Drug Prescribing Information in the United States and Other Countries

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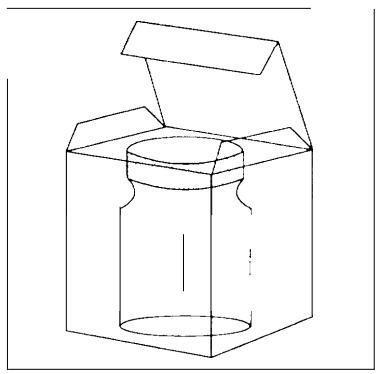
The approval and labeling of pharmaceuticals sold in the United States is governed by provisions of the Federal Food, Drug and Cosmetic Act of 1938, as amended (FDCA; 21 U.S.C. § 301-392). The Food and Drug Administration (FDA), within the Public Health Service of the Department of Health and Human Services, administers this Act. Under the FDCA, new drugs[1] cannot be marketed in the United States without explicit FDA approval, which is dependent on meeting the evidentiary criteria of detailed regulations that assure, to the extent possible, the safety and efficacy of pharmaceuticals. At the time of drug approval, proposed labeling must meet statutory requirements that have been translated into specific regulations addressing content and format. Review of all labeling materia1[2] for pharmaceuticals is a critical part of FDA's New Drug Application (NDA) process. The approved labeling provides information to physicians, pharmacists and, in certain cases, consumers. It also sets the legal bounds for promotional claims for the drug and for warnings and other infor-



[1] A drug is considered a new drug under the FDCA if: 1) it contains an active ingredient that has never been marketed in the United States; 2) it contains a derivative of an active ingredient i.e., the active ingredient is a chemical derived from an active ingredient already marketed; 3) it is a combination of two or more known and approved ingredients not previously marketed together in a single product; or 4) it is a drug already on the market, but it is to be marketed for use under different conditions, in a different dosage form for a new therapeutic use, in a new formulation or is manufactured in a different manner (157,244) (21 U.S.C. § 321(p)). A modification in the formulation includes a change in the active ingredient(s), inactive ingredients (excipients), preservatives, flavors, and/or dyes (222).

[2] "Labeling" includes both the "label," which is defined as a display of any written, printed, or graphic matter on the "immediate container" of the drug, and any written, printed or graphic matter that accompanies the drug, including package inserts, containers and wrappers 21 U.S.C. § 321(k)(m).

mation that must be disclosed in advertising and promotion of the drug (157).

Physicians, however, are not limited in prescribing to only those uses approved by FDA; they are permitted to use drugs "according to their best knowledge and judgment" (44 FR 37434). "Off-label" uses of prescription drugs are common and include uses for which there is substantial and convincing evidence of safety and efficacy (but which the sponsor has never submitted to FDA for consideration) as well as many uses for which convincing data of efficacy are absent. Many off-label uses of pharmaceuticals are medically acceptable and, for the purposes of this study, the medically acceptable indications for products are not limited to those indications that are approved by the FDA. FDA-approved labeling was not used as a "gold standard."

This chapter describes the FDA labeling requirements for prescription and over-the-counter (OTC) drugs sold in the United States and for those exported to other countries, and discusses parts of the drug approval process that are relevant to labeling. The off-label use of prescription drugs in the United States is also discussed. The chapter ends with a brief discussion of some aspects of pharmaceutical labeling in other industrialized countries that may help to explain why those labels often differ from U.S. labeling, and a description of drug information sources in developing countries.

U.S. DRUG LABELING LAWS AND REGULATIONS

Prescription Drug Labeling

Prescription drug labeling provides information that medical practitioners need in order to use a drug safely and effectively in the care of patients (44 FR 37437). Labeling consists of a package label (including the immediate container and associated material, e.g., a box) and all other labeling material included with the package, such as a package insert. FDA first required that a package insert be included with most drugs in 1961, with the intent of ensuring that every drug was accompanied by adequate directions for use, including indications; effects; dosages; routes, methods, frequency and duration of administration; and any relevant warnings, side effects, and precautions (114, 25 FR 12592 (1960); 26 FR 8389 (1961)). Although FDA regulations do not specifically require a package insert, it is usually not possible to fit adequate directions for use and warnings on a drug package (21 U.S.C. § 352; 21 C.F.R. § 201.100), so inserts have become standard for prescription drugs (21 U.S.C. § 352; 21 C.F.R. §201.22,201.50-.59, 201.100 and 21 1.137).

The *package label* for a prescription drug must include:

1. the name and place of business of the manufacturer, packer, or distributor;
2. the name or names of the drug, both proprietary and official or commonly recognized names;
3. the names and quantities of active ingredients and in certain cases, inactive ingredients;[3]
4. the route of administration;
5. a statement about the quantity of the container, such as weight, measure, or numerical count;
6. an identifying lot or control number;
7. a warning that "Federal law prohibits dispensing without a prescription;"
8. a warning that the product may be habit forming, if applicable;

[3]The following inactive ingredients, including quantity and proportion, must be included in the labeling: alcohol, bromides, ether, chloroform, acetanilid, acetophenetidin, amidopyrine, antipyrine, atropine, hyoscine, arsenic, digitalis, digitalis glycosides, mercury, ouabain, strophanthin, strychnine, thyroid, or any derivative, thereof (21 U.S.C. § 352(e)(l)).

9. additional warnings, when appropriate, for products containing certain ingredients, e.g., phenylalanine or sulfites;
10. a recommended dose, and the expiration date; and
11. a statement to the pharmacist indicating the proper container for dispensing.

If there is insufficient space on the package, certain information, such as dosage and route of administration, may appear only on the package insert (21 C.F.R. $ 201.100).

FDA regulations (21 C.F,R. $$ 201.56, 201.57) require that the labeling (which usually consists of a package insert) contain adequate directions for use, including information in the following areas:

1. description of drug, including qualitative and/or quantitative ingredient information;
2. clinical pharmacology;
3. indications and usage;
4. contraindications;
5. warnings;
6. precautions;
7. adverse reactions;
8. warnings about drug abuse and dependence;
9. overdosage information;
10. proper dosage and administration;
11. how supplied; and
12. date of most recent revision.

The following sections may be included, if appropriate:

13. animal pharmacology and/or animal toxicology;
14. clinical studies; and
15. references.

FDA regulations (153, 21 C.F.R. § 201.57(f)) require significant detail in each information category. The "precautions" section, for instance, must contain each of the following subsections:

1. general precautionary information for the physician;
2. precautionary information the physician should provide the patient;
3. laboratory and clinical tests that can be used to monitor the patient;
4. information on possible interactions with other drugs, foods, or laboratory tests;
5. a summary of findings from animal studies of carcinogenesis, mutagenesis, and impairment of fertility;
6. if applicable, information on any potential for the drug to cause physical defects and other harm to a fetus when taken during pregnancy;
7. for drugs used during labor and delivery, potential effects on the mother, or on the later growth, development, and other functional maturation of the child;
8. precautions for nursing mothers; and
9. precautions for pediatric use.

In contrast to most other countries, prescription drug labeling in the United States is directed primarily to the physician. The patient usually receives prescription drugs from a pharmacist in a container that specifies, at a minimum, the name and address of the dispenser, the prescription serial number and date it was filled, the name of the prescriber, and, if stated by the physician in the prescription, the name of the patient, directions for use, and cautionary statements (21 U.S.C. § 353(b)(2)). More detailed patient labeling, usually in the form of a patient package insert, is required when the risk of serious side effects makes it essential that patients have complete instructions (157). Patient package inserts are required for oral and injectable contraceptives, intrauterine devices, estrogens, and progestational products (21 C.F.R. § 501, 502, 515, 516). In other countries, including most developing countries, patients usually purchase prepackaged pills or liquids that come with a package insert (207).

