

Current Status and Practice in Pharmaceutical Regulations and Technical Requirements in Thailand

Before 1909, there was practically no control of drugs in any aspects. In 1909, regulations were begun only on prohibition of adulteration in drug products and control of narcotic substances. The first legislation promulgated was the *Harmful Habit-forming Drug Act 1922 (B.E. 2465)*. Control of production, of pharmacists and of their rights to dispense drugs had been enforced since 1929. The outbreak of the problems on extensive manufacture and sale of alcoholic preparations containing indigenous, medicinal herbs had attracted an attention of the Medical Association of Thailand. The problems eventually led to promulgation of an *Act on Sale of Drugs 1936 (B.E. 2479)*. The first legislative measure implemented in the field of drug control dealt only with sale practices regardless of formulas or ingredients. At that time, neither producers, importers nor retailers paid much attention or assumed their responsibilities to either quality or safety of the drugs.

The control of drugs was much improved following an enactment of the *Sale of Drug Act 1950 (B.E. 2493)*, which became effective in 1951. This law encompassed many more aspects of drug control other than the control of sale practices. For instance, control of production and registration of pharmaceutical products, and standard requirements of drug quality were included in the Act 1950.

The Act made possible the elimination of substandard, deteriorated and adulterated drugs. Consequently, manufacturing standard of local drug firms and dispensaries was upgraded to a certain extent. The Act did not only apply to production, importation and sale practices but also to product registration, labelling requirements, and advertisement control as well. Few revisions were emerged from time to time to update the law and to cope up with the changing circumstances of pharmaceutical businesses.

Pharmaceutical Affairs Administration

Started in 1922, drug control in Thailand were merely on adulteration of toxic substances in drugs. The first legislation promulgated was the **Harmful Habit-forming Drug Act, 1922 (B.E. 2465)**. The authorized agency was the Division of Habit-Forming Drugs, Ministry of Interior. Later in 1942, the Division was transferred to the Ministry of Public Health and was renamed as **Food and Drug Division**. The division was divided into three sections : food, drug and statistic sections. The name of the division was once again changed in 1965 to **Food and Drug Control Division** functioning as a separate unit under the Office of the Permanent Secretary for Public Health. The division was also expanded to five sections namely, technical, registration, narcotic, advertisement control and inspection division. The Division was then transferred to be under Health Promotion Department and reorganized into six subdivisions : technical, provincial inspection, central inspection, narcotic and toxic substances, registration, advertisement and information subdivisions.

On **December 11, 1974**, the Food and Drug Control Division was promoted to be the **Office of Food and Drug Administration**, having status equivalent to a department of the Ministry of Public Health.

The Office of Food and Drug Administration (FDA) is one of the departments under the Ministry of Public Health (see Chart 1). The FDA is divided into ten divisions and two units as shown in Chart 2.

