Malaysia

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The evaluation and registration of pharmaceuticals prior to marketing in Malaysia began in 1985 with the promulgation of "The Control of Drugs and Cosmetics Regulations 1984", made under "The Sales of Drugs Act 1952 (revised 1989)". However, pharmaceuticals in Malaysia have been tightly regulated by several laws in the early 1950s. These laws control the practice of pharmacy and the manufacture, importation, exportation, distribution and sale of pharmaceuticals, including traditional medicines and cosmetics. Control is achieved through the registration of pharmacists, the licensing of premises, the issuing of import and export permits, and the screening of advertisements of pharmaceuticals and other substances of therapeutic value. The extension and expansion of control on pharmaceuticals have been done through a set of programmes that take into consideration manpower and facilities development as well as regulatory trends worldwide.

COUNTRY DESCRIPTION

Country Profile

Malaysia occupies a central position within southeast Asia and includes two landmasses separated by the South China Sea. Peninsular Malaysia, comprising 11 states, forms the southern tip of the Asian mainland, bordered by Thailand to the north and the island of Singapore to the south. The states of Sabah and Sarawak are located along the northern fringe of the island of Kalimantan, bordered by Indonesia, and in the northeastern state of Sarawak, by Brunei Darussalam. The total area of the country is 329,758 square kilometers of which peninsular Malaysia is 131,598 square kilometers, Sarawak 124,449 square kilometers and Sabah 73,711 square kilometers. The population of Malaysia in 1997 was estimated to be

21,666,000 at a growth rate of 2.3 percent annually. Some 79 percent of the population resides in peninsular Malaysia, 12 percent in Sabah and 9 percent in Sarawak. The country is characterised by a youthful population with around 36 percent under the age of 15.

Malaysia is a multiracial country composed of Malays (50 percent), Chinese (31 percent) and Indians (10 percent). The remainder includes Khadazans, Ibans, Orang Asli (Abrogines) and others. Malaysia's variegated ethnic mix makes it one of the prime examples of a multiracial society in the world.

Health Status

Marked improvement in the health status of the Malaysian population is indicated by the steadily decreasing mortality rates, longer life expectancies, considerable success in controlling communicable diseases and increasing efforts to address and combat new diseases. Mortality rates, particularly among the specific risk groups of mothers and young children, have declined. Over the last decade, the infant mortality rates have fallen from 13.0 per 1,000 in 1990 to 9.5 in 1997. The maternal mortality rates have dropped from 0.6 in 1980 to 0.2 in 1997.

Epidemiologically, the country's disease pattern is in a transitional phase from a domination of infectious diseases and malnutrition associated with underdevelopment to one of predominantly noncommunicable diseases, reflective of the socioeconomic and life-style changes. The threat of AIDS is evident in the increasing number of cases and HIV carriers identified. As the country becomes increasingly industrialised, occupational health will be a priority.

Health System in Malaysia

The health sector in Malaysia is no longer homogeneous and solely in the public domain. The growth of private sector health services has changed the structure of the healthcare sector toward dualism. Previously, the healthcare sector was dominated by government health services provided in hospitals, health centres, clinics and other health facilities. Public sector health services encompass the entire range of promotive, preventive, curative and rehabilitative care. The growth and development of the Ministry of Health's services have followed administrative boundaries. Hospitals are located in state capital cities and district capital towns, whilst health centres and rural clinics are located in villages. In 1997, there were 118 public hospitals with a total bed count at about 33,900, providing secondary and tertiary care. There were 772 public health clinics and polyclinics for primary care, located strategically in both urban and rural areas throughout the country. Additionally, there were 2,089 rural clinics and maternal and child health clinics located mainly in rural areas.

The private sector provides primarily curative care and some personal promotive and preventive care. Being profit-driven, the private sector tends to be concentrated in urban areas. It has grown at an impressive rate and has become an important part of the healthcare system. There are currently 197 hospitals and

maternity/nursing homes with a total bed count of 7,000 in the private sector. There are also about 3,000 private clinics and 897 pharmacies located mainly in urban areas and about 4,000 traditional medicine outlets scattered throughout the country.

In 1997 the number of doctors stood at 12,895, a doctor-to-population ratio of 1:1,322 whilst the number of dentists was 1,710, a 1:9,969 the dentist-to-population ratio. In 1998, the number of pharmacists was 1,592, a pharmacist-to-population ratio of 1:10,708.