STANDARDS OF EVIDENCE

The FDA permits listing only those indications that can be supported by "substantial evidence of effectiveness based upon adequate and well-controlled" clinical trials submitted to FDA by the manufacturer for formal review (21 U.S.C. § 355(c)(3)(d); 21 C.F.R. § 201.57(e)). Warnings must be placed on the label if there is a "reasonable association" between a drug and a serious hazard; a causal relationship need not be proven (21 U.S.C. § 355(d); 44 FR 37434). In addition, the FDA may require warnings against using the drug for specific, common, off-label indications if there is a lack of substantial evidence of effectiveness and if using the product for those off-label indications my result in serious adverse effects (21 C.F.R. § 201.57). In addition to the items that must appear in labeling, there is also a stricture that the label *not contain any* false or misleading statements (21 U.S.C. § 353(a)). The FDA may allow the manufacturer to omit any clearly inapplicable section or subsection of the labeling. (21 C.F.R. $ 201.56).

CHANGES IN LABELING

The FDA must approve all changes in labeling; however, companies may implement changes that provide physicians with additional *safety* information before receiving FDA approval. Changes of this type include:

- adding information to, or strengthening, sections on warnings, precautions, adverse reactions, drug abuse or dependence, or overdosage;
- adding instructions about dosage and administration that will increase the safe use of the product; and
- deleting false, misleading, or unsupported claims for effectiveness.

Labeling changes that have little impact on the safe use of the product may also be made without FDA approval (e.g., minor editorial changes, an extension of the expiration date based on data from an FDA-approved study, a change in the size of the container for drugs sold in pill or capsule form, or changes in information on how the drug is supplied provided they do not alter the dosage information) (21 C.F.R. $ 314.70). All other changes require *prior* FDA approval (21 C.F.R. $ 314.70).

OTC Drug Labeling

OTC products are sold directly to consumers, and requirements for their labeling differ from those for prescription drugs. OTC labeling must contain adequate directions for use by the general public, adequate warnings against unsafe use, and must be (51 FR 16259):

> clear and truthful in all respects, not false or misleading in any particular, and understandable to the ordinary citizen, including individuals of low comprehension, under customary conditions of purchase and use.

Before purchase, the consumer will see only the information on the outside package label, and FDA specifies the format for information that must appear there. The principal display panel (the part of a label most likely to be presented, displayed, shown, or examined under customary conditions of display for retail sale) must identify clearly the name of the product, state the quantity of contents (e.g., 100 capsules, 125 milligrams each), and include a statement identifying the pharmacological category or principal intended action[s] (e.g., analgesic, antacid, decongestant). These identifying statements must be in bold type of a size that is comparable to the most prominent printed material on the package (a minimum size of print is prescribed by regulation) (21 C.F.R. $5201.60, 201.61, 201.62). The immediate container must also include a declaration of the active ingredients; the name of the manufacturer, packer, or distributor; lot number; expiration date; and any special warning required by the FDA (e.g., presence of yellow dye no. 5 as inactive ingredient or the Reye's syndrome warning for aspirin-containing products) (21 C.F.R.

$$201.1, 201.17, 201.18, 201,20, 201.314(h)). All this information must appear on the outside labeling or be visible through the outside labeling.

Information on the ingredients, directions for use, adequate warnings, and dosage information must be included in the labeling, as it is for prescription drugs. In most cases, labeling covers the entire package, and a package leaflet may also be included (56, 21 C.F.R. § 201.1-201.20).

In 1972, the FDA began a review of OTC drugs then on the market. This was an extension of the Drug Efficacy Study Implementation (DESI) that included *all drugs* with New Drug Applications (NDAs) approved by the FDA before 1962. Both reviews were prompted by the 1962 amendments to the FDCA which, for the first time, required that a manufacturer prove the efficacy of a new drug (in addition to its safety) before the FDA would approve it for marketing (170). Because of the large number of OTC drugs on the market (estimates varied from 100,000 to 500,000) (100), it was impractical to review efficacy data for each one. Instead, the FDA established panels of experts to examine products by therapeutic class. As of July 1991, final monographs had been published for 33 classes of OTC drugs including antacids, antibiotics (first aid), stomach acidifiers, stimulants, and certain cough/cold medicines (246). These monographs, and others still under review, set forth the conditions under which an OTC drug is considered safe and effective, and they contain specific ingredient requirements, testing procedures, and labeling standards (166, 21 C.F.R, Part 33 1).

With the exception of the indications section, all other labeling information (e.g., directions for use, statement of identity, warnings, etc.) must be taken verbatim from the OTC monograph (21 C.F.R. Part 330; 51 FR 16258). Labeling information for an OTC drug for which there is no monograph is reviewed by the FDA on a product-by-product basis, the same as for prescription drugs (21 C,F.R. $$330.11, 330.12, 330.13).

Advertising of Prescription and OTC Drugs

FDA-approved labeling is the basis for all prescription and OTC drug advertising, and FDA regulates promotional material for prescription drugs.[4] OTC drug advertising is regulated primarily by the Federal Trade Commission (15 U.S.C, § 45, 52, 55). FDA regulations require only that advertisements recommend or suggest the product for the approved uses under the conditions contained in the labeling (21 C.F.R. § 330.l(d)).

FDA regulations for prescription drugs require that every advertisement contain an accurate summary of the side effects, contraindications, and efficacy, consistent with the prescribing information contained in the package insert (21 U.S,C. § 352(n); 21 C.F.R. § 202.1 (e)).[5] In addition, a prescription drug advertisement is subject to a "fairness and balance" test. The advertisement must present a balanced account of the clinical information, i.e., the indications cannot be overstated or the side effects and warnings minimized (21 C.F.R. § 202.1(e)). Misleading or false information in one part of the advertisement cannot be corrected by a brief statement containing accurate information in another part (21 C.F.R. § 201.l(e)(3)).

Regulation of advertising involves not only judging the content of a particular advertisement, but also deciding what constitutes an advertise-

[4] Advertising includes all multimedia delivery of product information to prescribing physicians (170).

[5] Reminder advertisements-advertisements that call attention to the name of the drug but do not include indications or dosage information—are exempt from including all clinical information. Instead, these advertisements need only contain the name of the drug, the active ingredients (and quantitative information on active ingredients, optional), quantity of package information, and name and address of manufacturer, packer, or distributor (21 C.F.R. 202. l(e)(2)(i)), The FDA has the discretion to require more complete information if the use of the drug is 'associated with serious injuries or significant incidence of fatalities (21 C.F.R. 202.1 (e)(2)(i)).

ment. Companies promote their products through many different media, including press conferences, scientific symposia, supplements to medical journals describing company-funded studies, and industry supported journals for physicians (123). If the activity is purely educational, it does not fall within FDA's jurisdiction. However, if it is primarily promotional it may be subject to FDA review (123). The line between these two activities is not always clear.

Labeling of Pharmaceuticals for Export

FDA labeling requirements apply to drugs marketed within the United States and are designed to protect U.S. citizens. The U.S. Government has no authority to impose U.S. labeling requirements on foreign countries. The FDCA, however, does address some aspects of labeling for drugs exported from the United States.