Chart 1 Organization of the Ministry of Public Health

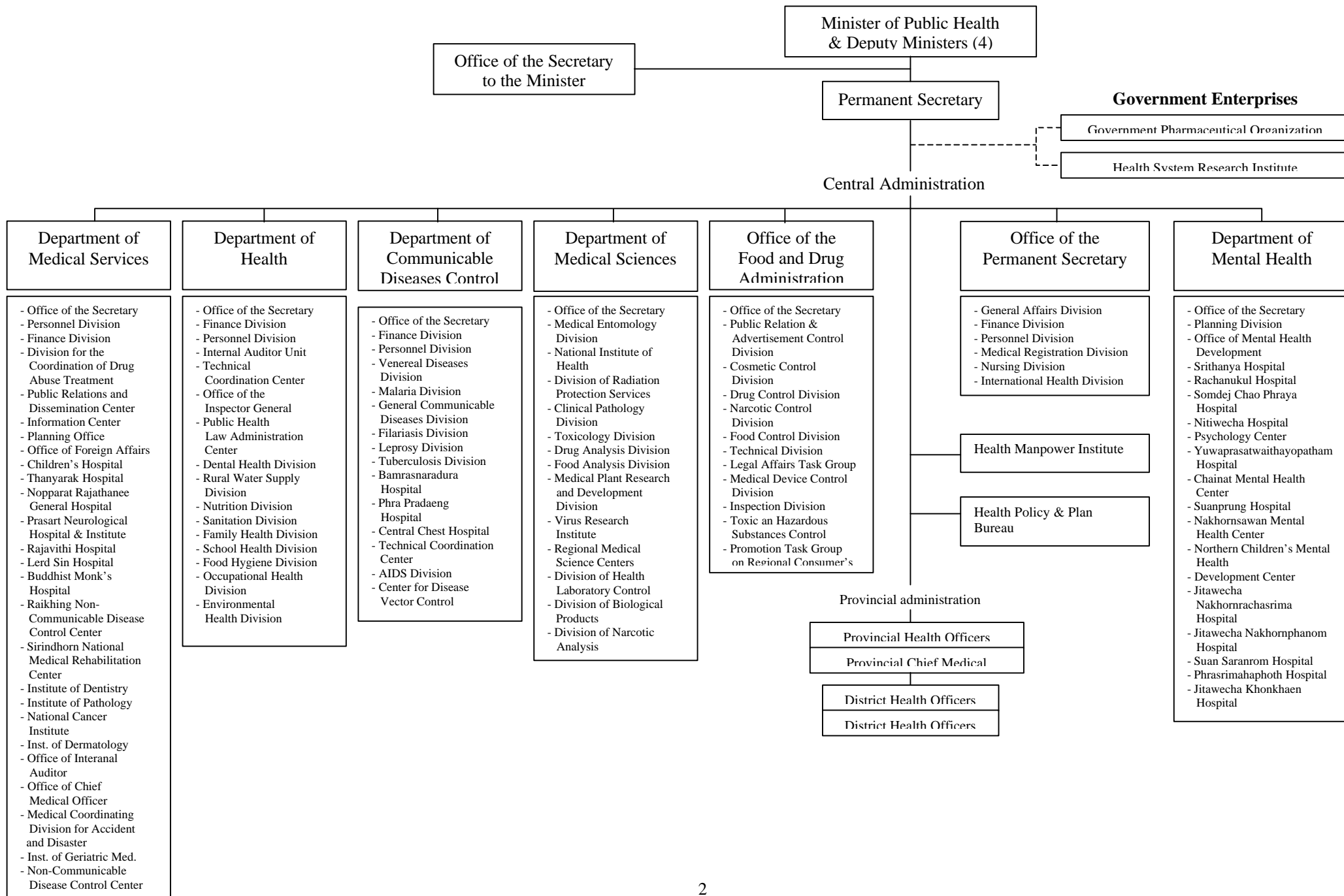
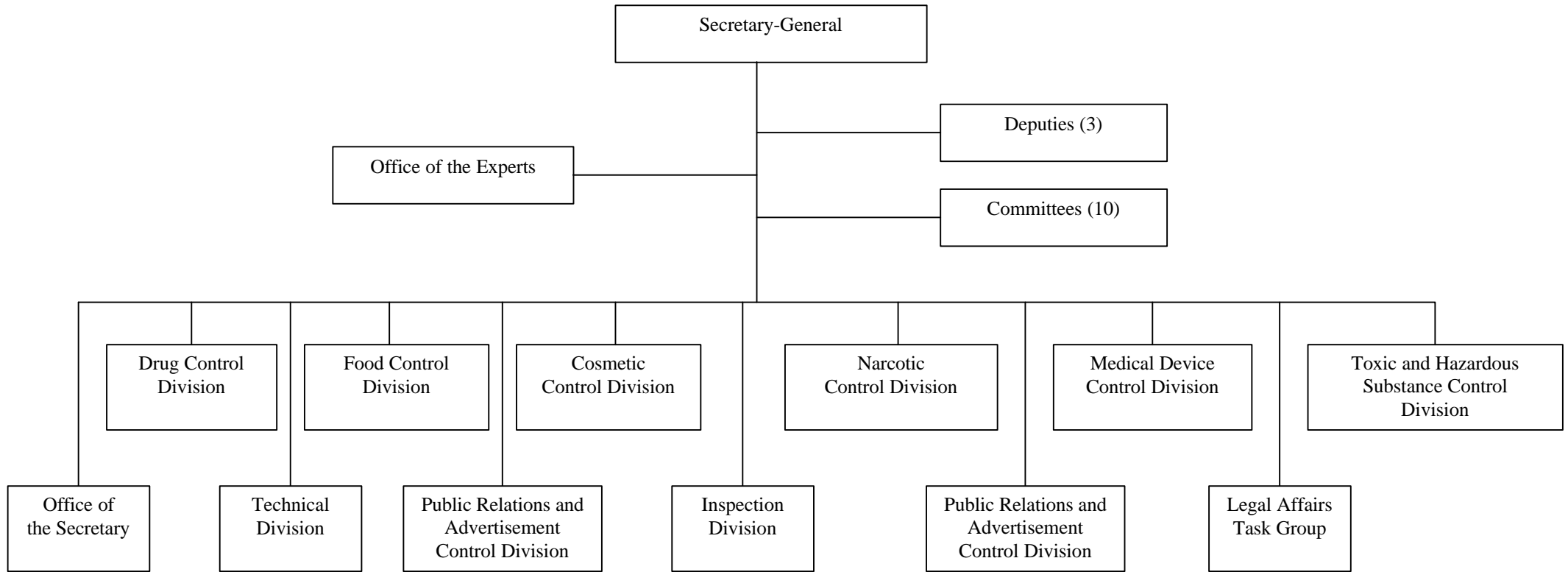


Chart 2 Organization of the *Food and Drug Administration*



The main roles and responsibilities of FDA can be summarized into 4 parts :

- 1. Pre-marketing control** of locally produced and imported health products and household hazardous substances.

This part of the roles deal mainly on issuances of notifications, setting up quality standards, inspection and testings before approval and granting of licences for business operation and registration certificates of controlled products.