OVERVIEW OF THE REGULATORY ENVIRONMENT

The Relevant Acts

The Pharmaceutical Services Division of the Ministry of Health is responsible for regulating the pharmaceutical market in Malaysia. The powers that allow this division to regulate the pharmaceutical market are embodied in the following legislation:

- The Sales of Drugs Act 1952 (revised 1989) and the Control of Drugs and Cosmetics Regulations 1984 regulate the sale of pharmaceuticals through a system of product registration and licensing of manufacturers, importers and wholesalers. The regulations empower the formation of the Drug Control Authority.

- The Poisons Act 1952 (revised 1989) regulates the importation, possession, manufacture, compounding, storage, transport, sale and use of poisons. Essentially, the act determines whether a pharmaceutical product is a prescription item, a pharmacy-only item or an over-the-counter (OTC) item. The classification of a pharmaceutical product into the various categories is the function of the Poisons Board whose secretariat is placed at the offices of the Director of Pharmaceutical Services. The Director of Pharmaceutical Services is also the competent authority for the issuance of import and export authorisation of psychotropics under the Convention on Psychotropic Substances 1971.

- The Medicines (Advertisement and Sale) Act 1956 (revised 1983) regulates the advertisement of OTC products in the lay media. The Medicines Advertisement Board vets all applications for advertisement of OTC items. The secretariat of the board is also at the offices of the Director of Pharmaceutical Services.

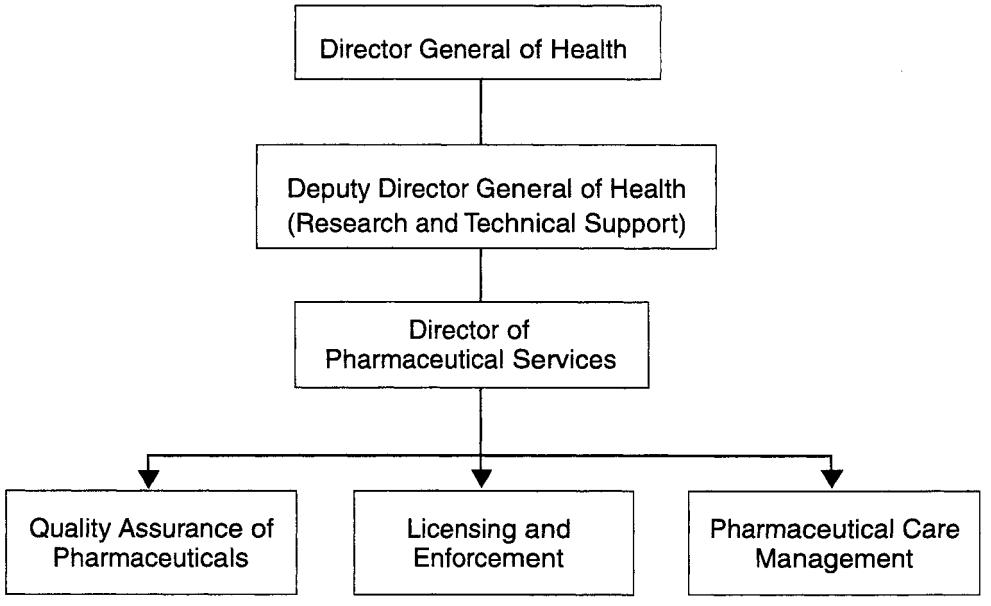
- The Dangerous Drugs Act 1952 (revised 1980) regulates the manufacture, importation, exportation, sale and use of narcotics. The Director of Pharmacy is the competent authority to issue import and export permits for narcotics under The Singles Convention on Narcotic Drugs 1961.

The Pharmaceutical Services Division enforces preceding legislations through the Pharmacy Enforcement Unit, whilst the function of product registration and licensing is delegated to the National Pharmaceutical Control Bureau (NPCB) of the Division. The organizational structure of the Pharmaceutical Services Division of the Ministry of Health Malaysia is depicted in Figure 1.

Registration of Pharmaceutical Products

The Control of Drugs and Cosmetics Regulations which came into effect on 14 June 1984, marked the commencement of a systematic regulatory control of pharmaceuticals in Malaysia. The regulations provide for the establishment of the Drug Control Authority (DCA), which has the power to implement a scheme for the registration and licensing of pharmaceutical products to ensure safety, efficacy and quality prior to marketing. The Control of Drugs and Cosmetic Regulations 1984 requires all products to be registered with the DCA prior to being manufactured, imported, sold or supplied unless the product is exempt under specific provisions of the regulations. A product is defined as "a drug in a pharmaceutical dosage form or a cosmetic having a singular identity, composition, characteristic and origin". In turn, a drug is defined as "any substance or mixture of substances used by man as a medicine, whether internally or externally, and includes anesthetics, vaccines, biologicals and vitamins".

