmacopoeia or in the approval for a manufacturing license from the Minister of Health and Welfare. (3:364) According to the Pharmaceutical Affairs Law, the manufacturing facility must be supervised by a pharmacist. (3:364)

A copy of the application forms for a license to manufacture is contained in Appendix B. In addition to the information required in the application forms, the following must be provided:

1. A complete set of plans for the facility, including a sketch of the vicinity, a layout of each building and a floor plan
2. The company registration form
3. A copy of the employment contract of the supervisor of the facility (3:373)

The application is initially submitted to the local prefecture. The local authority then completes a full inspection of the manufacturing facility, including all equipment and personnel. If the inspection is satisfactory, the application is

forwarded to the Minister of Health and Welfare. If the application is approved, the applicant receives a license certificate to manufacture the drug or drugs originally requested at the particular facility. This certificate has a two year expiration date, after which it must be renewed biennially (Appendix C contains the application form for renewal of a manufacturing license).

Any changes in products to be (or being) manufactured, supervision or ownership of the manufacturing facility or working schedules (stoppages) must be reported to the Minister of Health and Welfare. There are specific forms to be submitted in the event of any change. (3:379-397)

IMPORT AND EXPORT DRUGS

In the period of 1970-1980, imports of pharmaceuticals into Japan rose at an average annual rate of 13.63%. During the same period, exports rose at an average annual rate of 10.4%. The trade deficit during this period grew by 16.13% per year (average). Table III provides additional details of Japanese pharmaceutical trade from 1970-1980.

There are a number of factors which have been cited as a basis for the negative Japanese trade balance in pharmaceuticals from 1970-1980. Some of the key factors are related to the market in Japan in

TABLE III

JAPANESE IMPORTS, EXPORTS AND BALANCE OF TRADE IN PHARMACEUTICALS 1970-1980

PRODUCTION Billion	IMPORTS Yen Million	% Change	IMPORTS % Production	EXPORTS Yen Million	% Change	EXPORTS % Production	IMPORT/ EXPORT RATIO	DEFICIT Yen Million	% Chang
,025.3	81,000		7.9	36,000		3.5	2.25	45,000	
,792.4	139,435	+14.4*	7.8	52,111	+9.0*	2.9	2.68	87,324	+18.8
,162.4	172,445	+23.7	8.0	63,672	+22.2	2.9	2.71	108,773	+24.6
,458.3	177,252	+ 2.8	7.2	72,830	+14.4	3.0	2.43	104,422	- 4.0
,793.9	183,416	+ 3.5	6.6	68,337	- 6.2	2.4	2.68	115,079	+10.2
,042.3	218,779	+19.3	7.2	83,463	+22.1	2.7	2.62	135,316	+17.6
,482.2	249,926	+14.2	7.2	90,018	+ 7.9	2.6	2.78	159,908	+18.2
AVERAGE GROWTH RATE 80		+12.7			+12.1				+13.3

al average growth, 1970-1975

SOURCE: "Japanese Pharmaceuticals: A Special Report by Scrip" (Surrey, England: Scrip World Pharmaceu-ews, September 1981), p. 16.

comparison to the rest of the industrialized world. The other key factors are related to Japan's regulatory environment.

The key market factors are as follows:

1. the domestic market has been sufficiently large and profitable for the Japanese either not to need, or not to want, to venture overseas:
2. being a relatively young industry compared, for example, with the Swiss, British, Americans and Germans, the Japanese do not possess traditional established export markets:
3. for this reason, Japanese companies are faced with a formidable level of competition when trying to export to overseas markets:
4. in the past, few drugs of Japanese origin have been of export potential, although a number of Japanese-developed drugs are currently scheduled for worldwide marketing, mainly through licenses to foreign companies. (14:16)

The regulatory factors revolved around the issue of acceptance of foreign data as a basis for manufacturing (or import) approval in Japan. Until 1976, no foreign data was acceptable as substantiation of product quality, safety or efficacy for a manufacturing approval to license. Notice 970 from the Ministry of Health and Welfare, dated October 1976, permitted submission of foreign chronic toxicity data for Japanese drug registration. This was followed in April 1980, with the Ministerial Ordinance implementing revisions to the Pharmaceutical Affairs Law which permitted submission of foreign stability data (Refer to Appendix D and Appendix E for the

detailed requirement of chronic toxicity testing and stability testing carried out in foreign countries [outside of Japan] for Japanese submission. These regulatory changes probably had a great effect upon the import of pharmaceuticals in 1979 and 1980. These regulatory changes resulted not only in an easing of testing requirements, but also in sending a clear signal of encouragement to multinational pharmaceutical companies seeking to do business in Japan.