- 2. Post-marketing monitoring and surveillance**

Monitoring and checking whether the approved products in the domestic market really conform to the proclaimed quality and safety. The post-marketing activities also cover surveillance programs to watch for unforeseen hazards, abuse, or any unsafe for use cases.

- 3. Consumer education and dissemination of information**

Once people have well-educated, well-informed and well-understood, they can help the government watching themselves and others from violating the laws. Education and dissemination of information are therefore the most efficient means of getting things under control. FDA policy and plans has always focused and put a lot of efforts on public relations and education through all kinds of media.

- 4. Promotion of technological development, researches and manufacture for export**

In the era of globalization, no one can refuse changes and business competition in technological development and advancement. While the country is jumping more and more into the industrial world, it is very important that the government play the supportive roles of developmental researches and transfer of technological know-how. FDA also plays such roles and has put the commitment in its policy. Research activities and technology transfer in the health industry are cooperatively and collaboratively carried out with universities and concerned private agencies. Advices and recommendations on either technological development or sources of getting assistance are provided for the requesting operators. The FDA has also used various means including its authorities on enforcement of Good Manufacturing Practice to upgrade the local industry of health products.

Laws / Regulations covering Pharmaceutical Affairs

After several years of endeavouring, the *Drug Act 1967 (B.E. 2510)* was promulgated to supersede the 1950 Drug Act. The Drug Act 1967 has been employed for almost two decades, it brought in quite substantial improvement in all aspects of drug control. However, four more revisions were subsequently emerged in order to cope up with the growing numbers of pharmaceutical manufacturers and the world situation. The latest *Drug Act 1987 (B.E. 2530)* comprises the following important features.

- I. Drugs are classified into two major groups – *modern* and *traditional drugs*.
Modern Drugs are further divided into four categories, namely (1) household remedies of which sale requires no licence; (2) ready-packed drugs sold in stores by nurses or other medical professions; (3) dangerous drugs; and (4) specially controlled drugs. Drugs which may possess a potentially harmful effect to health, if misused, will be

enlisted in the last category of which sale requires a prescription. Dangerous drugs can be bought without prescription but must be dispensed by pharmacists.

Traditional drugs are the group of those intended to be used in indigenous treatment as monographed in the official pharmacopoeia of traditional medicines or those declared by the Minister of Public Health as traditional drugs or those permitted to be registered as traditional drugs. The control and registration of drugs in this group are less stringent than those of the modern drugs.

- II. The Ministry of Public Health is authorized to publish in the Government Gazettes, the list of specially-controlled drugs, the list of dangerous drugs as well as the lists of particular drugs requiring additional labelling (e.g. expiration date, warning, etc.)
- III. Licensing for manufacturing, importation and sale of drugs is required by law. Applications for permission and licences are in accordance with the rules, measures and conditions as prescribed in the Ministerial Regulations.
- IV. Duties of licensees and pharmacists on duty at the place of production, importation or sale of drugs are also described. For instance, a licensee who produces modern drugs must have each batch of finished products analyzed for quantities of their active constituents before the products can be released to the market.
- V. Licensees must register the drugs before they can manufacture or import them. Details of the drugs and their formulas, as being registered, cannot be altered without approval or permission from the authorities.
- VI. The Minister is empowered to either suspend or revoke the licence if the licensee violate the Act.

Product Registration and Licensing System for Pharmaceuticals

1. Subcommittees

According to the *Drug Act 1987 (B.E. 2530)*, a Drug Committee has been appointed every two years to advise the Minister of Public Health on both regulatory and technical aspects concerning administration of the drug control. The committee is also authorized to approve pharmaceutical registration and to withdraw or suspend the licences. There are 14 regular members in the committee; five of them are positionally appointed from related organizations; the others are drug experts. The committee can then appoint subcommittees to assist them. Up to now ten subcommittees are appointed; these are:

1. Subcommittee on Approval of Human Drug Registration.
2. Subcommittee on Approval of Veterinary Drug Registration and Standard Usage of Veterinary Drug in Animal Feeds.
3. Subcommittee on Approval of Traditional Drug Registration.
4. Subcommittee on Approval of Investigation of Manufacturing Premises and Warehouses.
5. Subcommittee on Adverse Drug Reaction.
6. Subcommittee on Approval of Drug Advertisement.
7. Subcommittee on Setting up Requirements of Biological Products.
8. Subcommittee on Approval of New Drug Registration

9. Subcommittee on Re-evaluation of Human Drugs.
10. Subcommittee on Evaluation and Approval of Drug Quality and Analytical Control Method.

2. Licensing

The Drug Act requires that any persons who wish to sell, produce or import drugs into the Kingdom must obtain licences from the licensing authorities. The Drug Control Division is the licensing authority for manufacture, import and selling of drugs in Bangkok metropolitan and its territories. Provincial Health Offices are the licensing authorities for manufacture and import of traditional drugs and sale of drugs in other provinces.