Figure 1. Organisation chart of the Pharmaceutical Services Division. *Source: Pharmaceutical Services Division, Ministry of Health.*



The Regulations apply to products for human consumption or use only. These include any drug or biological product in a pharmaceutical dosage form intended to be used, or capable or claimed to be capable of being used in or for the following:

- Alleviating, treating, curing or preventing a disease or pathological condition, or symptoms of a disease or pathological condition.
- Diagnosing disease or ascertaining the existence, degree or extent of a physiological or pathological condition.
- Contraception.
- Anesthesia.
- Maintaining, modifying, preventing, restoring or interfering with the normal operation of a physiological function.
- Control of body weight.
- General maintenance of health or well-being.

The following borderline products are also required to be registered with the DCA prior to marketing:

- Dietary and health supplements in pharmaceutical dosage forms containing vitamins either singularly or in combination.
- Pharmaceutical products used as antiseptics or disinfectants in or on any part of the human body.
- Diagnostic agents for internal use in humans.
- Medicated medical and contraceptive devices.
- Medicated bandages, surgical dressings and medicated plasters.

The regulations do not apply to the following products:

- Diagnostic agents and test kits for laboratory use.
- Nonmedicated medical and contraceptive devices.
- Nonmedicated bandages, surgical dressing, plasters and dental fillings.
- Instruments, syringes, needles, sutures, catheters.
- Food.

The first phase of the registration exercise was implemented in 1985 for prescription medicines, followed by the second phase in 1988 for OTC products and the third phase in 1992 for traditional medicines. Registration of cosmetic products has been proposed for 2000. The legislation has recently been revised to include the registration of veterinary products.

REGULATORY AUTHORITIES

The DCA

The DCA, Ministry of Health, was formally established on 1 January 1985. The DCA consists of the following members:

- The Director General of Health—Chairman.
- The Director of Pharmaceutical Services—Alternate Chairman.
- The Director, NPCB.
- Seven other members appointed by the Minister of Health (a consultant physician, a pharmacist, three persons from local universities and two medical practitioners).

The regulations also provide for the appointment of advisers for the purpose of assisting the DCA to discharge its functions. In this respect, the DCA seeks the advice of any three relevant consultant physicians in the public service when deliberating on the application of any new chemical entities. The DCA may also set up subcommittees such as the National Adverse Reaction Advisory Committee (ADRAC) to help discharge its functions.

Briefly, DCA's role includes the following responsibilities:

- Registration of pharmaceutical products.
- Issuing of licences provided for under the Regulations, i.e., manufacturer's licence, importer's licence, wholesale licence and clinical trial import licence.
- Issuing any directions pertaining to product recall from the market.
- Determining the requirements governing manufacturing operations of pharmaceutical.

The NPCB

The NPCB, Ministry of Health, was established on 1 October 1978. It functions as a quality control laboratory for pharmaceuticals for the Ministry. With the establishment of the DCA, the role of the NPCB was expanded to support the functions of the DCA. The NPCB is responsible for the following:

- Evaluating applications for the registration of pharmaceuticals
- Processing applications for manufacturing, import and wholesale licences and clinical trial import licences.
- Monitoring adverse drug reactions (ADRs).

- Analysing pharmaceuticals and cosmetics.
- Establishing reference substances for the pharmaceutical industry.
- Providing of drug information service.
- Training professionals.