EXPORT OF APPROVED DRUGS

Once a drug has been approved by FDA for sale in the United States, it may be exported to other countries either in unfinished (bulk) or finished (packaged in final dosage) form. If exported in finished form, it must (with a few exceptions) be accompanied by the FDA-approved labeling, regardless of which country is receiving it. Most pharmaceutical products exported from the United States are not in finished dosage form, but in bulk form for repackaging and labeling abroad (178,243). One company in the OTA survey stated that less than 1 percent of its foreign sales consist of exports of finished dosage form pharmaceuticals that include FDA-approved labeling (96),

There is no statutory provision that permits a company to export finished approved pharmaceuticals with labeling that differs significantly from the FDA-approved version (45).

EXPORT OF UNAPPROVED DRUGS

One of the many and wide-ranging effects of the **1938 FDCA was to curtail the export of drugs that** had not been approved in the United States (69). This condition held absolutely until passage of the Drug Export Act in 1986, which amended the FDCA to allow limited export of unapproved drugs under specified conditions.

The Drug Export Act was driven by the economics of the pharmaceutical industry. Congress determined that the total ban on exports of unapproved drugs imposed hardships on the U.S. pharmaceutical industry and the domestic economy without providing significant health benefits (241). The reason was that some products developed by U.S.-based companies were approved for sale in other developed countries before they were approved for sale in the United States. Since most pharmaceutical companies were multinational, they could shift their production facilities abroad to avoid the export ban. Presented with evidence from the congressional General Accounting Office and other experts that up to 70 percent of the pharmaceuticals approved in the United States were first approved in another country, the Senate Committee on Labor and Human Resources concluded that the net result of the export ban was to drive capital investment and jobs abroad and widen the trade deficit (24 1).

Congress estimated that if exports of unapproved drugs were allowed, the U.S. economy might benefit from an increase of between 2,482 and 40,000 jobs, and an increase in annual exports worth as much as $1.76 billion (241).

Provisions of the Drug Export Amendments Act

To be eligible for export, a drug must be shown to be acceptably safe in preclinical tests (including pharmacologic and toxicologic tests on animals) and be under an approved Investigational New Drug (IND) exemption for clinical trials in human beings in the United States (i.e., the manufacturer must be actively seeking approval in the United States). An unapproved drug may be exported only to an industrialized country listed in the Act and only after the country has approved its sale (21 U.S. C. § 382(b)(l)(B)). Twenty-one countries judged to

have adequate regulatory systems are listed in the Act, and the Secretary of HHS is given the authority to add others.

The U.S. exporter of an unapproved drug must certify that all regulatory requirements of the importing country will be met (21 U.S. C. § 382(b)(l)(F)). In addition, the drug must be manufactured in accordance with current FDA standards for good manufacturing practice, must be unadulterated, and the manufacture of the drug for export must not have an adverse impact on the public health or safety of U.S. citizens (21 U.S.C. § 382(b)(l)(D),(E)). The exporter must also obtain a written agreement from each importer stating that (69):

- the importer will not re-export the drug to a country not included on the list of countries to which unapproved drugs may be exported from the United States,
- the importer will provide the exporter with any information on re-export of the drug, and
- the importer will maintain records of wholesalers to whom the drug is sold (21 U.S.C. § 382a(b) (3)(B) (vii)).

These latter requirements are designed to prevent drugs from being re-exported to countries not on the approved list[6].

The U.S. exporter must cease exporting a drug if:

- the receiving country withdraws approval of the drug, or withdraws the drug from sale;
- the drug is withdrawn from the U.S. approval process; or

FDA rejects the drug for marketing in the United States (i. e., does not approve the completed New Drug Application) (21 U.S.C. § 382(c)(l)(A)-(C)).

Finally, the exporter must file an Annual Report with the Secretary of Health and Human Services demonstrating that the exporter is still in active pursuit of FDA approval (21 U.S.C, § 382(c)(l)(D)). As of April 1991, the FDA had approved 74 applications and 38 amendments (an amendment is submitted for approval to export to additional countries) for exporting drugs under the Drug Export Amendments (60).

There is no U.S. label for unapproved drugs, and the only labeling requirement for drugs exported under these provisions is an outside shipping label stating that the drug may be sold or offered for sale only in the countries to which export of the drug is authorized.

Selection of Countries Listed in the Drug Export Act

Congress selected countries for listing in the Drug Export Act only if they had "sophisticated drug approval system(s) comparable" to the FDA. In the original Senate bill, 15 "first tier" countries were designated. These countries were selected on the basis of having (241):

- adequate resources to do comprehensive scientific and medical evaluations of the safety and efficacy of the drugs evaluated,
- sufficient resources to effectively regulate the content of labeling,
- sufficient resources to monitor adverse drug reactions, and
- a drug authority that had "general characteristics" of an effective regulatory authority (e.g., appropriately trained personnel and enforcement procedures).

Pharmaceuticals that were not approved in the United States could be exported to these countries in accordance with the provisions discussed above.

The original bill also designated "second tier" countries, which the Secretary of Health and

[6] A letter sent by 52 members of the European Parliament to Senator Edward Kemedy confirmed that re-export was a concern since no country in the European Community "has laws to prevent the re-routing of such imports to other countries" (69).

Human Services would select. These were to be countries with adequate health authorities and the means to assure that labeling of the unapproved drugs would be consistent with labeling from first tier countries. In essence, labeling used in the first tier countries would be required in second tier countries as well. Finally, the bill recognized as a "third tier" those developing countries with extensive health needs, but without the capacity to develop or test pharmaceuticals for unique needs, particularly for "tropical diseases." These countries would be allowed to receive exports of unapproved drugs for these diseases only (see discussion on *Export of Tropical Disease Drugs*, below).

The final version of the bill was passed in a hurried compromise reached after certain provisions of the Senate bill met with opposition from members of the House Subcommittee on Health and the Environment of the Committee on Energy and Commerce (45,72). The compromise bill passed with a single list of 21 countries that could receive exports of unapproved drugs other than tropical disease drugs, and the notion of first and second tier countries was dropped (45). The Secretary of Health and Human Services was given authority to add to the list of 21 countries using the same criteria as in the original bill; to date, no counties have been added (21 U.S.C. § 382(b)(4)(B)). The current list includes all of the European Community countries (except Greece)[7] plus Australia, Austria, Canada, Finland, Iceland, Japan, New Zealand, Norway, Sweden, and Switzerland.

EXPORT OF TROPICAL DISEASE DRUGS

The Drug Export Amendments also contain special provisions governing the export of unapproved drugs for tropical diseases, These provisions differ from those for all other unapproved drugs in that they allow export to developing countries with less sophisticated regulatory systems, and they allow export of drugs that are not in the U.S. approval pipeline. This latter provision acknowledges that few manufacturers will make an investment in pursuing FDA approval of tropical disease drugs which have a negligible U.S. market (72). For a tropical disease drug to be eligible for export, the Secretary of Health and Human Services must find "credible scientific evidence;' including human studies, that the drug is safe and effective in the prevention or treatment of a tropical disease in the importing country (21 U..S.C. § 382(f)(l)(A)).

The procedural requirements for exporting tropical disease drugs are similar to those for other unapproved drugs: the drug must be manufactured in accordance with current good manufacturing practices and must not be adulterated; the manufacturing of the drug in the United States must not pose a threat to U.S. public health; the outside shipping package must carry a statement that it is for export only and indicate the specific counties in which it may be sold; the drug must accord with the specifications of the importer; sale of the drug must be in accordance with the laws of the importing country; and finally, the exporter may not sell the drug in the United States.