Application for a licence must be submitted to the licensing authority. Buildings and facilities will then be inspected. A licence will be given after the inspection has confirmed that the applicant has adequate capabilities of doing such business, and he/she can secure appropriate facilities and personnel for that purpose.

There are nine different categories of licences:

- Licence to produce modern drugs
- Licence to sell modern drugs
- Licence as a wholesaler of modern drugs
- Licence to sell ready-packed modern drugs which are neither in the categories of dangerous nor specially-controlled drugs
- Licence to sell ready-packed modern veterinary drugs
- Licence to import modern drugs
- Licence to manufacture traditional drugs
- Licence to sell traditional drugs
- Licence to import traditional drugs

3. Drug Registration

Registration process is necessary to ensure efficacy, safety and effectiveness of the drugs freely sold in Thailand. Only the authorized licensees are qualified to apply for drug registration certificates. The manufacturing plant, in which a drug is manufactured, is subject to inspection for compliance with WHO GMP (Good Manufacturing Practices of the World Health Organization) and quality assurance. According to the Drug Act 1987 (B.E. 2530), the granted certificate is valid to the validity of its authorized licensee.

The process of drug registration is divided into 5 procedures:

1. Generic drug registration
2. Traditional-drug registration
3. New drug registration
 - 3.1 Original New Drug
 - 3.2 New Generic Drug
4. Biological product registration
5. Herbal medicine registration

Generic Drug Registration (see Chart 3) involves *three* steps:

1. Application for permission to manufacture or import of drug samples. (at Food and Drug Administration)

2. Application for an approval of drug quality control and analytical methods. (at Department of Medical Science)
3. Application for granting of a drug registration certificate. (at Food and Drug Administration)

Traditional Drug Registration (see Chart 4) is much simpler than that of the generic drugs. Applicants simply apply for drug registration certificates without application for an approval of analytical methods.