The main reason for these regulatory changes was apparently the feeling by the Japanese authorities that the United States and the European Economic Community countries were moving rapidly toward an understanding concerning drug testing standards (preclinical and clinical requirements). The Japanese were anxious to be involved in any moves toward uniformity of drug registration. Secondarily, the major pharmaceutical manufacturers in Japan were contemplating international expansion. Thus, regulatory uniformity was in the best interests of both the government and the pharmaceutical industry of Japan. (14:104)

THE SMON DISASTER - A BASIS FOR REGULATORY REFORM

The initiative for drug regulatory reform legislation in Japan was similar to that experienced in other industrialized countries during the 1960's and 1970's, that is, an adverse drug reaction "disaster."

In the United States and Europe, the teratologic effects of thalidomide brought out-cries for stricter examination of the safety and efficacy of new drugs.

The Japanese experience, which paralleled the thalidomide incident in the United States and Europe, is referred to as the SMON disaster. (14:111, 13:19, 25:20) The SMON disaster was so named due to the subacute myelo-optic neuropathy which appeared in about eleven thousand patients following treatment for nausea with clioquinol (entero-vioform). (14:111)

Originally developed by Ciba-Geigy, clioquinol was first approved in Japan in 1953, and subsequently listed in the Japanese Pharmacopoeia. The drug was marketed in Japan by Ciba-Geigy's subsidiary, Nippon Ciba-Geigy and two of its licensees, Tanabe Seiyaku and Takeda Pharmaceuticals. (14:111) Having been registered in 1953, clioquinol came under the grandfather classification of drugs when the Pharmaceutical Affairs Law was enacted in 1960. It was not, therefore, subject to the new safety and efficacy standards. In fact, having been listed in the Japanese Pharmacopoeia, it was considered to be a safe drug. (14:112)

During the 1970s, reports of SMON side effects began to surface. It was not until 1976, however, that Nippon Ciba-Geigy and Takeda conceded that SMON reactions were due to clioquinol. (14:111) Tanabe

Seiyaku maintained, as late as 1978, that the SMON adverse reactions were not related to clioquinol (Quinoform^{R}). (25:20)

It has been estimated that eleven thousand Japanese people suffered SMON side effects during the 1970s. (14:111) By 1978, twenty-one lawsuits were filed, representing about 35% of the victims. (14:112) In March 1978, a landmark decision was handed down by the Kanazawa District Court, which directly provided the stimulus for revision of the Pharmaceutical Affairs Law and establishment of a relief fund for victims of adverse drug reactions.

The Kanazawa Court, in deciding the initial SMON suit, awarded the sixteen plaintiffs $1.1 million in damages. The damages were assessed as follows:

1. 20% (or $222,000) to each of the three manufacturers
2. 40% (or $444,000) to the Japanese government

The government was held liable because:

> The Pharmaceutical Affairs Law requires that the state investigate the safety and effectiveness of drugs when applications are made for manufacturing approval. The state is guilty of negligence if it eliminates steps in its investigation solely because the principal ingredient is listed in the pharmacopoeia.
>
> Every conceivable means should be used by the Minister of Health and Welfare to ensure drug safety. The body of law requires that the Minister examine safety in the light of the most advanced scientific methods, and it would have been foreseen by him what toxic effects of clioquinol were when it was first approved in 1953.

> That approval was improper in content: it involved no time limit; was likely to lead to over-use or long-term use; and it deviated from the safety stipulations for clioquinol. The then Minister of Health thus erred in respect of the approval for manufacture and license, since these passed the bounds of common sense, and were not within the conventional discretionary power to evaluate drug availability. (14:112)

Other lawsuits followed the Kanazawa District Court case. In each suit, the victims of SMON were awarded large monetary damages. Finally, in 1979, the Minister of Health and Welfare decided to address all of the outstanding SMON cases at one.

