

Appendix B: Drug Registration and Labeling in Brazil, Kenya, Panama, and Thailand

The following sections describe the legal requirements for drug registration and labeling in Brazil, Kenya, Panama, and Thailand, the four countries of the OTA survey. OTA did not evaluate how well these requirements are met in practice. There is considerable evidence in the literature, however, that in many developing countries limited resources and personnel make full implementation of the requirements virtually impossible.



Brazil

DRUG REGISTRATION

At the time of the OTA survey, the Division of Drugs of the Ministry of Health (DIMED) had primary responsibility for drug regulation and enforcement. Since then, the Ministry of Health has been reorganized (under the Collor government) and DIMED no longer exists as a distinct entity. Its functions have been taken over by the Division of Products (DIPROD) of the National Secretariat for Sanitary Surveillance (Vigilância Sanitária) (207).

All drugs not included in the Brazilian Pharmacopoeia are considered “new drugs”¹ and must be registered with the Ministry of Health (this excludes raw materials, which are regulated under other legislation)

(106). To register a drug for marketing in Brazil, a company must submit an application that includes:

1. a drug registration petition;
2. a report on the experimental therapeutics (pre-clinical and clinical trials) of the proposed drug, in conformity with detailed rules issued by the National Health Council in Resolution No. 1 of 1988;
3. a technical report on the product, including chemical and pharmaceutical detail, principal indications, method of use, complementary indications, contraindications, side effects, adverse reactions, restrictions or precautions, expiration period, storage conditions, and instructions for use, when applicable;
4. pharmacodynamic data, including method of action and dosing information with justifications;
5. report on production and quality control, including full details of the production process and proposed quality control mechanisms for all stages;
6. models of labels and packaging; and
7. bibliography, including translations of original papers, if foreign.

Brazilian law states that an application for registration must be processed in 90 days. In the past, delays were **common** and the average processing time was 2

¹A new product is considered any type of new molecular substance; new salt of previously approved ingredient **modification** in the quantity, number, or identity of active ingredients or **pharmacokinetic** characteristics of an existing medication or any new combination of registered substances.

to 3 years (192). The type and urgency of the registration may affect its handling. According to a former DIMED director, some petitions took as long as 6-8 years to process while others were handled rapidly (206). Registration is valid for 5 years, but if new information about adverse reactions, precautions, or contraindications for the product becomes known, it must be reported to the Ministry of Health. For renewal, a simplified application form with recent analytical, preclinical, and clinical data, along with a renewal fee, must be submitted.

In August 1990, the Ministry of Health began restructuring the SNVS (National Secretariat for Health Monitoring), including a new program called "INOVAR," to streamline the registration system and handle the backlog of approximately 18,000 product approval applications (197). With about half a dozen professionals working on drug regulation, the following approvals were granted in a period of 7 months (September 1991 through March 1992): 425 petitions to change the composition (active ingredients) of drugs already on the market, without changing the name of the drug; 455 registrations of drugs that are similar to others already approved; 293 transfers of registry from one producer to another, and 457 registrations of new commercial presentations (207).

DRUG LABELING

Brazilian labeling requirements are the same for over-the-counter (OTC) and prescription drugs (106). As a general rule, neither labeling nor advertisements may include geographic names, symbols, figures, designs, or other indications that might be misleading. In addition, any unauthorized modification of the label is punishable by cancellation of the registration.

Preclearance of labeling is required as part of the registration procedure. The *package label* must include the following (106):

1. name of product (trademark or generic);
2. pharmaceutical form;
3. number of units in package;
4. active ingredients;
5. complete formula of the product with quantitative composition;

6. name and address of manufacturer;
7. responsible pharmacist;
8. license number and date of issue;
9. batch number;
10. expiration date and date of manufacture;
11. storage instructions;
12. for prescription products, statement that it is supplied on prescription only;
13. indications;
14. side effects; and
15. precautions, if any.

Package inserts are not compulsory for all products, but if the company intends to include a package insert, it must be approved in advance. Inserts are usually physician-oriented (201). Once labeling is approved, all changes must be submitted for review, including a technical justification for the proposed change,



Kenya

DRUG REGISTRATION AND LABELING

At the time of Kenyan independence in 1963, almost all available pharmaceuticals were imported from Great Britain, and there was no formal registration system. As products from around the world began to enter the country in the 1970s, the government instituted import permits. The primary purpose of the permit system is to control the amount of foreign currency moving out of the country, rather than specifically to control the flow of drugs. The need to assert some control over the drug supply itself led to the passage in 1981 of laws governing drug registration.² The statutes do not define the registration process in detail, but authorize the Ministry of Health to develop detailed guidelines (40). The Pharmacy and Poisons Board of the Ministry of Public Health has the responsibility to review drug registration applications and product advertisements.