Chart 3 Diagram showing the registration process of *Generic Drugs*

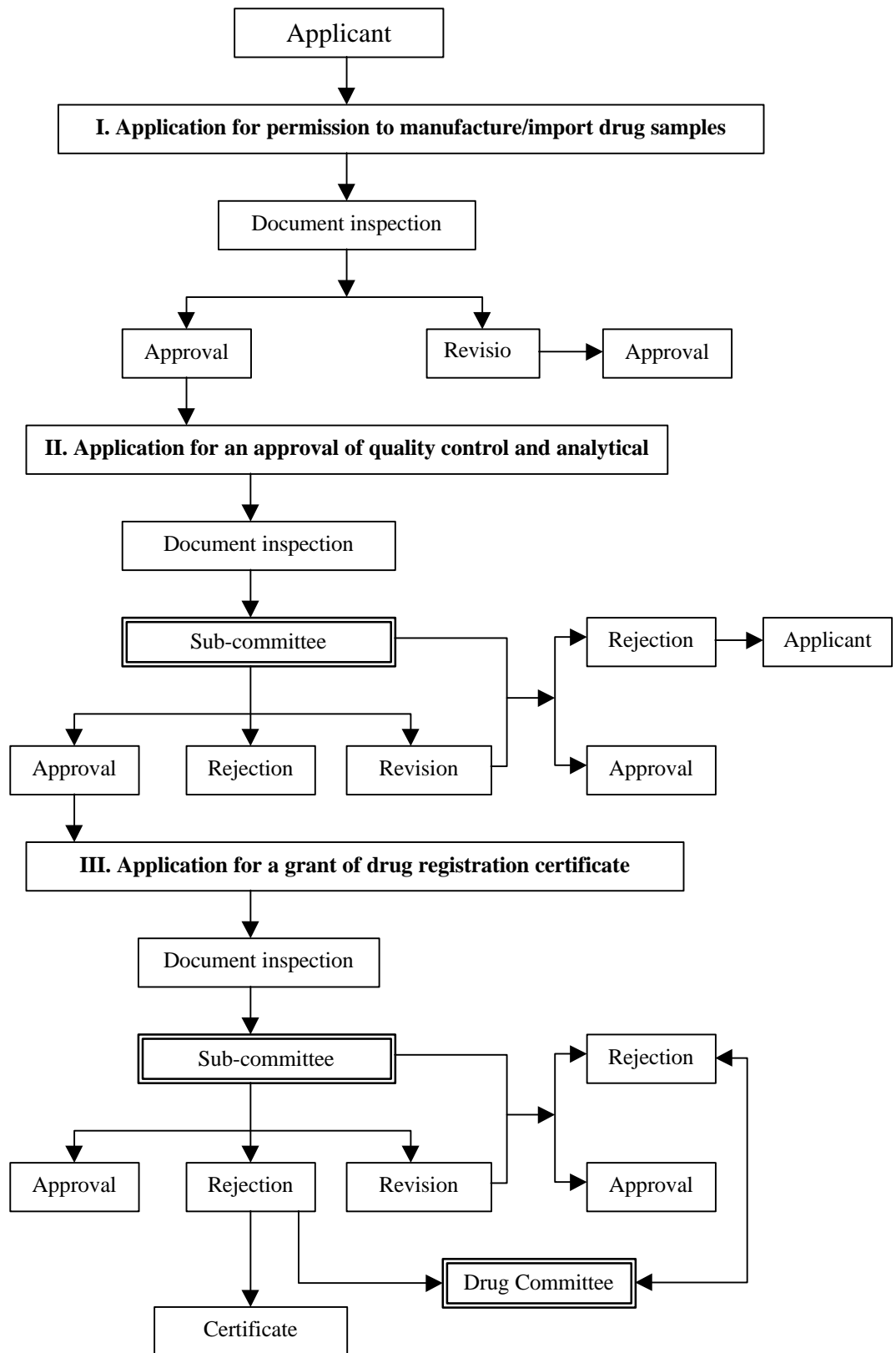
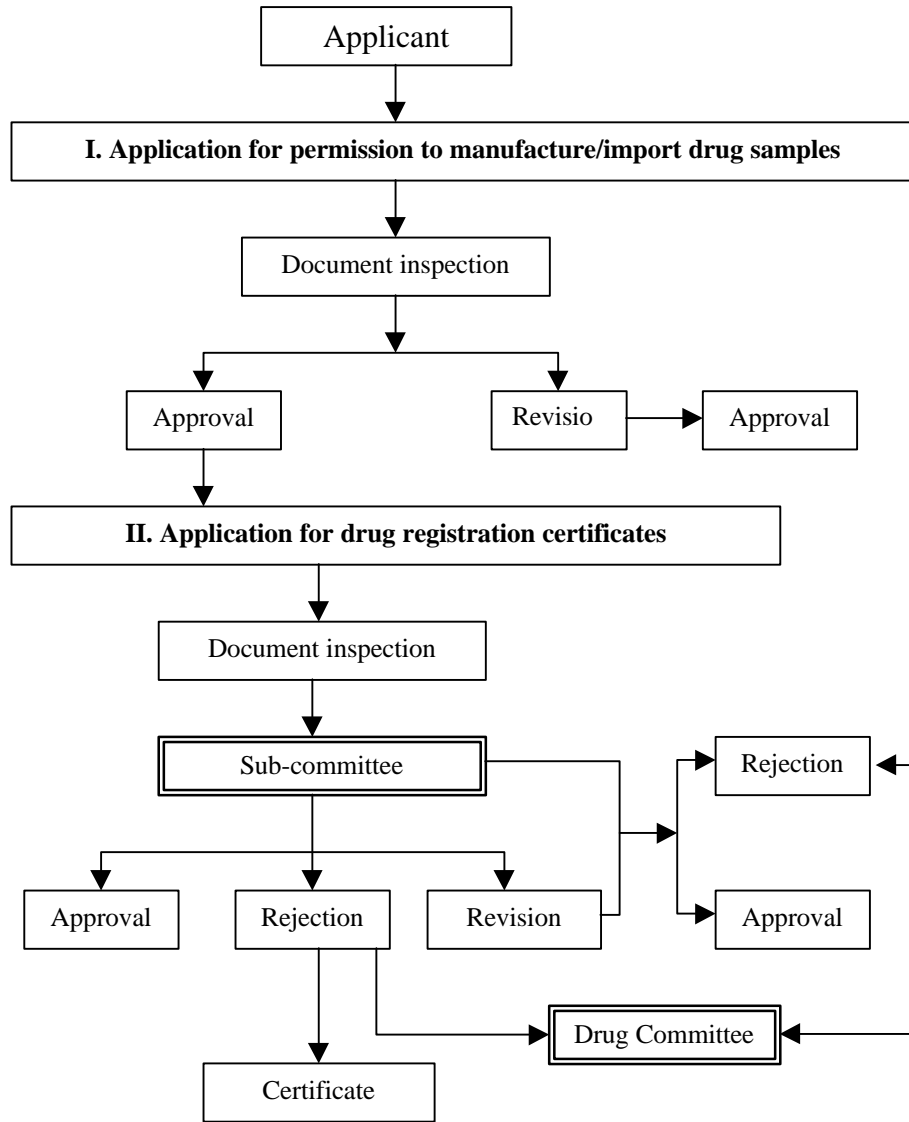


Chart 4 The registration process of *Traditional Drugs*



New Drug Registration is the most stringent of all. New drugs cover products of new chemical entities, of new indications, of new combinations or of new delivery systems.

The new amended procedure for new drugs, adopted in **August 1989**, involves a period of safety monitoring program and of limited distribution is required prior to an approval for unconditional registration and distribution. Meanwhile, generic products have to pass bioequivalence studies in order to assure their efficacious quality. The bioequivalence data must be submitted as a proof of their standard quality to the FDA along with an application for drug registration.

It is the responsibility of the Expert Subcommittee on Approval of New Drug Registration, appointed in August 1989, to evaluate efficacy and safety of new drugs, both original and generic, before a registration certificate can be issued.