An agreement was reached among the manufacturers of clioquinol, the government and the SMON victims (represented by the National Liaison Council of SMON patients) for a settlement to be paid by the state and the manufacturers to the SMON victims. The compensation fund that was created totalled 100 million yen. Each victim received $111,000 as a lump sum payment. Monthly health allowances of $135 - $450 were also paid to each victim based upon the extent of ongoing medical treatment in each case. (14:113)

At the same time, as the agreement for settlement of the SMON suits was reached (September 1979), the Pharmaceutical Affairs Bureau gained Diet (the Japanese Congress) approval of its Adverse Reactions Compensation Bill. This bill created a fund for the compensation of victims of adverse reactions caused by drugs. The fund was to be administered by a ten member

board of trustees and a thirteen member board of directors, each with industry representation. (14:115) In addition, the bill created a Special Accounting Committee to administer SMON victim relief. Other provisions of the bill were:

1. Establishment of a "judgment committee" as a subgroup at the Central Pharmaceutical Affairs Council to identify (define) victims of adverse drug reactions
2. The government would provide monies for a maximum of one-third the costs of the fund beyond 500 million yen ($2.35 million)
3. All drug marketing organizations, including importers, were required to support the relief fund through a general subscription (based upon sales and classes of medications marketed) and a specific subscription (payable only when individuals seek compensation from a specific company for an adverse reaction to one of its drugs)
4. No retroactive claims will be considered. Only adverse effect claims filed subsequent to passage of the law will be accepted
5. Adverse effects stemming from improper use of a drug will not be approved, with the exception of anti-cancer agents

6. Six classes of compensation were defined ranging from medical expenses and benefits to funeral expenses (14:116)

At precisely the same time as the Adverse Reaction Compensation Bill was passed, the revisions to the 1960 Pharmaceutical Affairs Law were enacted.

These regulatory changes brought about the present day environment for drug development in Japan.

THE EFFECTS OF REGULATORY AFFAIRS UPON PHARMACEUTICAL RESEARCH AND DEVELOPMENT IN JAPAN

Japanese regulatory affairs have moved in a number of distinctly different directions during the period of 1960-1980. Perhaps the outstanding thrust has been in the direction of increased control and testing of new drugs prior to marketing. Another area of regulatory attention has been the movement by the Minister of Health and Welfare to control drug costs (through the pricing standards) and the health insurance reimbursement (to physicians and pharmacies) in an attempt to reduce health care costs.

Equally important has been the regulatory reform aimed at rewarding and encouraging research and development by pharmaceutical companies. These reforms have included the extension of the exclusive marketing period for a new drug from three to six years (revision to the Pharmaceutical Affairs Law, April 1980 [14:127]), the introduction of the drug pricing

standards which places a premium price on new innovative drugs and the introduction of product patents in 1975. (14:127)

Licensure of product patents in Japan has had a devastating effect upon smaller pharmaceutical companies and generic manufacturers. (14:132) Prior to 1975, only process patents were recognized in Japan. Under the process patent system, generic companies or small manufacturers could obtain rights to an important drug (whether marketed or not) simply by finding a new way to produce it (i.e., not covered by an existing process patent). The new process would be documented by the filing of a new process patent, thus providing the small or generic company with the right to obtain a manufacturing approval and license to an important drug with a minimum of research and development. In fact, much of the research and development efforts in Japan prior to January 1976, were aimed at circumventing existing process patents, rather than identifying new compounds. (14:127)

By adopting a product patent system, i.e., permitting only products to be patented, Japan placed all drug companies on an equal footing with regard to their dependence upon internal research and development. The product patent system clearly rewards firms with superior research and development skills and personnel. The law, however, covers products patented

since January 1976, only. It appears that a slow transition toward dominance of the market by research-and-development intensive companies will take place.

Patents in Japan are issued for fifteen years, as compared to seventeen years in the United States. It is estimated that ten years are required to bring a new chemical entity to market in Japan. (14:127) With only five years (on the average) remaining of patent protection for exclusive marketing, the Japanese industry complained of an insufficient return on investment to justify or stimulate research and development.

The revised Pharmaceutical Affairs Law provided a response to the patent law dilemma by extending the exclusive marketing period to six years. The exclusive marketing period supercedes patent rights, thus insuring a six year period of exclusive product marketing regardless of the time spent in research and development prior to registration.