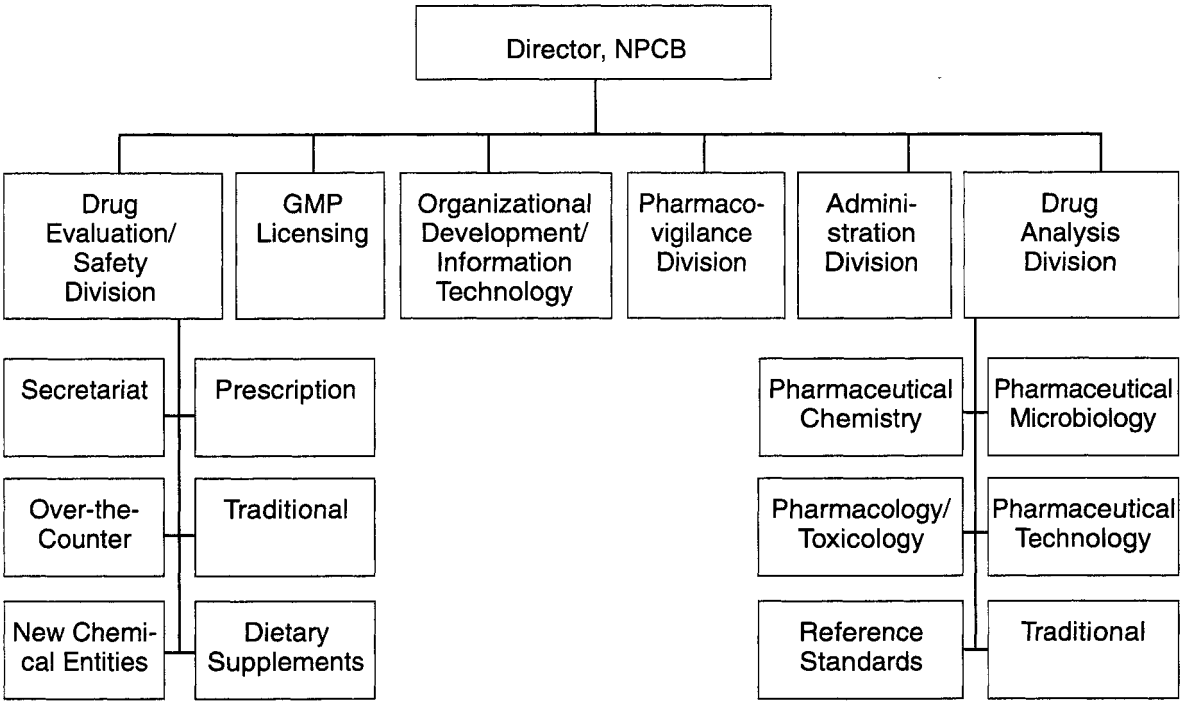
The organisation chart of the NPCB is depicted in Figure 2.

Correspondence Addresses

The contact information for the Pharmaceutical Services Division (for matters pertaining to enforcement of pharmacy legislation) follows:

The Director,
Pharmaceutical Services Division,
11th Floor, PERKIM Building,
Ipoh Road,
51200 Kuala Lumpur, Malaysia.
Tel: 603-4412958
Fax: 603-4457387
e-mail: anis@moh.gov.my

Figure 2. Organisation chart of the National Pharmaceutical Control Bureau (NPCB). *Source: Pharmaceutical Services Division, Ministry of Health.*



The contact information for the NPCB (for matters pertaining to the functions of the Bureau other than product registration) follows:

The Director,
National Pharmaceutical Control Bureau,
Jalan Universiti, P.O. Box 319,
46730 Petaling Jaya, Malaysia.
Tel: 603-7573146
Fax: 603-7562924
e-mail: lails@bpfk.gov.my

The contact information for the Drug Control Authority (for matters pertaining to product registration)

The Secretary,
Drug Control Authority,
National Pharmaceutical Control Bureau,
Jalan Universiti, P.O. Box 319,
46730 Petaling Jaya, Malaysia.
Tel: 603-7573146
Fax: 603-7581312
e-mail: zin@bpfk.gov.my