Original New Drug Registration Procedures (see Chart 5)

1. Apply for a permission to import or manufacture product samples at the Drug Control Division.
2. Submit an application for registration along with a suitable quantities of samples and complete evidence or technical data on efficacies, safety and quality of the drugs. The required evidence and data are as follows:
 - Application forms,
 - Labels and leaflets,
 - Animal – pharmacological and toxicological data,
 - Human – pharmacological and clinical data,
 - Chemical and pharmaceutical data,
 - Certificate of free sales for importing drugs,
 - Certificate of raw materials for local manufacturing drugs,
 - Current status of drug approval in foreign countries.
3. After receiving a conditional approval, the company has to perform the followings:
 - a) Sell the drugs only in medical institutes (government or private section) with close supervision of doctors, in which safety monitoring can be proceeded.
 - b) Concisely record, evaluate all adverse drug reactions and report to the FDA at the end of the monitoring program along with other drug information experienced in foreign countries.
4. The FDA will approve the registration unconditionally provided that the submitted data and reports are scientifically correct and complete. The drug can then be distributed through normal market channels.

New Generic Drug Registration Procedure (see Chart 6)

1. A protocol on Bioequivalence Study must be submitted for an approval at the Drug Control Division.
2. Application for a permission to import or manufacture the drug samples.
3. Performing the Bioequivalence Study according to the approved protocol in a specified government institute.

- Submitting an application for registration along with the bioequivalency report and other useful documents.