It is interesting to note that in the revisions to the Pharmaceutical Affairs Law, the exclusive marketing period is justified based upon post-marketing adverse-reaction surveillance rather than return on investment economics. (14:128)

Taken in total, Japan has succeeded in making its domestic firms more competitive and research-and-development dependent, while establishing a more

receptive market image in order to attract entry by multinational pharmaceutical companies.

JAPANESE RESEARCH AND DEVELOPMENT STATISTICS

An examination of the research and development activities of the Japanese domestic firms since the enactment of the Pharmaceutical Affairs Law yields the facts as presented in Table IV. The sixteen top manufacturers are: Takeda, Fujisawa, Shionogi, Sankyo, Eisai, Yamanouchi, Tanabe, Daiichi, Chugai, Yoshitomi, Dainippon, Banyu, Green Cross, Nippon Shinyaku, Toyama and Ono. (14:26)

By 1979, the seventy-eight companies which comprise the Japanese Pharmaceutical Manufacturers Association (JPMA), invested 8.72% of sales (on the average) in research and development. (14:26) This figure was approximately one-fourth less than the average American investment during the same year. (22:26) However, the comparative cost of developing a new drug in Japan (through registration approval) in the 1979-1980 period on average was $21 million. The comparative figure in the United States was $60.5 million. (14:27) Based upon the costs of research and development per new chemical entity registered, Japan has become about three times more productive (or efficient) than the United States.

TABLE IV

RESEARCH AND DEVELOPMENT BY THE TOP SIXTEEN JAPANESE PHARMACEUTICAL COMPANIES 1967-1980

YEAR	R & D EXPENDITURE IN MILLIONS OF YEN	% CHANGE
1967	12,724	
1968	13,942	+ 9.6
1969	16,611	+19.1
1970	20,699	+24.6
1971	26,176	+26.5
1972	30,584	+16.8
1973	35,090	+14.7
1974	42,048	+19.8
1975	51,329	+22.1
1976	57,091	+11.2
1977	65,331	+14.4
1978	72,223	+10.5
1979	83,870	+16.1
1980	98,598	+17.6
AVERAGE	44,701	+17.15

SOURCE: "Japanese Pharmaceuticals: A Special Report by Scrip" (Surrey, England: Scrip World Pharmaceutical News, September 1981), p. 26.

Another indication of Japan's pharmaceutical output having been spurred by the regulatory changes previously described can be seen in the licensing figures of the 1970s. In the period of 1971-1977, Japan licensed out 87 new drugs to foreign-based companies with a resultant income to Japan of 1,344 million yen. During those years, 78 new drugs were licensed in with a net cost of 1,627 million yen. Nineteen seventy eight figures reveal a marked turn around in the income vs. cost figures. In that year, Japan received 1,229 million yen for 18 new drugs licensed out while paying 1,056 million yen for 18 new drugs licensed in. (14:30)

Total new drug production by Japan's pharmaceutical industry for the period 1961-1977, was 130 chemical entities (these data represent the current available information). This placed Japan in fourth place among the world's pharmaceutical producing countries, with 10,23% of all compounds discovered world wide. Current research figures indicate a significant increase in Japan's new drug production. Japan is currently developing 20.24% of all new compounds in the major therapeutic areas according to an analysis of industry figures. (14:28)

It is clear that this country of 117 million people has developed into a major force in the international pharmaceutical marketplace.

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APPENDIX A

Application for approval to manufacture / import a drug / quasi-drug

Name
Non-proprietary name
Proprietary name

Ingredients, quantities or nature

Manufacturing method

Directions and dose

Indications and effects

Storage conditions and expiry date

Standards and test methods

Remarks

As indicated above, we hereby apply for approval to manufacture / import this drug / quasi-drug

Date

Name (name and name of representative in case of an organization)

Address (head office in case of organization)

APENDIX B

Form 8 (1)

Revenue stamp

License application form for the Manufacture / Import of Drugs / Quasi-drugs

Name of factory or business office				
Address of factory or business office				
Items to be manufactured or imported				
Outline of equipment and facilities in the factory or business office			As on attached sheet	
Supervisor or responsible technician	Name		Qualifications	
	Address			
Type of other business conducted				
Disqualification conditions for applicants (including active executives in case of an organization)	(1) Cancellation of license according to stipulations in Article 75, Item 1 of Pharmaceutical Affairs Law			
	(2) Punishment involving imprisonment or more severe measures			
	(3) Violation of laws related to drugs or measures based on such laws			
	(4) Sentence of legal incompetency			
Remarks				

I hereby apply for a license to manufacture / import drugs / quasi-drugs as indicated above.