REQUIREMENTS AND PROCEDURES FOR REGISTRATION

Stages in Application for Registration of Pharmaceuticals

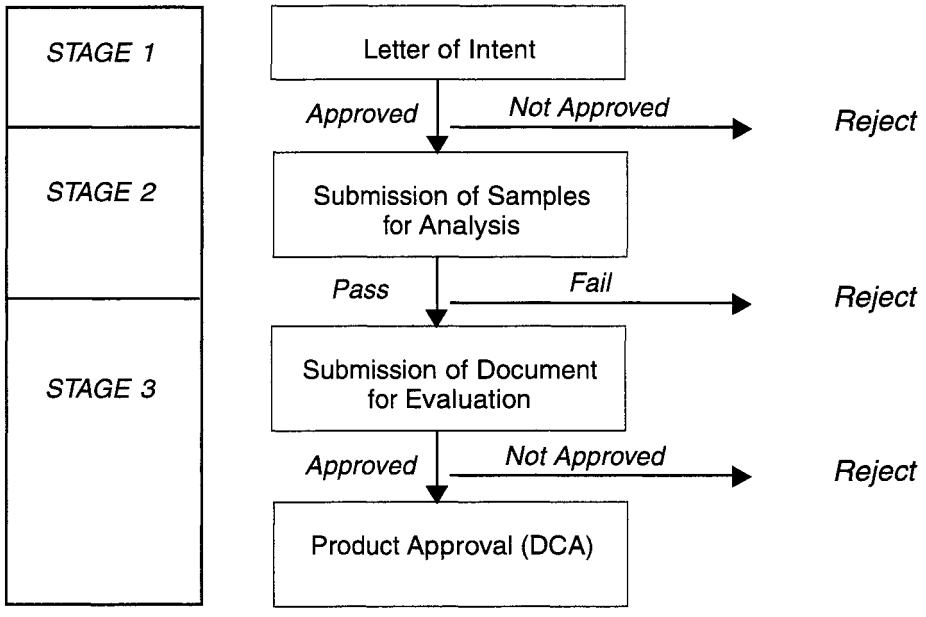
A company intending to register a pharmaceutical product in Malaysia is required, in most circumstances, to submit the application in three stages. A flow chart of the three stages is shown in Figure 3.

Stage 1

The main objective of registration at this stage is to evaluate products that are submitted for registration to ensure that the active ingredient(s) or formulation is registrable with the DCA. Factors considered at this stage include:

- infringement of patent right;
- active ingredient of standard strength;
- nonactive ingredients that do not contain banned or disallowed substances; and
- certificate on Free Sale from the exporting country.

Figure 3. Processing procedures for drug registration. *Source: Pharmaceutical Services Division, Ministry of Health.*



All applications for stage 1 will be notified in writing within a certain time period. For applications which are approved, the DCA will issue a permit to import or manufacture samples for submission of stage 2 application.

Stage 2

The main objective of stage 2 processing is to evaluate the quality of the pharmaceutical product approved in stage 1. Laboratory testing of the sample carried out at the NPCB laboratories. Some of the requirements of stage 2 evaluation follow.

- Samples must be from one production batch.
- Expiry date of sample must not be less than 1 year.
- Analytical protocols must be submitted.
- Certificate of analysis of sample must be submitted.

Only samples which pass laboratory testing will be allowed to proceed to stage 3 of the evaluation process. Resubmission of new samples for testing is only allowed in special circumstances when explanations for the failure are given.

Stage 3

The purpose of stage 3 is to evaluate the safety, efficacy and quality of the pharmaceutical product. Although the regulations do not specify the criteria for registration, the DCA used the criteria of safety, efficacy and quality for considering the issue of registration or nonregistration of a particular product. Evaluation of the product is based on data submitted by the applicant, as well as any other data made available to the DCA. For new chemical entities, the DCA will also seek the view of at least three consultant physicians appointed to review the date submitted.

For new chemical entities, the following data are required:

- Letter of application by a locally incorporated company, including a letter of authorization from the manufacturer of the product if the applicant is not the manufacturer.
- Product particulars as they normally appear in product monographs, package inserts and drug information sheets.
- Pharmaceutical data on dosage form, including product specifications, manufacturing data, quality assurance procedures, stability data, validation procedures and bioavailability studies.
- Data on the chemistry and pharmacy of the active ingredients, including their physicochemical structure, method of manufacture, quality control, impurities control, specifications and any other relevant data.
- Preclinical data, including pharmacology and toxicity.
- Clinical data, including the various phases of clinical trials conducted on the product.

For generic products, the submission of the stage 3 application consists only of:

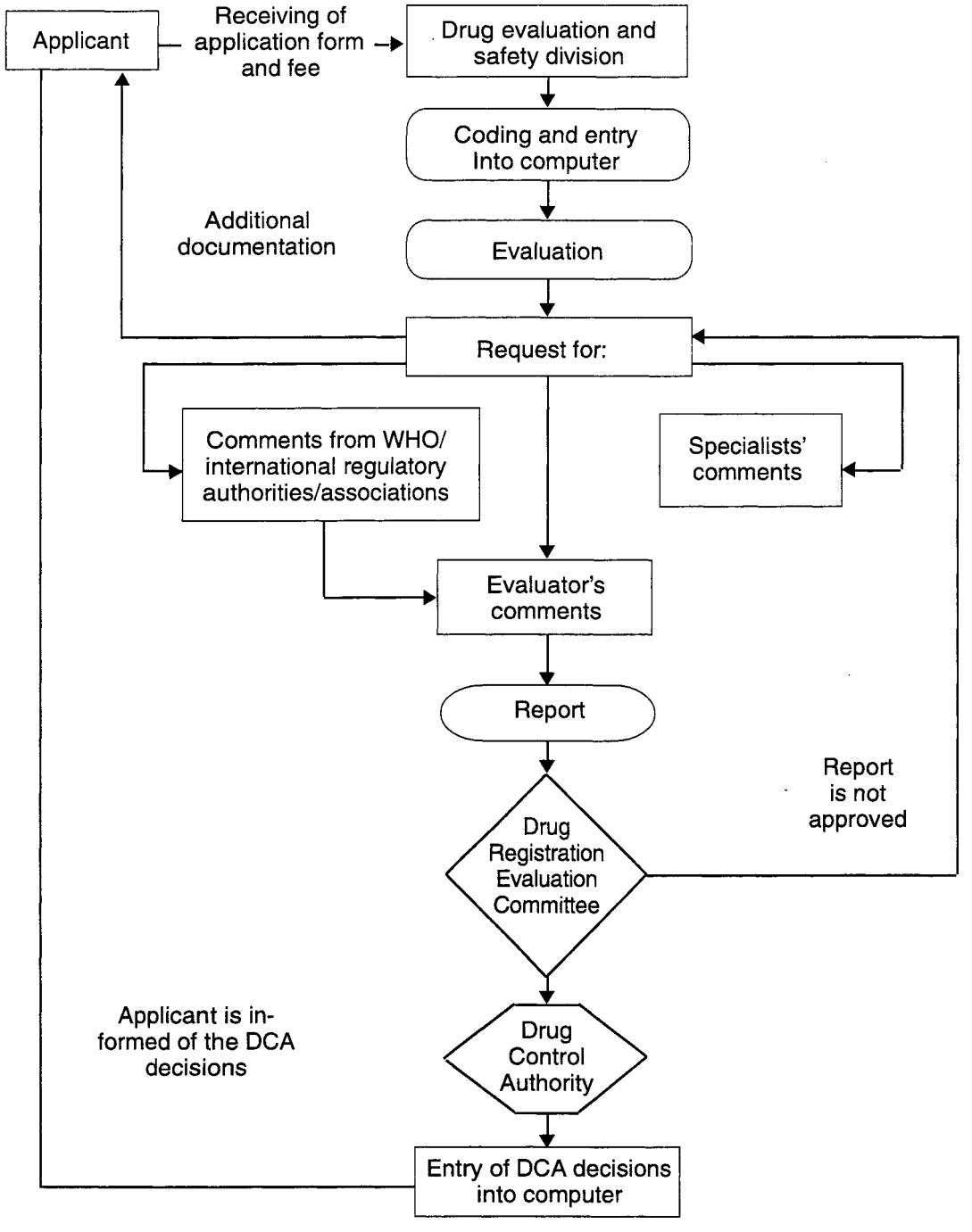
- the letter of application;
- product particulars; and
- pharmaceutical data on the dosage form.

However, the DCA reserves the right to request any other additional information deemed necessary for its evaluation. A flowchart of the processes involved in the stage 3 evaluation is depicted in Figure 4.

Abridged Evaluation

Submission of samples is not required for certain categories of OTC products. Therefore, processing of this category of products does not have to undergo the stage 2 evaluation. After stage 1 approval is obtained, the applicant can submit documents needed for the stage 3 evaluation. These documents consist of the letter of application, product particulars and pharmaceutical data on the dosage

Figure 4. Procedures for processing stage three registration application for pharmaceutical products.



form. The classes of OTC products for which laboratory testing is exempt include the following:

- Oral dietary and health supplements.
- Antiseptic/disinfectants.
- Anti-dandruff preparations.
- Anti-pigmentation agents.
- Oral healthcare and dental products.
- Topical analgesics and counter-irritants.
- Nonsterile medicated bandages/dressings/plasters.
- External emollients, demulcents and protectants.
- Anti-acne preparations.
- Lozenges and pastilles.
- Traditional medicines.

Laboratory testing of this category of products will be done through a post-marketing surveillance programme in which these products will be systematically sampled at the points of distribution or sale after the products have been registered. Serious nonconformity of the product to its specifications as submitted in the registration data will lead to the product being deregistered and taken off the market.