A drug may be registered for 5 years in Kenya, after which the company must apply for renewal.

²The requirements for registration are provided for in the Pharmacy and Poisons Act and the Pharmacy and Poisons (Regulation of Drugs) Rules of 1981.

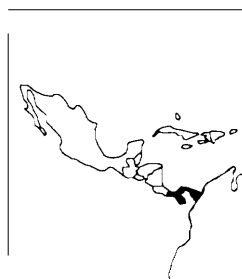
Initial applications for drug registration are assessed on grounds of safety, efficacy, and quality. Each registration application must include the following information (106):

1. administrative data;
2. pharmaceutical formula;
3. name and structural formulae of the active ingredients;
4. specifications of ingredients (active and excipient);
5. analytical control of ingredients;
6. analytical control procedures during manufacture;
7. shelf life;
8. summary of the method of manufacture and assembly;
9. summary of the experimental tests for pharmacological effects;
10. summary of tests for physiological availability; and
11. summary of clinical tests for efficacy.

In addition, the application must include labels, package inserts, and any promotional literature. The label should include the following (106):

1. therapeutically active substances, specified by name, qualitatively and quantitatively, per suitable unit;
2. inactive ingredients, which may be specified under a common term such as "excipients" unless such ingredients may be of some special significance in the use of the product;
3. name and percentage of any bactericidal or bacteriostatic agent;
4. expiration date;
5. batch number;
6. where necessary, directions of a technical nature for the use of the product;
7. particulars on the normal dose and indications;
8. name and business address of manufacturer; and
9. registration number of the product.

Kenya does not require package inserts, but if a company chooses to include one, it must be approved by the Ministry of Health. All changes to the approved labeling must also be reviewed by the Ministry.



Panama

DRUG REGISTRATION AND LABELING

According to Decree 93 of February 16, 1972, the Regulation on Registration of Pharmaceutical Specialties, almost all pharmaceuticals must be registered in Panama,

The Ministry of Health controls the registration process and works in conjunction with the National University of Panama and specialized laboratories to review applications. In evaluating an application, the Ministry compares the safety and therapeutic advantages of the drug with similar products, and bases its decision on these comparisons.

The following information must be included in a registration application (106):

1. trade mark or generic name of product;
2. name and address of manufacturer and distributor;
3. dosage form and route of administration;
4. name of the responsible pharmacist;
5. details of therapeutic class;
6. a sample of the container
7. complete formula of finished dosage;
8. draft of proposed packaging copy and package insert;
9. active ingredients;
10. indications;
11. contraindications;
12. warnings, precautions;
13. recommended route of administration;
14. draft outline of proposed information to the medical profession;
15. recommended dosage: usual dose, frequency, range;
16. summary of pharmacological data and data relevant to proposed use;
17. summary Of all clinical trials; and
18. data on adverse reactions and drug interactions.

Panama also requires that any "physician-oriented" information be included with the registration application.

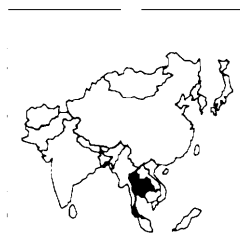
It takes an average of 2 years for a full registration application to be approved. Drugs that are not new

chemical entities and that already are listed in locally approved pharmacopoeias are subject to lesser requirements, which include provision of a Free Sale Certificate, a Certificate of Analysis, the product formula, and samples of the product (106).

Printed packaging copy and package inserts also must be reviewed at the time of registration. The following information, in Spanish, is required on the package label (106):

1. qualitative and quantitative formula;
2. strength and pack size (contents);
3. registration number;
4. trademark;
5. manufacturer's name and address;
6. statement that dose must be as prescribed by physician, and that sale is subject to prescription; and
7. expiration date and batch number.

Package inserts are not required for all products. The decision to include a package insert is left to the discretion of the manufacturer (106), but there are legal requirements for their content if an insert is included. Inserts usually are physician oriented. Companies are not required to notify the government of changes in labeling for registered products.



