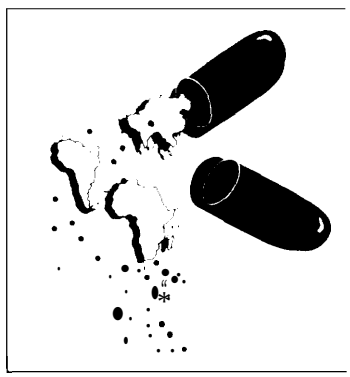
Summary and Options 1

Effective pharmaceuticals have been directly responsible for major gains in health around the world during the latter half of the 20th century. Continued growth in the international pharmacopoeia creates the potential for greater improvement, but only if prescribers of products have the information they need to use products safely and effectively. While appropriate "labeling" is the norm in the United States, it has not always been so in developing countries. Out of concern for this issue, OTA was asked to examine the current labeling practices of U.S.-based multinational corporations for the products they sell in the developing world.

OTA evaluated a sample of labeling by U.S. companies in four developing countries. Half the products evaluated had labeling that was either entirely appropriate or had relatively small problems. The other half diverged significantly and seriously from the standard. Physicians relying on the information provided with those products could put patients at undue risk, provide less-than-effective therapy, or both. This may happen whenever physicians are not fully informed about specific dangers of the drugs they are prescribing, or when they are given to believe that the drug is effective for a condition when effectiveness has not been established.



It should be emphasized that OTA examined only the labeling of U.S.-based companies because it is those companies that are of interest to Congress, and those companies that can be influenced by U.S. law and policy. Previous studies in this area have found, uniformly, that U.S. companies provide at least as good or better information than do companies based elsewhere. Nothing in this report should be used to denigrate the operations of U.S.-based companies in comparison with their international competitors.

The results of the OTA survey set the stage for exploring ways to improve drug labeling in developing countries. This report discusses the pharmaceutical labeling requirements imposed on U.S.-based companies by the laws of the United States and the barriers to U.S. regulation of their labeling in other countries. Concern about prescribing information in developing countries is demonstrated by activities of United Nations agencies, particularly the World Health Organization, and those of private industry and consumer groups, which also are described in this report. Options for the Congress to consider are presented at the end of this chapter.

THE REQUEST FOR THIS ASSESSMENT

In debates preceding passage of the Drug Export Act of 1986, concern surfaced about the quality of drug labeling by U.S.-based multinational companies for the products they sell in developing countries. The concern was prompted particularly by a series of highly visible studies that had uncovered seriously inadequate labeling by multinational companies for a number of products (see appendix A). As a result, Congressman John Dingell, Chairman of the House Committee on Energy and Commerce, Congressman Henry Waxman, Chairman of its Subcommittee on Health and the Environment, and Senator Edward Kennedy, then Ranking Minority Member of the Senate Committee on Labor and Human Resources, asked OTA to undertake this assessment. They asked OTA to evaluate labeling by U.S.-based companies by:

> comparing] the labeling of the drugs sold in such country and the labeling approved for such drugs under the Public Health Service Act of the Federal Food, Drug and Cosmetic Act and determine whether any labeling differences are based on valid scientific evidence, including clinical investigations.

PHOTO CREDIT: P. MERCHEZ, WHO

Hospital pharmacy in Latin America.

THE OTA DRUG LABELING SURVEY

This study, the first on this topic sponsored by a national government, began in 1987, and the labeling evaluated was current from about 1988 to 1990. Samples of labeling from Brazil, Kenya, Panama, and Thailand were evaluated during this time. The process involved recognized medical experts recruited to an "Expert Review Group" in addition to OTA staff. The participating companies were provided two successive opportunities to respond to OTA's evaluations of their labels and to provide additional material to support their cases when they disagreed with OTA.

The major research-based multinational pharmaceutical companies with headquarters in the United States, 18 in all, were included in the survey. Their cooperation, in providing labeling material and reviewing two iterations of the product evaluations, was essential to the completion of this study.

The type of labeling information analyzed varied according to what was available. In general, OTA tried to use the most complete source that would be available readily to most physicians in the study countries. The preferred source was a package insert and the associated information printed on drug containers. In some cases, companies supplied package inserts pending approval by the foreign drug regulatory authority,

and in those cases, that was OTA's source material. Since not all products are accompanied by inserts, "prescribing guide" entries were used for a number of products. This was more prevalent for products from Panama, as inserts are not required there. Prescribing guides-quick reference volumes—are ubiquitous in developing countries, and are acknowledged to be the first line information source for physicians in many places.