Approval of New Drugs in the United States

Before a new drug may be marketed in the United States, it must be approved by the FDA, following a process laid down in the FDCA and codified in regulations. FDA's approval process must balance the need to assure the safety and efficacy of products entering the U.S. market with the desire to make new therapeutic products available as quickly as possible. A drug is defined as "new" if:

[7] The European Community Countries included are: Belgium, Denmark, France, Germany, Ireland, Italy, Luxembourg, the Netherlands, Portugal, Spain, and the United Kingdom,

- it contains an active or inactive ingredient that has never been used in a pharmaceutical marketed in the United States;
- it contains a derivative of an active ingredient, i.e., the active ingredient is a chemical derived from an active ingredient already marketed;
- it is a combination of two or more known and approved active ingredients that were not previously marketed together in a single product; or
- it is already on the market but is to be marketed for use under different conditions, in a different dosage form, for a new therapeutic use, in a new formulation,[8] or is manufactured in a different manner (157,244) (21 C.F.R. § 310.3(a)).

If a company seeks to market a product that duplicates one already on the market (but no longer under patent), it is also subject to FDA review, but the process may be an abbreviated one (222). In each case, the company seeking FDA approval for marketing must submit ample evidence that the drug is both safe and effective for the recommended uses.

The safety and efficacy of a new drug is demonstrated with evidence gathered by the company from laboratory, animal, and clinical research. Highly specific FDA regulations guide the types of studies required and allowed (particularly once clinical trials begin). The research, development, and review process for a new drug comprises four stages: preclinical research and preparation of an Investigational New Drug Application (IND), clinical trials, approval of New Drug Application (NDA), and postmarketing surveillance. The complex process of development and approval can take many years to complete. In 1988, the FDA estimated that the preclinical research and development phase takes an average of 18 months, clinical research averages 5 years, and the NDA review process, 24 months. These periods are subject to considerable variability, however, and in extreme cases, the approval process may take up to 15 years (244).

PRECLINICAL RESEARCH AND THE INVESTIGATIONAL NEW DRUG APPLICATION

Preclinical research covers the period between identification of a chemical or biological agent that may have therapeutic value and the submission of an application to the FDA requesting permission to begin studies in human beings. During this time, experiments are conducted in vitro[9] and in laboratory animals to determine whether:

- the substance is likely to provide a therapeutic benefit in humans and
- the administration of the substance, under tightly controlled circumstances, is not likely to cause undue harm or otherwise unreasonably endanger human subjects (235) (21 C.F.R. § 3 12.23(8)).

During this phase, the company carries out toxicologic and pharmacokinetic studies to determine how the drug is metabolized and excreted in animals, and what the lethal dose is in several animal species (235).

When data are sufficient to justify clinical tests in humans, the company submits an IND application to the FDA. Technically, the IND is a request for an exemption from the legal prohibition on the interstate transport of unapproved pharmaceutical products (21 U.S.C. § 355(a)). However, it is far more than a technical step. FDA scrutinizes the IND application and will not permit clinical trials unless the pharmacologic and toxicologic information gathered from in vitro and animal studies adequately supports the sponsor's

[8] In addition to the active ingredient, almost all drugs contain one or more of the following: inactive ingredients (excipients), preservatives, flavors, and dyes. Any modification in formulation can affect a drug's activity (222).

[9] In vitro studies include all laboratory tests carried out on biochemical elements, cell cultures, and isolated animal organs.

conclusion that it is "reasonably safe" to conduct studies in humans (21 C.F.R. § 312.23(a)(8)). In addition, the design of the proposed initial clinical trials must be such that valid evidence, satisfying the statutory standards for safety and efficacy, will be produced by them, and that risk to human subjects will be minimized (52 FR 8798). The FDA also requires that the clinical trial be approved by the Institutional Review Board (IRB) of the institution at which it will take place. The primary function of the IRB is to "assure the protection of rights and welfare of the human subjects" (21 C.F.R. § 56.102(g)). To further insure the safety of the human subjects, the FDA requires prompt reporting of any serious[10] and unexpected adverse reactions associated with the use of the drug (21 C.F.R. § 312.32).

The IND contains the first sample of labeling material in the form of a brochure that will be provided to each clinical investigator.[11] The investigator's brochure must contain a complete description of the drug substance and chemical formulation, if known; a summary of the pharmacologic and toxicologic effects of the drug in animals and, if known, in humans; a description of possible risks and side effects to be anticipated on the basis of previous experience with the drug or with similar compounds, and requirements for special precautions and monitoring during the clinical trials (239) (21 C.F.R. § 312.23 (a)(5)) .12 The investigator's brochure is updated as the clinical trials proceed (21 C.F.R. § 312.55).

If the FDA does not issue a "clinical hold" order within 30 days of receiving an IND application, the sponsor may begin clinical trials (21 C.F.R. § 312.40). FDA's involvement in the drug approval process begins once the IND is allowed to proceed. The FDA must be kept apprised of ongoing clinical trials through annual reports, amendments, and safety reports (21 C.F.R. § 312.30-33). The IND becomes a working document for the sponsor and the FDA as the drug moves through the clinical testing phase. Although FDA does not manage the clinical trials, it has the legal authority to monitor progress and to halt further studies if necessary (21 C.F.R. § 312.42).

CLINICAL TRIALS

Clinical trials are conducted in three stages, though the divisions are somewhat arbitrary—FDA describes the process as "organic and evolutionary" (52 FR 8798, 8806 (1987)).[13] Phase I of clinical testing focuses on safety, and accordingly, the FDA protocol review is limited to safety issues (21 C.F.R. § 312.22(a); 52 FR 8798, 8806 (1987)). These trials provide data on how the drug is metabolized in the body and its effect on the various organs and tissues, including side effects associated with increasing doses (21 C.F.R. § 312.21). Phase I studies may also provide some early evidence on effectiveness. Phase I trials generally involve a relatively small number of healthy volunteers (20 to 80 people) who take the drug for a short period of time (21 C.F.R. § 312.21). These studies measure changes in the individuals taking the drugs, and do not usually compare them with a "control" group. According to the FDA, about 80 percent of the drugs that enter Phase I do not lead to NDAs (53 FR 8798, 8807). Often, toxic effects at doses too small to

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[10] A serious adverse drug effect in humans is defined as cancer, a congenital anomaly, or a fatal, life-threatening, or permanently disabling event. A serious adverse drug effect in animal studies is defined as evidence of mutagenicity, teratogenicity, or carcinogenicity (21 C.F.R. 312.32; 52 FR 8798 (1987)).

[11] An investigator is the person who actually conducts the clinical investigation by directing the administration or dispensing of the drug to the subjects. There maybe more than one investigator for a single study.

[12] If the drug was used previously for another indication, or if the drug was approved in another Country, the sponsor may have information on prior use in humans.

[13] This description of the phases of clinical trials for new drugs does not apply in the specifics to certain therapeutic classes of drug, notably anti-cancer and anti-AIDS agents, though the general principles are similar.

provide a therapeutic benefit are revealed at this stage (244) (52 FR 8797, 8807).

The purpose of Phase II and Phase III clinical tials is to "distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation" (21 C.F.R. § 314.126). The design of the clinical trial is critical to insure that the results are reliable. The FDA requires that a "well-controlled" clinical trial have the following elements (21 C.F.R. § 314.126(b)(3)):

- a clear statement of the objectives of the study and the proposed or actual methods of analysis;
- a design that permits a valid comparison with a control group (patients that receive either a placebo, no treatment, or active treatment with a drug of known efficacy) or, in special cases, comparison of historical experience in patients; [14]
- the subjects selected have the condition being studied, or have been exposed to a condition against which prophylaxis is being tested;
- the method of assignment of subjects to treatment or control groups minimizes bias and is intended to insure comparable groups of subjects with respect to such variables as sex, age, severity of disease, duration of disease, and use of medications in addition to the drug being tested; and
- measures are taken to minimize bias by the subjects, observers, and analysts of the data.