Chart 5 Original New Drug Registration Process

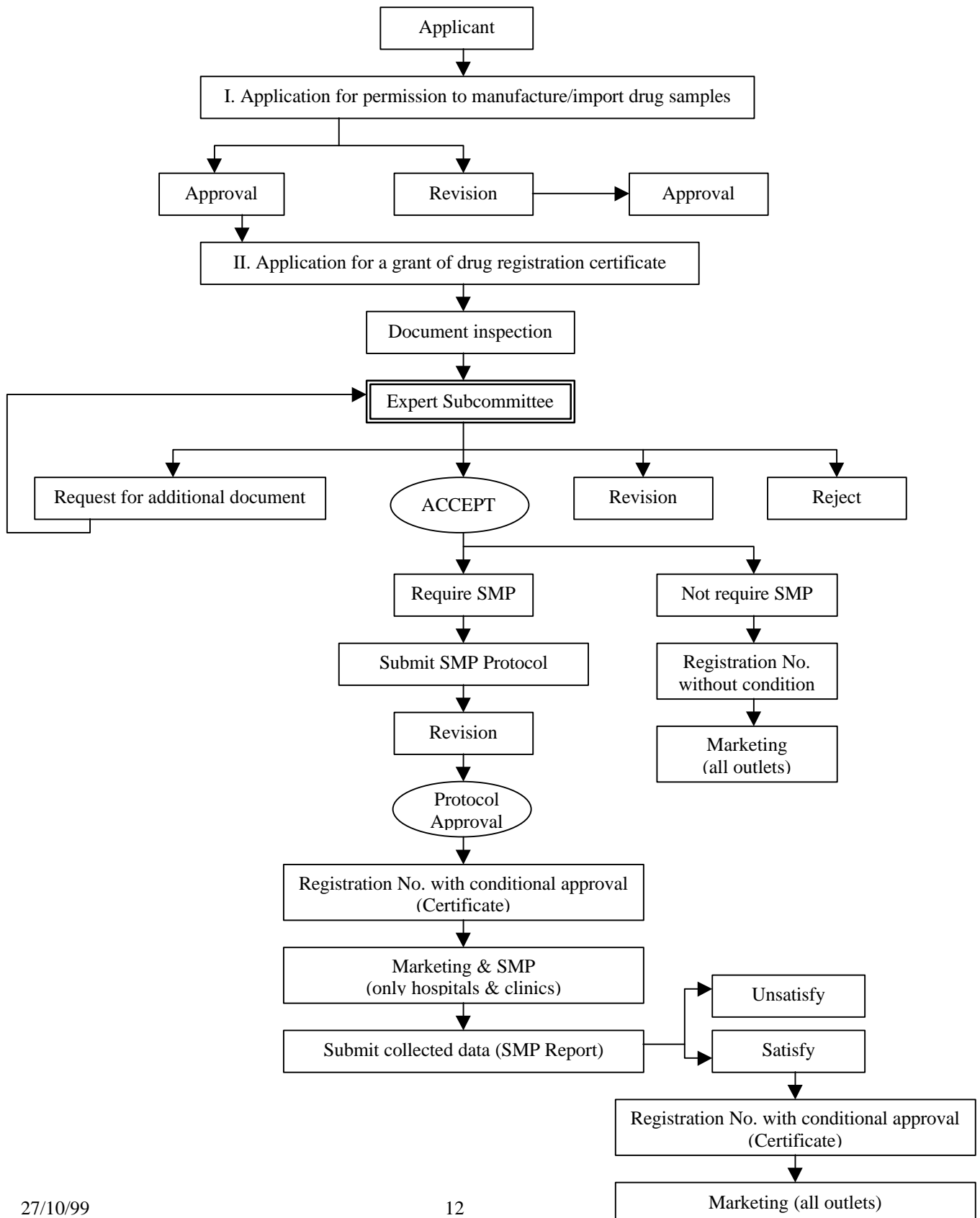
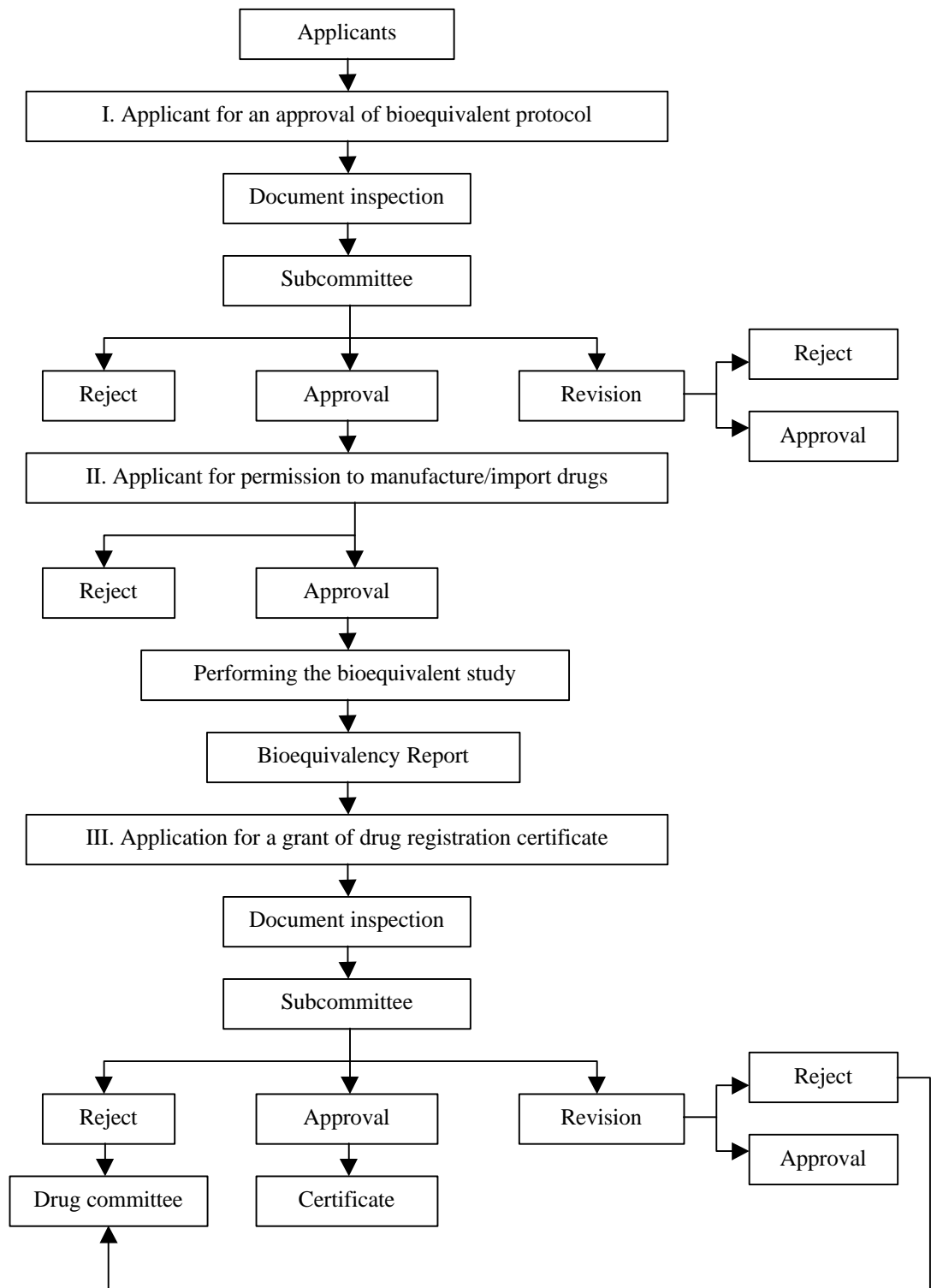


Chart 6 : The registration process of *New Generic Drug*



Biological Products registration is similar to Generic Drugs and Original New Drugs (Chart 3 and Chart 4) excluding stage II in Chart 3, is not applicable to vaccine for veterinary use.

Herbal medicines registration is similar to Generic Drugs and Original New Drugs.

Inspections

Inspection of drug manufacturers, importers or retail pharmacies are regularly carried out. Sampling of drug samples from the markets, manufacturers and importers for analyses is conducted through cooperation with Drug Analysis Division of the Medical Science Department. In addition, monitoring at customs and auditing manufacturers, import and sale of pharmaceutical products is performed. Whenever non-compliance with the laws and regulations are found the team of inspectors may firstly notify and/or take legal action to the offenses and/or report the whole issues to the subcommittees for further considerations.