There is no gold standard to apply as an objective comparator for drug labeling around the world. Even the U.S. labeling, approved by the Federal Food and Drug Administration (FDA), is not the only or most authoritative source of prescribing information. Any standard that could be adopted for this study incorporates an element of subjectivity, leading to results that might differ somewhat depending on who was making the judgments. OTA adopted a standard of "medical importance" for judging the information on sample labels. It was intended to identify definite problems with labeling information that would be subject to little or no variation in different parts of the world. It would *not* be appropriate, nor was it intended, as a standard for developing new labeling. In practice, this means that OTA initially questioned, and in the end identified as problems, points of potential importance to physicians attempting to use the products in a safe and effective manner. Both information judged missing from the label and information present but misleading in some way contributed to the evaluations.

OTA did use the FDA-approved labeling as an initial "screen" for the sample labels of products that were available in the United States. If one were to stop at that point, however, the result would be a long list of "differences'' -thousands for the 241 products evaluated fully in the survey, the meaning of which would be uncertain. OTA used the "medical importance" standard to separate the important differences from trivial ones. Only the important differences entered into the further evaluation and analysis. A significant point is that no labeling was held to a higher standard than that set by the U.S. labeling.

The OTA survey captures a "snapshot" of developing country labeling in the late 1980s to early 1990s-one point in a dynamic process. All the companies that participated in the survey are continually updating their labels all over the world, so the problems identified by OTA might be the result simply of a time lag between changes made in the United States but not yet completed in the study countries. This does not appear to be the case: while some of OTA's queries concerned recent developments, e.g., the need for warnings based on relatively new information, the vast majority did not.

Survey Results

Of the **273** products in the survey, 241 were evaluated fully. The remaining 32 were excluded for a variety of reasons, most because they were no longer being marketed at the time OTA evaluated them. The information for each product was examined and scored in each of 8 categories (based on the structure of the U.S. label, but without regard to where the information appeared in the sample labels):

1. description and clinical pharmacology,
2. ingredients,
3. indications,
4. contraindications,
5. warnings and precautions,
6. adverse reactions,
7. dosage and administration, and
8. overdosage.

Scores for individual categories were based on the amount and seriousness of divergence from the medical importance standard, and ranged from O (no significant divergence) to 2 (greatest divergence). This can be taken as a measure of the potential risk to patients from the labeling.

Overall product scores were calculated on the basis of the category scores, and ranged from O to

3, with O signifying no important divergence and *3* signifying the **greatest** divergence. About half the products had labels that were either completely in accord with OTA's medical importance standard, a score of O (using the FDA-labeling as a ceiling), or diverged to a small but medically important degree (score of 1). About 25 percent scored 2, and about 25 percent scored 3 (see table l-l).

Table l-l-Summary of Overall Scores

Overall score	Number of products
0	78(32%)
1	40(17%)
2	64(27%)
3	59(24%)
All fully evaluated	241 (1OO%)
Not fully evaluated	32
Total in original sample	273

Degree of divergence from medical Importance standard:
0- No divergence from medical importance standard
1 -At least one category score = 1; no score >1
2 -No more than one category score= 2; other categories may -0 or 1
3 -At least two category scores -2

NOTE: Sea text for details of scoring.

SOURCE: Office of Technology Assessment, 1993.

ANALYSIS BY CATEGORY OF INFORMATION

The results by category of information are summarized below and in table 1-2. The numbers and percentages reported in each section are based on the 241 products that were evaluated fully.

Description and Clinical Pharmacology

Problems were found in 51 (21 percent) of the *description and pharmacology* sections of the labels, most of them *(45)* rated 1, and *6* rated 2. The most frequent concerns were failure to identify the drug class of the product and, more commonly, failure to include adequate pharmacokinetic information (especially half-life, metabolism, and route of elimination).

Ingredients

The *ingredients* section contributed to a divergence from OTA's primary or secondary score in only four cases. This does not include labeling that failed to list inactive (inert) ingredients, except in cases where a particular inactive ingredient was known to cause an allergic reaction in a substantial number of patients. Instead, lack of inactive ingredient lists elicited a score of "R" which was tracked separately from the rest of the scores. (In the United States, FDA does not require that all inactive ingredients be listed in U.S. labeling, but the companies do list them all routinely.) In all, 74 labels lacked lists of inactive ingredients.