To support an indication for a drug, a company must provide FDA with at least one well-controlled clinical trial demonstrating efficacy. In most cases, two are required (100).

Phase II clinical trials may begin as soon as Phase I studies have provided sufficient evidence that there are no unacceptable safety risks, and the investigators have sufficient information about pharmacokinetic and pharmacologic effects to design scientifically valid studies (21 C.F.R. § 312.21) Phase II studies are designed to provide the first clear demonstration of the efficacy of the drug for a particular indication, and to identify short-term, common side effects and other risks. They may test different dosage levels and schedules, typically on 200 or so people who have the condition for which the drug is being tested, under highly controlled conditions (244) (21 C.F.R. § 312.21).

Phase III studies are designed to measure and evaluate the overall risks and benefits of the drug (21 C.F.R. § 312.21). Often, several thousand patients will participate over several years, under conditions more similar to clinical practice (244). Because of the number of participants, Phase III studies may reveal less common, though not truly rare, side effects. Information about side effects will be included in product labeling if the drug is approved (244) (21 C.F.R. § 312.21(c)).

As clinical trials are progressing, the company may be completing additional animal studies. Depending on the nature of the drug, the sponsor may have to test for special toxic reactions caused by chronic use, or determine whether the drug is carcinogenic, mutagenic, or impairs fertility (157,235). This information will be required for the product's label. When all clinical and animal studies are completed, the sponsor may submit an NDA for approval to market the drug.

NDA REVIEW

FDA regulations specify the format for presenting information and data in the NDA, and require certain analyses (21 C.F.R. § 314.50). Assessment of proposed labeling, which must be supported by research findings, is part of the NDA review. If the company wants to omit any

[14] Historical controls are generally seen as the weakest type of control and are used only in special cases, such as in studies of diseases with high and predictable mortality or studies of drugs in which the effect of the drug is obvious (e.g., general anesthetics) (21 C.F.R. 312.126(I))(v)).

section or subsection normally required in prescription drug labeling, it must explain why this information is not necessary (21 C.F.R. $312.50 (c)(2)(i)). For example, if the drug is absorbed systemically and there is no evidence that the drug can cause any harm to a fetus, the required precautions for use during pregnancy might be omitted (157).

According to statute, FDA has 180 days to review an NDA, not including time waiting for additional information from the company (244) (21 C.F.R. § 314.100). The 180-day period is often extended, in large part because the company may be required to submit amendments (244,248) (21 C.F.R. § 314.160). During the review period, the sponsor must submit quarterly reports with any new safety information about the drug that might affect labeling statements about contraindications, precautions, warnings, and adverse reactions (21 C.F.R. $314.50 (vi)(b)), and to propose amendments to labeling based on these findings. In the end, an NDA may consist of 2 to 15 volumes of summary data and 10 to 100 volumes of raw data (consisting of more than 100,000 pages of text, data tabulations, statistical analyses, and patient case report forms) (235,244). In 1989, FDA estimated that the average approval time for a completed New Drug Application was 30.9 months and the median was 25.9 months (83,245). Some drugs are given higher priority and are reviewed in shorter time.[15]

Once the FDA has completed its review, it will either not approve the product or it will approve it with or without certain changes in labeling or restrictions on conditions of marketing (21 C.F.R. $$314.110, 314.120). If the sponsor accepts the changes and restrictions that the FDA requests, the drug may be marketed. The NDA will be rejected if the sponsor has failed to submit sufficient evidence to demonstrate the safety and efficacy of the drug under the proposed conditions for use (21 U.S.C. § 355(d); 21 C.F.R. § 314.125; 50 FR 7452, 7486). An NDA will also be rejected if the proposed labeling does not comply with the specific requirements in Part 201 of the FDA regulations (21 C.F. R. Part 201; 21 C.F. R. § 314.125) A sponsor whose NDA is not approved may amend the application, withdraw it, or request a hearing (21 C.F.R. § 314.120).

Post-Marketing Surveillance

The approval of an NDA does not mark the end of a sponsor's obligation to submit data to FDA. The sponsor must continue to monitor the performance of drugs in the market and must submit various reports to FDA summarizing its findings. FDA imposes post-marketing surveillance reporting because the marketing of the drug to a much larger population than included in clinical trails may result in the discovery of rare, latent, or long-term adverse effects (50 FR 7452, 7471).

The company must file a report within 15 days of discovering either a new adverse drug experience that is serious and unexpected or that an expected serious reaction is occurring with increased frequency (21 C.F.R. § 314.80; 50 FR 7452,747 1). The sponsor must also file quarterly reports for the first 3 years after a new drug is approved, summarizing all other adverse reactions and providing an overview of all safety-related information gathered over that period. After the initial 3 years, these reports may be submitted annually (21 C.F.R. § 314.80). The sponsor must file another annual report summarizing all significant new information that might affect the labeling, safety, or effectiveness of the product (21 C.F.R. § 314.81). The sponsor must also file copies of mailing pieces, labeling, or advertising devised for the promotion of the drug at the time

15 Until January 1992, the FDA ranked new drugs on the basis of chemical type and the perceived potential benefit. In general, a new molecular entity was given a higher ranking than a new formulation of a drug already on the market. The FDA recently revised the classifications into two categories: "priority" and "standard." Promising drugs for AIDS have been given especially high priority (100,239).

of initial public dissemination (21 C.F. R. § 314.81(3)).

These reporting requirements insure that companies continually monitor the safety and efficacy of their products. The discovery of a new side effect or adverse reaction may prompt a change in labeling, or in rare cases, withdrawal of the drug from the market (50 FR 7452, 747 1). Failure to respond to new safety and efficacy data may place the label in violation of FDCA's requirement that it not contain any false or misleading statements, or the company may find itself subject to a product liability suit if the omission leads to personal injury.

The DESI Review

The 1962 amendments to the FDCA propelled U.S. drug regulation into the "modern" era by requiring that sponsors prove the efficacy of their products before they could be sold. This was the first major overhaul of the law since amendments in 1938, which for the first time required a showing of safety. The provision requiring evidence of efficacy applied not only to new drugs, but also to drugs approved between 1938 and 1962. Like all other major industrialized countries, thousands of products were on the U.S. market, most having been approved at a time when standards for clinical trials had yet to be developed. Nonetheless, the FDA was required to review the evidence of efficacy for all these products and determine whether they met the new criteria for approval (see above, Drug Approval section).

As an early step, FDA published a *Federal Register* notice asking industry for effectiveness data on all drugs approved between 1938 and 1962, They received responses on 3,443 drug products with a total of 16,000 indications, each of which had to be evaluated. FDA contracted with the National Academy of Sciences (NAS) to carry out the initial review. NAS formed 30 expert panels to evaluate the information, and completed the task in 1969. They found that almost 60 percent of the products had at least one "effective" indication; 6 percent had at least one "probably effective" indication; 19 percent, "possibly effective;" and 15 percent, "ineffective" or "ineffective as a freed combination." (For only 12.2 percent of the drugs were all indications "effective.") They also reported that, overall, the drugs were not effective for about 60 percent of the therapeutic indications listed in the labeling (215).

This was not the end of the process, since eventually every product had to be classified either as having at least one indication for which it was effective, and therefore marketable under the amended FDCA, or as being ineffective for all indications. The middle categories could not remain. FDA took direct control over the remainder of the process, which was named the Drug Efficacy Study Implementation, or DESI. Companies were invited to submit further data on indications rated as less than effective and, if necessary, to carry out additional studies, developed in consultation with FDA. All drugs undergoing additional testing were allowed to remain on the market until a final determination was made, but each was required to carry a "DESI box" in the labeling, stating the category in which it had been placed by the NAS review (215).