Registration of Traditional Medicines

The DCA also requires that traditional medicines marketed in a pharmaceutical dosage form be registered. Traditional medicine is defined as "any product employed in the practice of indigenous medicine, whereby the drugs used only consist of one or more naturally occurring substances of plant, animal or mineral origin, or in extracted form or nonextracted form". Indigenous medicine is defined as "a system of treatment or prevention of disease established through traditional use of naturally occurring substances". The following classes of traditional medicinal products need to be registered:

- Pharmaceutical dosage form containing natural substances of plant, mineral or animal origin in the unextracted or crude extract forms.
- Externally used traditional medicines containing combinations of camphor, menthol and/or essential oils.
- Dietary or health products containing solely natural substances of plant or animal origin in unextracted or crude extract form.

The basis for registration is to ensure the quality and safety of traditional medicines marketed in Malaysia. Unlike western medicines, evaluation of traditional medicines does not cover efficacy. The evaluation of quality and safety encompasses several criteria as laid down by the DCA. These include the following:

- Limits for heavy metals such as lead, arsenic and mercury.
- Limits for microbial contamination as set by the DCA. Pathogenic bacteria such as staph. aureus, pseudomonas aeruginosa, E.coli and salmonella should not be present.
- Absence of steroids and other adulterants.
- Limits of disintegration time for solid oral dosage forms.
- Indications which prohibit claims made with reference to the 20 diseases listed under the Medicines (Advertisement and Sales) Act 1956.
- Prohibition of certain herbal ingredients which have been documented as having adverse effects on humans.
- Prohibition of the use of animal parts derived from endangered animal species.
- Compliance with Good Manufacturing Practice (GMP) in relation to its site of manufacture.
- For imported products, the application must be accompanied by a Certificate of Free Sale (CFS) from a recognised authority.

Renewal of Registration

The registration of a pharmaceutical product is valid for 5 years, after which the registration will be cancelled. A new application for registration is required for renewal. The respective registration holder is required to submit an application for renewal of registration no later than 1 year prior to the expiry of the product registration. This is an abridged registration application consisting of the following:

- Application form on a prescribed format.
- Product particulars, namely:
  - Complete master formula.
  - Finished product specification.
  - Recent certificate of analysis of two batches
  - In vivo bioavailability data for sustained/controlled release preparations.
  - Complete stability studies to support the approved shelf life.

- Letter of authorization from the manufacturer authorising the local agent to be the registration holder.
- Current Certificate of Pharmaceutical Product and GMP from the country of origin.
- List of changes made to product particulars and pharmaceutical date with reference to that originally approved by the DCA.
- Any intended change to product particulars and pharmaceutical data, provided the change does not affect the pharmacological and pharmacodynamic characteristics and stability profile of the products.

The same registration number issued earlier is specific for the product and will be retained. A new certificate of registration with the provisions, duration, conditions and limitations of the registration will be issued for a product approved for reregistration.

Appeals

The DCA may reject, cancel or suspend registration of any product if the product creates serious injury or illness. Other reasons for cancellation include deficiencies in safety and efficacy or failure to comply with the conditions of registration.

Any applicant/holder of a registration certificate who disagrees with the decisions of the DCA may make a written appeal to the Minister of Health. All notices of appeals must be made within 14 days from the date the decision of the DCA is made known. A period of 90 days from the date of appeal is given for submission of any supporting data or documents. All appeals are processed by the secretariat and submitted to the Minister of Health for a final decision.

Reapplication of rejected products for reasons of safety and efficacy will normally not be accepted within 2 years after rejection. However, if the product meanwhile gains registration in the reference countries, the application can be submitted earlier.

Processing Time for Registration

The DCA is committed to a client's charter, which stipulates the maximum time it will take to process an application for registration as well as an application for other licences. The following time frames have been agreed upon for processing an application for registration of a pharmaceutical product:

- Stage 1 Not more than 6 weeks
- Stage 2 Not more than 4 months
- Stage 3 Not more than 6 months for generic products

  Not more than 12 months for NCEs

  Not more than 6 months for additional indications

Therefore, the total time taken for the registration of an NCE should not exceed 17.5 months, whilst the equivalent time for generic products should not exceed 12.5 months. In reality, the DCA is able to process stage 1 applications within the stipulated time. However, stage 2 applications can take as long as 6 months. Discounting the time taken for submission of additional data by the applicant, the processing of stage 3 applications for generic products is within the limits stipulated by the client's charter. For NCEs, the time taken for processing stage 3 applications generally depends on the completeness of the data submitted as well as the current status of registration of the product in the reference countries used by the DCA. The secretariat of the DCA is constantly reviewing its work processes with a view to shorten the processing times.