Thailand

DRUG REGISTRATION AND LABELING

Thailand's pharmaceutical market is actually two markets that exist side by side: a public market, supplying government health centers and hospitals, and a large private

market. The regulation of these two markets differs.

Regulation of the Private Market

As established by the Drug Act of 1967, the main legislation affecting the pharmaceutical industry in Thailand, every pharmaceutical product intended for sale must be granted a marketing approval by the Thai Food and Drug Administration (TFDA) of the Ministry of Public Health (MOPH) (193). The Drug Act applies to the private market, but since 1986 has not applied to the Governmental Pharmaceutical Organi-

zation (GPO), the government's own drug production company (272).

At the time of OTA's survey, a company was required to submit a registration application containing some or all of the information in the list that follows (in Thai or English). Since that time, more specific regulations have been issued, requiring more types of information.

In 1989, the following information was required for registration (272):

1. product name and formulation;
2. dosage form and regimen;
3. origin and background of discovery;
4. conditions of use in foreign countries;
5. properties and comparative studies with other drugs;
6. physiochemical properties;
7. standards and method of product analysis;
8. long-term storage tests;
9. pharmacological and toxicological data;
10. data to support efficacy;
11. general pharmacology;
12. biological data;
13. data on clinical trial results;
14. label claims and package insert; and
15. existence of registration from the country of origin for imported drugs (WHO certification scheme form may be used).

Applications are evaluated on the basis of safety, efficacy, and quality. Registration officials are required to consider the product safety and therapeutic advantages compared with similar products. According to the law, all products must be analyzed before registration (106). The Division of Drug Analysis (DDA) in the Department of Medical Sciences is responsible for conducting quality assurance tests, but due to limited manpower, is able to test only about one-fourth of the products (272). Approval of applications takes 6-18 months.

Thailand registers a few thousand formulations a year including many locally produced combination products (272). Since 1985, registrations are permanent and do not require renewal (106).

Regulation of the Public Market

In 1981, the Thai Government announced a National Drug Policy. The main goals of the new pro-

gram were to provide an adequate supply of safe and good quality drugs, to reduce drug waste by using the essential drug strategy, to strengthen drug quality assurance, to develop pharmaceutical raw material production capability, and to explore the potential of traditional medicines (272). This national drug strategy was included in the government's Fifth Five-Year Plan (1982-1986). The Sixth Five-Year Plan (1987-1991) focuses on rationalizing drug use and strengthening ongoing activities.

Thailand published its first national list of 372 essential drugs in 1981. A 1982 revised list increased the number to 450 essential drugs in 30 therapeutic categories (272). The most recent revision, in 1992, reduced the list to 348 items in 29 therapeutic categories (179). In university hospitals and in institutions such as the Ministries of Defense, Interior, and Education, drugs from the essential drug list must account for 60 percent of the drug budget. Community and provincial hospitals in each of Thailand's 72 provinces must select 80 percent of their pharmaceuticals from the essential drug list (272). Local health centers are also required to stock a certain percentage of essential drugs (272). The Government Pharmaceutical Organization (GPO) is one of the largest manufacturers of essential drugs in Thailand and it accounts for 11 percent of the prescription drug market (193).

Labeling and Promotional Regulation in Thailand

The Drug Act of 1967, as amended in 1988, contains labeling requirements. Printed packaging material, including package inserts, must be submitted for approval. The following information must appear on the package label (106):

1. product name;
2. registration certificate number;
3. content;
4. composition or active ingredient with quantity/potency;
5. batch number;
6. name of manufacturer with country of origin;
7. date of manufacture;
8. where applicable and on a red label: "Ya Antarai (Dangerous Drug)" in Thai, "Special Control" in Thai, "External or Topical Use" in Thai; and
9. the word "expiry" in Thai and expiration date of drug.

Package inserts also are required and are expected to contain the product name; active ingredients; indications; instructions for use, including warnings, precautions, adverse drug reactions, and contraindications; dosage, and storage information (272).

All labeling information must be in Thai or English. Thailand also requires that all other information companies intend to send to doctors, such as reminder advertisements or other promotional material, be included with the registration application. Any changes in labels for products already registered must be approved by the government (106).

The Thai Government limits advertising of prescription products. Promotion is limited to medical and pharmaceutical journals or through direct contact with the prescribers or dispensers. The agency requires that advertisements not exaggerate efficacy or broaden indications beyond those approved in labeling (106).