As of May 24, 1984, the FDA had taken final action on 3,355 individual drug products (98 percent). By that time, the percentage of products with acceptable evidence of efficacy for at least one indication rose from the original 60 percent to 64.6 percent. Very few products (3 percent) that had been judged "ineffective" by NAS were later determined to be "effective," but about 39 percent of the "probably effective" category and about 18 percent of the "possibly effective" category were eventually judged effective.

Many fixed combination products were casualties of the DESI process. Products rated as "ineffective as a fixed combination" had at least one effective drug component, but either lacked evidence of a therapeutic contribution of each of the other drug components or the fixed dosage relationship was considered unacceptable for reasons

of safety (215). The DESI review led FDA to publish regulations specifying when a combination drug is acceptable (21 C.F.R. § 300.50; 36 FR 3126; 36 FR 20038). Two or more drugs may be combined in a single dosage form when *each* component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring the concurrent therapy provided by two or more active ingredients (21 C.F.R. § 300.50). A second active ingredient may also be included if it *enhances the safety* or efficacy of the principle active ingredient, or if it minimizes the potential for abuse of the principle ingredient (21 C.F.R. § 300.50).

The DESI process changed not only which drugs remained on the market, but also the labeling of those drugs, which had to meet the new standards of the 1962 amendments. The NAS panels had been critical of the labeling they found initially, characterizing it as "poorly organized, repetitive, out-of-date, evasive and promotionally oriented" (215). Had the DESI process not taken place, the companies themselves would undoubtedly have made some of these changes, but some might have occurred much later or not at all.

Other countries have, to varying degrees, taken steps to remove ineffective older products from the market and to improve the labeling of those that remain, but their efforts have rarely been as thorough as the DESI process.

"Off-Label" Use of Prescription Drugs

In practice, U.S. physicians are guided in their drug prescribing only partially by FDA-approved labeling. Physicians may prescribe drugs not only for approved indications but also for unapproved ("off-label") indications. Some unapproved indications are appropriate and based on sound scientific evidence, but others may be based on little or no evidence, and may be useless or even harmful when used for those indications. Unless formal application is made to the FDA, with evidence from well-controlled clinical trials, as is required for NDA approval, these other indications may never be evaluated fully and will not appear on the label. Pharmaceutical companies are prohibited from promoting their products for unapproved indications, but unapproved indications appear commonly in medical literature, and some achieve a somewhat formal status by their listing in respected drug compendia (see below).

The "medical importance" standard used by OTA in evaluating foreign labeling for this project is described in chapter 2. This discussion of off-label drug use further explains OTA's rationale for supplementing FDA-approved indications with indications from recognized compendia and using expert opinion as the final arbiter of decisions on the appropriateness of the labeling of survey drugs.

The practice of off-label prescribing has been a longstanding topic of discussion. For many years, individual physicians were concerned primarily with potential malpractice claims for prescribing outside of FDA-approved indications. More recently, concern has shifted to questions of reimbursement by insurers for products prescribed for unapproved uses (167). FDA's position is *not* that unlabeled uses are illegal; in fact, FDA has no official position on unlabeled indications unless and until the drug's sponsor submits an official petition for a labeling change. FDA made its position known in a 1982 article that stated that unlabeled uses of drugs might represent the very best medicine or might be extremely hazardous, but it stressed that the medical literature and drug compendia are often more up to date than the approved label. At the same time, FDA did not sanction information appearing elsewhere as equivalent in quality to the FDA-approved label (167).

Despite continued interest, almost nothing had been done until fairly recently to quantify the extent of drug use for unapproved indications. Two recent studies, published in 1991, have confirmed high rates of off-label prescribing: one study

(203) examined a selection of 15 popular outpatient drugs and the other (126) focused on cancer chemotherapeutic agents. A lower rate of off-label prescribing was found in a study of pediatric inpatients (217).

Serradell and Patwell used claims for physician visits and outpatient prescription drugs from a large prepaid health plan to determine the extent of drug use for indications other than the FDA approved ones, and to identify some patterns of use (203).

The analysis was based on claims made during the frost half of 1988 for 15 drugs which were linked with physician visits where these drugs were prescribed. Sample drugs were chosen among: 1) oral or topical dosage forms, and 2) those "most frequently mentioned by surveyed physicians working in outpatient clinics" from a descriptive study of unlabeled indications (202). Drugs for AIDS and cancer were excluded.

The final analysis was based on 8,339 diagnosis-prescription pairs, placed in the following categories:

1. FDA-approved indication;
2. "non-label" use, meaning it is not an FDA-approved indication but is mentioned in major drug compendia;
3. unknown;
4. prescribed for "general symptoms;" and
5. "non-indicated," meaning it is listed in the *USP Drug Information* compendium (247) as an indication for which the drug *should no?* be prescribed.

Combining the "non-label" and "non-indicated" categories, from 22 percent to 50 percent of the prescriptions for each drug were written for off-label uses, with an average of about 30 percent. One limitation of this study is that some errors probably occurred in matching diagnoses with prescriptions, but the error is unlikely to be so great as to materially change the results of the study.

The General Accounting Office (GAO), an agency of the U.S. Congress, surveyed a sample of oncologists to find out about their off-label use of anticancer drugs (126). The Senate Committee on Labor and Human Resources asked GAO to investigate this issue because health insurers had begun denying reimbursement for off-label cancer drug use, causing oncologists to alter, or to consider altering, the way they practiced medicine. This issue had become a source of friction between third-party payers and the medical community.

The sample of oncologists was chosen to be nationally representative and to represent "11 States with the highest prevalence of cancer." They were asked to "provide information on age, sex, disease, and drugs prescribed for the next three patients they met with after receiving the questionnaire" (the study had two other parts that will not be discussed here). Fifty-six percent of the 1,470 oncologists contacted responded to the survey, so the analysis was based on 681 oncologists reporting on their treatment of 2,018 patients.

Out of more than 5,000 drug administrations, one-third were for off-label uses. About 9 percent of the off-label uses were for indications not cited in the major prescribing compendia. More than 50 percent of all patients received at least one drug for an off-label indication. The extent of off-label use varied with the type and stage of cancer. In general, off-label use was higher for patients who had cancers for which there was no generally accepted treatment, and for those with more advanced disease (126).

Pediatric drug prescribing presents a particular problem because most drugs have not been tested in children and therefore cannot be labeled for their use. Only one study has examined the rate of off-label pediatric drug use. The study examined the drugs prescribed for inpatients at a children's hospital over a 3-week period. (217). The appropriateness of each off-label use was judged by a group of experts who had evaluated the literature on each unlabeled indication. The investi-

gators found that 7 percent of the 951 prescriptions written were for unlabeled indications, and of those 7 percent, about 40 percent were considered appropriate. About 15 percent of the unlabeled uses were considered inappropriate, and on the remaining 45 percent, the experts did not reach consensus.

These studies demonstrate that off-label use of drugs is widespread; however, only the last study attempted to determine how much off-label use is "medically appropriate." In an editorial in the *Journal of the American Medical Association* accompanying the GAO article (158), a prominent Mayo Clinic oncologist discussed the ways physicians may rationalize off-label drug use in cancer treatment:

- because there are delays in FDA approvals for new indications;
- because there is no incentive for a company to seek approval for new indications if a drug is no longer under patent;
- because for rare tumors it is impossible to carry out definitive clinical trials;
- because current standards for approval, requiring evidence of improved duration or quality of life, are too stringent; or,
- the weakest argument of all, because patients and their families demand treatment, even when none is likely to help.