Good Manufacturing Practices

Quality assurance of drug safety and efficacy before marketing can undoubtedly be achieved through Good Manufacturing Practices. Inspection of drug manufacturers and sampling of drug samples from manufacturers, importers or retail pharmacies for analyses by the regulatory authorities cannot effectively solve the cause of the encountering problems. Drug manufacturers, importers and distributors must establish their quality system according to the GMP guidelines to ensure that the drug products have and always maintain the quality as claimed.

Thai FDA has started campaigning on GMP compliances since 1984. A project on development of local manufacturing standards in pharmaceutical industry is therefore stipulated in the Sixth (1987-1991) and also in the Seventh (1992-1996) of the National Economic and Social Development Plan. The aim of the project is to promote and support drug manufacturers on implementing Good Manufacturing Practice. A current code of Thai Good Manufacturing Practice was published in 1987 as the FDA recommended guideline.

Activities that have been carried out towards accomplishment of the goal are as follows:

1. Organizing a national seminar on GMP once a year and periodically training programs for both government and private personnel.
2. Production and dissemination of technical documents, slides and videos on upgrading and training technical skills of personnel in pharmaceutical industry.
3. Conducting regular GMP monitoring and auditing with recommendations to drug manufacturers if violation to Good Manufacturing Practice is found.
4. Revision of ministerial regulations to make GMP compulsory in drug industry.
5. Audit and Evaluation of drug manufacturers according to GMP compliances. Progress on GMP enforcement is shown in Table 5.

Table 5 : Progress on GMP enforcement and pharmaceutical exportation (1989-1995)

Year	No. of Manufacturers	No. of GMP certified	% Total	Export values (Million Baht)
1989	191	58	30.4	485
1990	188	79	42.0	610
1991	184	95	51.6	790
1992	180	105	58.3	1,202.5
1993	181	116	64.4	not available
1994	180	122	67.8	not available
1995	181	122	67.4	1,659
1996	175	122	69.7	1,940
1997	175	126	72.0	2,201
1998	176	130	73.9	2,582
1999	176	130	73.9	2,911*

Remarks * estimated export value

Meanwhile the GMP has not yet become a law, the Ministry of Public Health has indirectly enforced GMP through drug customers at government hospitals. Since 1992, it has been compulsory that drugs purchased under the allocated Royal budget must be from GMP certified manufacturers. In addition, the FDA has requested collaboration from retail pharmacy stores to do the same.

Post Marketing Surveillance

- Monitoring pharmaceutical products in the market.
Monitoring and checking whether the approved pharmaceutical products in the domestic market really conform to the proclaimed quality and safety.
- Surveillance programs to watch for unforeseen hazards, abuse or any unsafe for use cases.
- Re-evaluation of the registered pharmaceutical products.

Eventhough drugs have been rigidly examined for their efficacies and safety before they are certified, chronological data, findings and pharmaceutical progress may later reveal out of date, better alternation or danger of some drugs that was not known in the past. Balance of efficacy and benefit versus risk of danger are the raising issues that invoke a drug re-evaluation program. It is the time when a number of inappropriate or unsuitably-combined drugs need to be actually reconsidered.

Since 1991, a subcommittee has been appointed by the Drug Committee to carry out the re-evaluation task. The sub-committee will verify whether a drug, in view of available information, falls under any of the following denial conditions:

1. The drug does not possess indications or effects as specified in the application for registration.
2. The drug is evidently found unsafe.
3. The drug quality is extremely inappropriate to health and hygiene.

The **final decision of the re-evaluation** may be:

- (1) Any registered drugs can be continually manufactured or imported, if they do not fall under any of the above mentioned conditions of denying registration.
- (2) When the decision requires partial changes of the indications, effects, administration or dosage, manufacturing and import of the drug may be permitted only under condition that labels of drugs must be changed accordingly.
- (3) When the subcommittee verifies that the drug falls into any of the denial condition, manufacturing and import of the drug must be discontinued. Then all remaining products must be withdrawn from the market.

Drug Advertising and Promotion

Advertisement of any drugs must apply for an approval from the authorities. Advertisement of dangerous and specially-controlled drugs is definitely prohibited.

Definition of Drugs

“Drugs” means:

- (1) Substances recognized by pharmacopoeias notified by the Minister.
- (2) Substances intended for use in the diagnosis, treatment, relief, cure or prevention of human or animal disease or illness.
- (3) Substances which are pharmaceutical substances or semi-pharmaceutical substances.
- (4) Substances intended to affect the health, structure or function of the human or animal body.

Substances under (1) (2) or (4) shall not include:

- (a) Those intended for use in agriculture or industry as notified by the Minister,
- (b) Those intended for use as food for human, operating goods, medical apparatus, cosmetics or device for use in the practice of medicine and a component thereof,
- (c) Those intended for use in science laboratory for research, analysis or verification of disease which is not directly done to the human body.

Classification of Drugs

Drugs are classified into two major groups – *modern* and *traditional drugs*.

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