Application Formalities

Who Must Apply for Registration?

For an imported product, a locally incorporated company authorised in writing by the manufacturer of the product to be the holder of the registration certificate must apply for the product registration. A copy of the company incorporation or registration certificate must be submitted. Where a product contains a scheduled poison or dangerous drug as defined under the Poisons Act 1952 (revised 1989) and the Dangerous Drugs Act 1952 (revised 1980), the local applicant must possess the appropriate currently valid licences or authorization under these laws.

The applicant will be held responsible for the product and all information supplied in support of his application for registration of the product. In cases where secrecy considerations prevent disclosure of certain information to the applicant, such information may be furnished to the DCA through the applicant in a sealed envelope market "confidential", or sent directly to the Secretary of the DCA with the appropriate references.

Fees

Every application for registration of a pharmaceutical product must be accompanied by a processing fee fixed by the regulations. The processing fee is nonrefundable. Apart from the processing, the DCA will charge any applicant such costs as it may incur while carrying out laboratory investigations/testing prior to the registration of the product. A schedule of laboratory charges is available for reference.

CFS

A CFS and GMP certificate in the country of origin of the imported product must accompany the application for product registration. In cases where the product is packed by a different company, a GMP certificate of the packing company is required. The CFS must be issued by the authority recognised by the DCA—that is, the authorities listed in the World Health Organisation's (WHO's) "Certification Scheme on the Quality of Pharmaceutical Products Moving in International

Commerce", and must be in the format of the WHO's scheme or equivalent. If original certificates are not submitted, the copy submitted must be duly endorsed by the Malaysian Embassy in the country of origin.

Products Under Patent

The registration of a product under the Control of Drugs and Cosmetics Regulations 1984 does not exempt any person from the provisions of the Patent Act 1983. The DCA will, to the best of its knowledge, issue registration of products covered by patent rights to the patent owner only. When the patent owner is foreign, registration will be issued to the local firm authorised by the patent owner. Patent claims must be supported by evidence of Malaysian patent registration.

Submission of applications for registration of products covered by patent right from nonpatent holders will be accepted only after the patent rights of the product have expired.

Change of Holder of Registration Certificate

The DCA allows the manufacturer or owner of a registered product to change the holder of the registration certificate by submitting a letter of authorization from the manufacturer appointing the new holder and terminating the old registration holder, and giving the effective date that such a change will take place. The process of changing the holder normally takes place within 1 month.

Language

Applications for registration, submission of data, references and all other correspondence pertaining to product registration can be submitted in Bahasa Malaysia or English.

FUTURE TRENDS

Transparency of Processes

The NPCB is currently in the process of obtaining accreditation for ISO9000 for all its core processes, including the processing of applications for registration of pharmaceutical products. In line with this objective, the secretariat of the DCA is currently reviewing the core processes involved in the processing of applications of registration. This review is also aimed at decreasing the overall processing time for registration of a product to be in line with the time taken by other progressive regulatory bodies worldwide.

Information Technology

In line with the Malaysian government's aspiration to leapfrog into the information technology (IT) era, the NPCB is currently upgrading its IT capabilities. In terms of processing applications for registration of pharmaceutical products, the upgrading exercise will enable applications to be submitted through the electronic data interchange.

Harmonization of Registration Requirements

The Pharmaceutical Services Division of the Ministry of Health is currently working in collaboration with countries of the Association of Southeast Asian Nations (ASEAN) to work out a common approach to registration requirements. With this initiative, it is hoped that ASEAN countries will harmonise their registration requirements in the near future.

ABOUT THE AUTHOR

Anis Ahmad is a pharmacist who has been the Director of Pharmaceutical Services, Ministry of Health Malaysia since 1997, after having served as Deputy Director since 1992. Dr. Ahmad has also served as Secretary to the Pharmacy Board and the Poisons Board of Malaysia, first Secretary to the Drug Control authority, and Director of the National Pharmaceutical Control Laboratory. Dr. Ahmad is currently the Chairman of the Working Group on Pharmaceuticals for the Asean Consultative Committee on Standards and Quality, which is studying the possibility of harmonizing registration requirements of pharmaceuticals in the Asean region.