FDA's 1982 policy statement on unlabeled uses of drugs mentioned the existence of compendia and literature that might appropriately be consulted for prescribing information, though the statement did not include any particular publications by name. Among the most prominent in the United States are the United States Pharmacopeial Convention's *Drug Information for the Health Care Professional (USP DI) (247),* the American Medical Association's *Drug Evacuations (7),* and the American Hospital Formulary Service's *Drug Information (8).* All three of these publications contain some information about nearly all of the products sold in the United States (and Canada, for the *USP Dl).* They all represent consensus opinions of medical specialists, and all contain information about unlabeled indications. According to an analysis of the *USP DI* database in 1990, more than 25 percent of the accepted indications listed were not approved by the U.S. FDA or by the Canadian regulatory authority. The specialty area with the highest percentage of unlabeled indications was oncology; more than 50 percent of the indications accepted by the *USP DI* were not approved in the United States or Canada (121).

OTA chose generally not to question companies about off-label uses listed in the foreign labeling if they were mentioned in prominent U.S. drug information compendia. In the majority of these cases, OTA did not evaluate the evidence of efficacy independently, but chose to avoid becoming embroiled in disputes over the evidence, or lack thereof, for uses accepted by the U.S. medical community.

DIFFERENCES IN DRUG LABELING AMONG INDUSTRIALIZED NATIONS

Multinational corporations must abide by the laws of the countries in which they operate. A pharmaceutical marketed in Germany by a U.S. multinational must be labeled in accordance with German law, and the label may well differ from U.S. labeling. Registration requirements (including labeling provisions) differ somewhat among industrialized nations, but it is assumed that all such countries have the resources and expertise to enforce these requirements. Differences among nations in philosophy of drug approval and labeling, differences in the practice of medicine, and differences in the history of drug regulation all may affect what ultimately appears on a drug label. In the course of this study, OTA was criticized by a number of companies participating in the survey for relying to a great extent on the U.S. labeling in its evaluations; these companies argued that labeling from other industrialized countries was often at least as, if not more, relevant. What follows is a brief discussion of some

of the major sources of difference in labeling among industrialized nations. It is beyond the scope of this study, however, for OTA to evaluate in detail drug labeling regulations of the various industrialized countries. These regulations are in a state of flux owing in part to ongoing "harmonization" of regulations among members of the European Community. For the purposes of this report, however, the laws and regulations affecting labeling of the late 1980s are most relevant.

Differences in Labeling Objectives and Standards of Evidence

The FDA-approved package insert is intended to inform the practicing physician about a product, and to serve as a reference for key information. In other countries, only the judgment of the drug regulatory authority is presented on the label, without reference to the scientific evidence on which the judgment was based (23). In Germany, for instance, as of 1986 the law required only patient package inserts and not physician inserts (190). Germany and other countries may rely on physicians acquiring knowledge about drugs from other sources (23).

Not all countries require the same type of evidence for drug approval of efficacy for labeled indications as the United States. The regulatory agencies of France and Germany, for example, do not necessarily require demonstration of efficacy by placebo-controlled randomized clinical trials; in some cases observational trials may be sufficient (132,190). In Germany, proof of safety and efficacy were not required until 1978. Prior to that time, the German drug law required only that manufacturers register pharmaceuticals, and permitted the drug regulatory authority to prohibit the sale of a product only if it was found to produce intolerable side-effects (190). Prior to 1978, there were 145,000 drugs on the market; the German Government allowed these products to remain on the market until the end of 1989, at which time it was required that they be submitted for approval on the same basis as new pharmaceuticals (190). Similarly, in France the standards for review of new drugs were substantially revised in 1976, and drugs marketed prior to 1976 were to be reviewed between 1984 and 1990 (214).

The Approval Process

The manner in which drugs are approved may influence the content of the labeling. In France and Germany, committees of outside experts are brought together to evaluate the safety and efficacy of the drugs (190,252). In the United Kingdom, consultants and academic experts work with the staff of the Medicines Control Agency (the regulatory authority) to evaluate new drugs. In the United States, the technical evaluation is carried out by FDA staff, although FDA has the option to use advisory committees of outside experts (51). Some have suggested that in countries in which individual professional drug regulators (as opposed to committees) are responsible for approving a drug (as in the United States), there is a greater tendency to err on the side of safety (51). Although no single person is responsible for new drug approvals by FDA, individual reviewers are responsible for preparing summary reports on the NDA, which may become the basis of the approval. This contrasts with many European countries, where responsibility for an official decision is delegated to an expert committee (51). Also, unlike the United Kingdom, France, or Germany, the FDA has strict rules prohibiting individuals with conflicts of interest from participating in drug reviews (44).

COMPANY DEVELOPMENT OF INTERNATIONAL PRODUCT LABELING

All companies have some explicit policies and procedures for developing labeling information for new drugs and for updating existing labeling. OTA asked the companies participating in the survey to provide information on their labeling policies. This brief discussion highlights the sim-

ilar and dissimilar features of various company policies. Some companies requested that this information remain confidential, so no company names are given.

All companies state that their general objective in labeing is to provide full disclosure of information about their products. In a practical sense, the centerpiece of most labeling policies is a product document developed by the medical and regulatory staff at corporate headquarters. This may be called the "Medical Guideline Sheet;' "Corporate Product Document," "Global Prescribing Information," "International Product Document," or another name.

PHOTO CREDIT: W. LINDWER, WHO

Well-stocked pharmacy in Thailand.

Product documents are used to develop labeling for each country in which the product is sold, but the degree to which the full document is reproduced varies. One company stated that the product document is translated and submitted as a proposed package insert to the local authority. Another company submits labeling of the exporting country (an industrialized country in nearly all cases) to the local authority for drugs sold in developing countries, rather than reverting to the original product document. Another company stated that subsidiaries may request from headquarters deviations from or modifications to the text of the product document to comply with local requirements. Another stated that the product document is used in "negotiations" with local regulatory authorities. All the companies require modifications of the product document to be reviewed and approved at corporate headquarters.

Most companies described procedures for updating product documents and country-specific labeling. Some companies require review of company-specific labeling at the time of re-registration, where that is required (e.g., every 5 years in Panama). One company described a labeling review procedure carried out by visiting auditors. All companies require notification of subsidiaries when a product document is updated.

These procedures differ for some companies for "local" products, i.e., those manufactured and sold locally or regionally, but not worldwide. For local products, proposed labeling may be prepared locally and then approved by corporate headquarters.

One company's labeling policy specifies in detail the required content of the product document. Of particular interest for this study is the required listing of inactive ingredients for all oral preparations. (No other policy submitted to OTA included this requirement.)

One of the most important factors that influences the labeling requirement of developing countries is their ties to certain industrialized countries, particularly as former colonies. Developing countries often have adopted the legal systems of former colonial powers, including their drug registration and labeling laws. These countries may require that all new drug applications include the labeling used in the former colonial power. Kenya, for example, may look to English labeling and Cameroon might look toward France for labeling standards. Many companies stated that the labeling used in developing countries should be assessed in light of the labeling used in the former colonizing country. (See ch. 3 for discussion of how this was considered in OTA's evaluations.)

SOURCES OF PHARMACEUTICAL INFORMATION IN DEVELOPING COUNTRIES

Prescribing information in developing countries is usually available from the manufacturer through package inserts, product monographs or through other forms. Abbreviated prescribing information is made available through commercially produced local prescribing guides. In addition, physicians may have pharmaceutical reference texts. In many developing countries prescribing guides are the most widely distributed and frequently consulted source of pharmaceutical information.