Date

Address (of head office in case of a company)

Name (Name and name of representative in case of a company)

Minister of Health and Welfare

Attached form (1)

Types and Qty. of Manufacturing equipment and utensils used for product				
1. Plant	a. Classification between normally inhabited areas and unclean areas	As per attached plans		
	b. Total area	sq.m.		
	c. Floor area (excl. workrooms)			
	d. Waste water disposal facilities			
	e. Poisonous gas	Present Absent	When present, type and equipment for treatment	
	f. Equipment for disinfecting employees			
2. Workrooms	Name / Classification	a. Area	b. Type of ceiling	c. Type of Floor
	room	sq.m.		
	"	"		
3. Storage Facilities	Raw materials			
	Products			
4. Testing Equip.				
5. Remarks				

Attached Form (2)

1. Plant	Classification between drug manufacturing plant and plant spec. in Article 6, Para 1 of the Construction and Equipment Regulations for Pharmacy.					As per attached plans
	Ceilings (except work rooms)					
	Name of sterilization equipment					
	Equipment for filling washed containers with drug					
	Distilled water producing equip.	Location of equip.				
		Type and capacity		Type		Capacity
2. Workrooms	Name \ Classification		a. Area	b. Type of ceiling	c. Type of walls	d. Type of floor
	Preparation room		sq.m.			
	Filling and sealing room		"			
	Outline of equipment when above rooms are sterilized (including when sterilized compartments are provided)					
	Equip.	Filter equip.				
		Filling equip.				
		Sealing equip.				
		Facilities for changing clothes				
3. Test Equip.	a. Sealing test					
	b. Impurities test					
	c. Physical and chemical tests					
	d. Sterility test					
	e. Pyrogen test					
	f. Biological test					
4. Remarks						

Notes:

1. In the equipment column of the factory part, enter the building, location and type of the equipment.

2. When the plans required in the column for classification between drug manufacturing factories and those factories specified in the Japanese Pharmacopoeia (see form) are the same as those attached in the section for classification between inhabited and unclean areas in form (1), such plans may be omitted for form (2).

3. It is not necessary to enter test equipment in the test equipment column of form (2) when the equipment was already entered in the same column in form (1).

4. Enter any reference items in the "Remarks" column.

APPENDIX C

Form 14

Revenue stamp

Application for Renewal of Licence for Manufacture / Import of Drugs / Quasi-drugs

License number and date		
Name of factory or business office		
Address of factory or business office		
Items manufactured or imported		As on attached sheet
Outline of the equipment and facilities in the factory or business office		As on attached sheet
Disqualification conditions for applicants (including active executives in case of an organization)	(1) Cancellation of license according to stipulations in Article 75, Item 1 of Pharmaceutical Affairs Law	
	(2) Punishment involving imprisonment or more severe measures	
	(3) Violation of laws related to drugs or measures based on such laws	
	(4) Sentence of legal incompetancy	
Remarks		

I hereby apply for renewal of a license to manufacture / import drugs / quasi-drugs as indicated above.

Date

Address (of head office in case of a company)

Name (name and name of representative in case of a company)

Minister of Health and Welfare

Drug manufacturing
Quasi-drug manufacturing Manufacturing Licensed Product List

Name		Name of Factory		License No.	( ) No.
Series No.	Brand Name	Divided or commissioned		Approval No.	License Date

APPENDIX D

TOXICITY TESTING

New Requirements for Animal Tests Being Submitted for Approval to Manufacture (or Import) New Drugs in Japan

Tests relating to acute and subacute toxicity must be carried out in Japan on at least one kind of animal and results must be submitted. Beyond this requirement, studies conducted outside Japan are acceptable as long as the support data described below are furnished.

I. The animal tests concerned (hereafter referred to as 'tests') must be carried out at adequately equipped facilities by experienced researchers. The following must accompany submission of all test data, whether published or unpublished.

   a. Information relating to facilities where the tests took place, i.e.,

      1. Name and address of the testing laboratories.

      2. Date of establishment (not of the parent company, but the facilities in which the studies were actually conducted).

      3. Its parent body.

      4. Organization of the facilities and/or laboratories.

5. Composition of its personnel. (Total number of people in exact facility in which studies were conducted - assistants, supervisors, management personnel, together with degrees (e.g., Ph.D.'s) and number of licenses (e.g., radioisotope, etc.) involved in the studies).