Indications

Indications was one of the most problematic sections. Sixty-three labels (26 percent) were divergent in this area, and 43 of those were rated 2, representing the most serious problems. The reasons for these scores were mainly: 1) indications

Table 1-2-Summary of Category Scores

Category score	DCP	ING	IND	cl	WP	AR	DA	OD
1	45 (19%)	1 (o%)	20 (8%)	12 (5%)	49 (20%)	25 (10%)	17 (7%)	8 (3%)
2	6 (2%)	3 (1%)	43 (18%)	15 (6%)	79 (33%)	37 (15%)	11 (5%)	37 (15%)
R		74 (31%)						

Categories:
DCP - Description/Clinical Pharmacology
ING = Ingredients
IND - Indications
CI - Contraindications
WP - Warnings and Precautions
AR . Adverse Reactions
DA = Dosage and Administration
OD - Overdosage

Category scores:
1 -at least one unresolved query in category with score -1
2. at least one unresolved query in category with score -2
R - lack of inactive (inert) ingredient list

NOTE: The percentage calculations use 241, the number of fully evaluated products, as the denominator. See text for details of scoring.

SOURCE: office of Technology Assessment, 1993.

that did not appear in widely accepted drug compendia and for which inadequate evidence of efficacy was presented by the companies, 2) indications that were overly broad and vague, and 3) failure to inform when the product was not considered first-line treatment for an indication.

Contraindications

Contraindications were found to diverge from the medical importance standard for 27 labels(11 percent), including 15 rated 2, the most serious score. Contraindications describe patients who should not receive a drug because, for one reason or another, the risks of taking it are likely to outweigh the benefits. The reasons include:

1. a medical condition that might interfere with the metabolism or action of the particular drug in a dangerous way (e.g., kidney or liver disease);
2. the patient is taking a drug that is known to interact with the product in an unacceptable way;
3. the drug may harm a fetus in a pregnant woman, or pass through a nursing mother's breast milk, potentially harming the child; and
4. the drug should not be taken by children (because of lack of evidence of safety or because of a known unacceptable adverse effect) or by frail elderly people.

Warnings and Precautions

More problems occurred in *warnings and precautions than in any* other section, and they included a high percentage of more serious divergences. Over half the labels evaluated (128) deviated from the medical importance standard, and 79 of those were rated 2. Warnings and precautions cover a broad range of information, so it may not be surprising to find so many divergences there. The types of problem included:

1. failure to warn of relatively rare but potentially life-threatening effects;
2. failure to warn of less serious but more common effects;
3. providing too weak a warning in relation to the risk;
4. failure to warn particular high-risk patients (e.g., with other chronic diseases);
5. failure to note interactions with other drugs;
6. failure to note effects on laboratory test results;
7. omission of instructions for monitoring patients on the drug;
8. lack of specificity about possible adverse effects;
9. lack of information about use of drug in pregnancy, in nursing mothers, in pediatric patients, or in the elderly; and
10. lack of information on possible carcinogenicity.

Adverse Reactions

Widespread divergences were also noted in *adverse reactions* sections of the labels. Just over a quarter (62) had unresolved queries, of which 59 percent (37) were rated 2. Adverse reactions omitted ranged from those that might be worrisome to patients though not medically serious (e.g., discoloration of urine or other body fluids) to some that are life threatening (e.g., agranulocytosis, the complete suppression of blood cell production), but all were considered important enough for physicians to be fully informed about them. In some cases, an adverse reaction was listed on the sample label but its severity was understated.

Dosage and Administration (excluding Overdosage)

Most problems in *dosage and administration* had to do with regimens that were either higher or, in a few cases, lower doses than recommended in the comparison labeling or in drug compendia, and for which inadequate support existed in the literature. The divergences occurred both in

daily doses and in the length of the regimen, and often involved regimens specifically for infants or children. In a few cases, the label failed to state the maximurn length of time the drug should be taken before either stopping or taking other measures. Twenty-eight (12 percent) of the labels scored 1 (17) or 2 (11) in this area.

Overdosage

Failure to include information on the signs and symptoms of *overdosage,* and on its management, was common. Forty-five (19 percent) of products diverged from the medical importance standard in this section, and most of those (37) instances were placed in the most serious category (score of 2). Lack of this information was considered particularly important if there are specific measures, as opposed to just general monitoring and supportive measures, that should be recommended for treatment of overdose.

ANALYSIS BY COMPANY

The number of fully evaluated products per company ranged from 4 to 25, roughly in proportion to the number of products each company offered for sale in the sample countries. OTA calculated average overall product scores for each company (the scale for overall scores is O-3), and these ranged from O to 2.22, but most fell between 1 and 2. Two were less than 1, and two were more than 2. For several reasons, we do not believe it is useful to try to rank companies by their scores.