Package Inserts and Labels

Virtually every country, regardless of its state of development, has a system for registering drugs.[16] In general, drug registration systems in developing countries are less sophisticated than those of the United States and other industrialized countries in what they require of companies and in the way they review applications. Regulatory bodies in developing countries rarely have the resources or, in many cases, the expertise to carry out rigorous evaluations of new pharmaceuticals, including a thorough evaluation of the claims made about products.

Most developing country drug registration systems have some labeling requirements (159). Many developing countries require that the outside package carry a significant amount of information (159,273). According to a World Health Organization (WHO) survey, there is general agreement on what categories of information should appear in package inserts and/or on packaging and container labels. All together, the following information should be covered (107,273):

1. Brand name
2. Generic name
3. Names of active ingredients
4. Content of the active ingredients per dose
5. Major indications for use
6. Precise instructions for dosage
7. Form of administration
8. Major side effects
9. Major precautions and contraindications
10. Major interactions
11. What to do in case of side effects or overdosage
12. Expiration date
13. Storage conditions (at least when special)
14. Name and address of manufacturer (or license-holder or distributor)

The registration and labeling requirements for the four countries included in this study are summarized in appendix B.

PHOTO CREDIT: M. GRANT, WHO

Rural health facility in Kenya.

Although these labeling requirements appear to be fairly comprehensive, they provide little detail about the content of the information to be included in each category. The drug regulatory authority is responsible for determining whether the information submitted is complete and accurate.

[16] Drug registration refers t. the process by which drugs are approved for market@. In order to register a drug a company usually submits information on the safety and, in some cases, efficacy of the drug, as well as the labeling text that the company proposes to include with the drug.

This requires trained personnel who have the time and resources to thoroughly evaluate the proposed labeling submitted by a company (107,159). Developing countries may need to rely on the judgments of the regulatory systems of industrialized countries. WHO has taken several steps to assist developing countries in improving their pharmaceutical labeling and in providing more complete prescribing information to health care workers. (See ch. 7.)

Prescribing Guides

Commercial prescribing guides—mostly of the related "Index of Medical Specialties" (IMS) series and the "Para Los Medicos" (PLM) series in Latin America-are available in most developing countries and in some developed countries, and are distributed free to physicians. The stated aim of the guides is to provide physicians with a quick means of determining which drugs are available in their country. In practice, they often serve as the main source of prescribing information (212). They are published privately, paid for by advertising, and are updated at regular intervals (from monthly to 3 or 4 times a year). Prescribing guides (IMS-type and others) are organized differently in different parts of the world, but they typically have relatively short entries for products. Many of the early studies of drug "labeling" in developing countries actually were based on analyses of prescribing guide entries. (see app. A.) These studies have been critical of the entries, on the one hand, for failing to include all appropriate warnings and precautions, and, on the other hand, for including indications that lack evidence of effectiveness.

PHOTO CREDIT: P. MERCHEZ, WHO

Corner pharmacy in Latin America.

Prescribing guide entries are based on the data sheets submitted by companies to drug regulatory authorities when they seek approval. The content of prescribing guide entries, however, is not regulated by the government. Traditionally, the guides' publishers have controlled the length and content of the product entries. Since the mid-1980s, however, pharmaceutical companies have increasingly exercised their influence over the publishers in determiningg the content of the entries. In July 1988, publishers of the Index of Medical Specialties compendia for Africa, the Caribbean, and the Middle East agreed to allow companies to review the entries for their products. Negotiations with other publishers are in progress (212).

PHARMACEUTICAL ADVERTISING AND PROMOTION

Pharmaceutical companies promote their products through print advertising and directly to physicians and other health care providers through sales representatives (known commonly as "detail men"). These activities are, in general, less strictly regulated in developing countries than in the United States and other industrialized countries.

Detail men present product information to physicians and pharmacists, and are considered by the pharmaceutical industry as an important means of diffusing information quickly (160). A 1981 study suggested that the ratio of representatives to physicians was higher in developing than developed countries (1: 10 in the United States and most Northern European countries, 1:8 in

Ecuador; 1:5 in Colombia; 1:4 in Tanzania; and 1:3 in Guatemala, Mexico, and Brazil) (210). The United Nations Center on Translational Corporations reported that, in 1978, multinational corporations spent $250 million on promotional activities in Argentina (25 percent of the value of the companies' total sales in Argentina), and in 1979 foreign companies spent $320 million in Brazil (22 percent of total sales in Brazil). Both of these countries have large private pharmaceutical markets. Approximately two-thirds of the advertising budgets in Argentina and Brazil were spent on detail men and free samples (223). Detail men are widely acknowledged to be an important source of drug information in developing countries.

The role of the detail man is controversial. Most commentators agree that drug promotion that provides physicians with current, accurate scientific information about new products is very useful. However, by its nature, promotional activities are also used to gain and maintain market share (279). The detail man functions not only as an educator, but is also a salesperson, A study in the United Kingdom of sales representatives from 24 drug companies found that approximately 86 percent were given sales targets to achieve (78). Ideally, these functions are compatible, but in practice they may conflict. Pharmaceutical representatives operating in developing countries have been accused of exaggerating the claims for their products and glossing over potential risks (39,77,210).

Promotion by detail men has been studied by a number of researchers, and many potential problems have been identified. This OTA study did not include an independent evaluation of promotion by detail men.

Advertising in medical journals and prescribing guides is an important source of information for physicians in developing countries, as it is in the rest of the world. WHO, the International Federation of Pharmaceutical Manufacturers Associations, and various public interest groups have focused their attention to a much greater degree on advertising than on labeling because of the greater visibility and influence of advertising.

The extent to which authorities regulate pharmaceutical advertising varies considerably among nations. A number of developing countries, including those in this study, have comprehensive regulations governing pharmaceutical advertising but many countries are unable to monitor compliance because of lack of resources (107,137). Other countries have less comprehensive regulations for advertising, or none at all. In a number of countries (e.g., Costa Rica, El Salvador, Guatemala, Honduras, India, Nicaragua, Panama, Singapore, Syria, Thailand, Trinidad, and Zimbabwe), advertisements need not carry warnings and contraindications (20).

Consumer groups and academics have criticized advertisements that multinational corporations have used in developing countries (39,41, 67,154,210). A recent study examined pharmaceutical advertisements in independent medical journals from 18 industrialized and developing countries (Finland, Norway, Sweden, Spain, France, Italy, Ireland, United Kingdom, Switzerland, Turkey, India, Nepal, Pakistan, Sri Lanka, Tanzania, Zimbabwe, Brazil, and Denmark) (93). Researchers from each country examined advertisements according to a single protocol. A total of 6,710 advertisements, most for brandname drugs of MNCs, were included.

Many of the advertisements were found to be deficient. Using the WHO ethical criteria for drug promotion (see ch. 7) as a standard, warnings and precautions were missing in half the advertisements and side effects and contraindications, in about 40 percent. The information content of the advertisements differed "surprisingly little between industrialized and developing countries" (93).

Pharmaceuticals advertisements were given low marks in a recent study of advertisements in leading U.S. medical journals (262). In a detailed review of 109 advertisements, 92 percent were judged by medical and pharmacy professionals to be out of compliance with FDA standards in at

least one of 28 areas, with an average of four areas out of compliance. The reviewers would have rejected or required major revisions to 62 percent of the advertisements. Many problems related to an imbalance between information about efficacy versus side effects and contraindications.

Advertising and promotional materials are important ways to convey information to physicians, especially information about new products, or new information about old ones. There appears to be significant scope for improving the information content of these materials.