6. Site area - description of the individual lab (floor space, etc.).

7. Stories (number of floors) of the institute and total floor space.

8. List of main equipment belonging to the facility (not only that used for the studies) such as its type and other relevant details.

9. Any other available information.

B. Information (Curriculum Vitae) on the researchers who are listed in the research reports as having carried out the tests concerned:

1. Their personal histories.

2. Background details of research work done in the past.

3. Names of the scientific societies or organizations to which they belong.

II. All test data must be written in Japanese. If the material is translated from a foreign language, a total translation must be submitted as well as the original; in addition, the names, titles and qualifications of both the translators involved and the technical personnel who finally examined the content must be mentioned.

III. In the case of any material being submitted which is based on tests carried on outside Japan, the contents of such tests must meet Japanese standards.

New drugs which are submitted for import approval accompanied by data from tests conducted outside Japan must have been approved previously in other countries. All animal test data made available

to foreign (non-Japanese) authorities, concerned at the time of approval of the drug, must be submitted, accompanied by a certificate from the relevant government or health authority that such data were taken into consideration at the time of granting approval.

IV. The principal parts of the test data must have been published or intended for publication at academic meeting(s) in the particular field(s) concerned or have been reported in academic journals or their equivalents.

In the case of journals published outside Japan, the publisher's name as well as the academic reputation of such journals should be given.

V. Test records and specimens must be preserved for a period of at least five years after the date of approval for the manufacture (or import) of the drug concerned.

APPENDIX E

STABILITY TESTING

The safety tests standards for the new drugs which the Health and Welfare ministry has notified are as follows:

I. Stability tests of the new drugs shall be made according to the following provisions:

1) Tests shall be made by II (long-keeping tests) and III (severity tests).

2) Long-keeping tests shall be made by A-method or B-method.

a) In case of using A-method, the keeping conditions (temperature, moisture, etc.) during the testing period shall be recorded. If the conditions are judged to be largely different from the Japanese standard atmospheric conditions, their test data shall not be adopted.

b) In case of using A-method and in case that the special conditions or effective

time for keeping conditions are set, the basis for setting the special conditions or effective time shall be clearly stated.

c) When production (import) approval is given on the basis of the test results according to B-method, safety shall be confirmed with A-method after production (import) starts.

II. Long-keeping Tests:

1) Purpose: These tests shall be made to confirm the product quality during the distribution of the products.

2) Testing methods:

a) A-method:

- Material to be tested: the finished product (new drug in the form of preparation and the bulks which contain new effective ingredients).
- The number of materials to be tested: 3 lots.
- Keeping conditions: room temperature (in case that the special conditions are set in approval applications sheet, the keeping time shall be longer than the prescribed time).
- Time of measurement: measurement shall be made at regular intervals between test starting time and 6 months after that.
- Points to be measured: points which are judged to be necessary for quality control.
- The number of times of measurement: 3 times, but the number can be decreased in accordance with the change of each characteristic of the materials and accuracy of the measurement method.

b) B-method:

- Material to be tested: same as A-method.
- The number of materials to be tested: same as A-method.
- Keeping conditions: $25^{\circ}C+1^{\circ}C$, 75%+5%
- Test Term: for 2 years

- Measurement time: at the starting of tests and at 3, 6, 9, 12, 18 and 24 months after that.
- Points to be measured: same as A-method.
- The number of time of measurement: same as A-method.

III. Severity Tests:

1) Purpose: This test shall be made to estimate the safety and to search for the decomposed substances at the room temperature.

2) Test conditions:

a) Test conditions shall be set in consideration of 3 conditions (light, temperature and moisture). As for the bulks, the tests in water solution shall be included on general principle.

b) About decomposed substances, identification shall be made and on major decomposed substances, toxicity and pharmacological function shall be investigated.

c) The tests which are purposed to confirm that there is no decomposed substances shall be made with chromatographies of more than 3 different conditions or with other proper methods.

IV. These standards shall be adopted to the production (import) approval to be applied on and after April 1, 1980.