A major factor affecting company scores is the mix of products in the OTA sample. Many company product lines tend to clump in particular therapeutic categories, e.g., antihypertensive medications or corticosteroid products. Certain types of product, no matter how they are used, are unlikely to have effects that are life threatening or even serious. Such products would almost never be rated a 3 regardless of the labeling. Products fitting this description do, in fact, dominate in the sample from the company with the best (lowest) overall score and form varying proportions of other companies' products.

In general, the samples by company are not large enough to sustain rigorous statistical analysis. The wide range of company scores in different countries also suggests the need for caution in generalizing at the company level.

ANALYSIS BY COUNTRY

The average overall product scores for the sample countries ranged from 1.1 to 1.6 (out of 3), with the average of all scores at 1.4. Medically significant problems occurred in all countries and no clear distinctions can be made in a country-by-country comparison. A sample of four countries is too small to conclude that labeling in *all* developing countries is in need of improvement, but it does suggest it is not an isolated problem.

Comparison of OTA Results for One Company With Labeling From Other Industrialized Countries

A number of survey companies criticized OTA's methodology for accepting a U.S. perspective on labeling, to the exclusion of established standards in other industrialized countries. In particular, they believed that labeling from the exporting country for each product should be given weight. Having heard this argument, OTA asked the companies to indicate the country of export for each sample product and to provide labeling from the exporting country so that a direct comparison could be made. One company responded during the study process by comparing OTA's interim scores for their products against labeling for the same or similar products in each of the 21 countries named in the Drug Export Act of 1986, and by providing the labeling from some of those countries to document their analysis. Sixteen other companies conducted a similar analysis during their review of the final draft, but did not provide the supporting materials for corroboration. Their results were reported to OTA

by the Pharmaceutical Manufacturers Association (PMA) in summary form and are not included in this report. The single company analysis is described here.

The 21 countries included in the "composite standard" are named in the Act as having regulatory systems adequate to allow the export to them of drugs not yet approved in the United States, provided they have already been approved in the importing country. The company analysis took each unsatisfied query that OTA had scored 1 or 2 and checked the labeling in each of the 21 countries to see whether they were similar to the original survey country label on the point OTA had questioned. If they found a correspondence with at least 1 of the 21 countries, they considered OTA's score invalid and rescored the query as O. They then retallied the overall scores.

The company's analysis demonstrates that labeling does differ among industrialized countries, and that if OTA had used a composite of all industrialized country labels as a standard, the results of the survey would have been very different, and clearly more favorable to the companies. Neither this company nor the PMA explains why this composite standard is more appropriate than OTA's. It could be argued that a composite standard incorporating *all the warnings*, precautions, etc., of the foreign labels, and restricting indications only to those approved in all countries would be appropriate, unless evidence suggested otherwise.

Comparison of OTA Results With WHO Model Prescribing Information

OTA compared its final product evaluations with recent WHO model prescribing information monographs (280,282,283,284,288,289), which are being prepared to cover all products on the "Model List of Essential Drugs." The monographs represent a consensus of WHO's Expert Advisory Panel on Drug Evaluation and are reviewed by selected members of Advisory Panels in relevant areas of medicine and nongovernmental professional and business organizations (including those representing the pharmaceutical industry).

Twenty-three drugs in the OTA sample were also included in one of six WHO model prescribing information monographs now available. OTA compared the monograph entries with OTA's final evaluations of those products. This was done by checking each of the unresolved queries with the monographs to see if the monograph "agreed" with OTA's evaluation (e.g., if OTA's query was for lack of a warning in the sample label, and the WHO monograph contained the warning, the monograph agreed with OTA).

Excluding queries about listing inactive ingredients, there were 52 relevant queries. Of these, the monographs agreed completely with OTA's evaluation in 40 cases. In five cases, the monographs were consistent with some, but not all, aspects of the query, and in seven cases, the monographs agreed with the sample label and not with the OTA evaluation. This analysis suggests strongly that the great majority of unresolved queries in OTA's product evaluations represent significant problems in the content of the label, when measured against another independent standard. It provides validation of OTA's method and standard of evaluation.

THE U.S. PHARMACEUTICAL INDUSTRY IN DEVELOPING COUNTRIES

U.S. pharmaceutical multinational corporations (NIFJCs) are leaders in the world market. In 1989, 8 of the top 15 pharmaceutical companies worldwide, ranked by total sales, were U. S.-based MNCS. Annual sales averaged $3.5 billion (198). U.S. companies hold their leading position by dominating the U.S. domestic market, but they also have a significant presence in foreign markets. Foreign sales account for 30 to 50 percent or more of total sales for most companies (178, 191). The largest foreign markets for U.S. pharmaceuticals are other industrialized countries, accounting for approximately 82 percent of foreign

sales in 1989 (177). Although only a minority of MNC foreign sales are in developing countries, the majority of drugs available in those countries are imported, because indigenous pharmaceutical industries are small (223,279).

With about 75 percent of the world's population, developing countries consume about 21 percent of the world's pharmaceuticals (by market value), and well over half of that 21 percent goes to just a few countries-India, Brazil, Mexico, Argentina, Egypt, Iran, and South Korea (67, 279). (The percentage of market value probably understates the percentage of the world's drug supply actually consumed in developing countries, but figures on consumption are not available.) Approximately $30 billion per year is spent by developing countries on pharmaceuticals, and this amount is expected to grow over the next decade, both in absolute terms and as a percentage of the world market (242).

Influences on Labeling Practices of U.S. Multinational Pharmaceutical Corporations

Drug labeling by pharmaceutical MNCs is influenced by the following factors:

1. *Home country: the* laws and policies of the country in which the parent company is headquartered (the United States, in the case of U.S.-based MNCs);
2. *Host country: the* laws and policies of the foreign country in which the MNC is manufacturing or importing;
3. *International organizations:* codes of conduct or guidelines developed by international organizations;
4. *Self regulation:* internal company policies, and national and international codes of conduct developed to standardize certain practices worldwide; and
5. *Public interest groups and consumer activists: political* and media pressure.

These forces, and how they affect the issue of drug labeling, are discussed in various chapters of this report, and summarized briefly here.

THE MULTINATIONAL CORPORATION– STRUCTURE AND LEGAL CONTROL

There is no single definition of a multinational corporation (MNC), but the most obvious distinguishing characteristic of an MNC is that it has direct investments in several different countries. The MNC does not merely market its product in foreign countries, but directly owns or controls production or service facilities in those countries. The foreign operations of a U.S. MNC may take a variety of forms. In the pharmaceutical industry, foreign operations are usually carried out by wholly or majority-owned foreign subsidiaries in "host countries" (65). A U.S. pharmaceutical MNC may have 50 or more foreign subsidiaries, but perhaps only a dozen major foreign operations. The typical MNC owns a small number of separate plants, each dedicated to manufacturing active ingredients of a specific type. The active ingredients are then shipped to local plants where the final product is formulated and packaged (205).

A parent corporation may exercise varying degrees of control over its foreign operations, from control of its day-to-day operations to less centralized management of operations, involving exchange of technology, information, capital, and personnel. Different subsidiaries of the same corporation may be subject to different degrees of control depending on their type, size, and importance. The type of corporate structure linking the parent company to a foreign subsidiary or other foreign operation is important in determining the degree of control an MNC has over the manner in which its drugs are marketed in other countries. Most pharmaceutical MNCs have majority equity control over their foreign operations, but corporate headquarters do not necessarily exercise close control over the management of those operations.

MNCs consist of multiple legal entities operating in various countries. Domestic operations of U.S. MNCs are subject to U.S. law, and with respect to certain laws—tax and securities, for example-a U.S.-based MNC must also account for its foreign subsidiaries to the U.S. Government. Aside from that, by and large, foreign subsidiaries are regulated by the laws of the countries in which they are located. But the MNC itself operates as a single business entity that may adopt business and marketing strategies that take into account the legal constraints and advantages of each country in which it operates. As a result of these and other complexities of MNC business, the United Nations and other international governmental organizations have sought to develop standards to govern the operations of MNCs in host countries. Pharmaceutical MNC practices, including labeling, have been the object of scrutiny by public interest groups which have attempted to change MNC behavior through adverse publicity and direct appeals to the companies. The pharmaceutical industry has responded to the combined influences of legal requirements and public pressure by creating a structure aimed at self-regulation. The International Pharmaceutical Manufacturers Association's "Code of Pharmaceutical Marketing Practices" sets out broad guidelines for the promotion of pharmaceutical products. Member companies believe that this measure is appropriate and that further regulation is unnecessary, but the effectiveness of the Code is a matter of dispute, particularly by consumer activists.

REGULATION OF DRUG LABELING BY THE U.S. FDA

All the companies in the OTA survey are U. S.-based corporations and all market products in the United States under the stringent controls of the Federal Food, Drug, and Cosmetic Act (FDCA)(21 U.S.C. §§321 *et. seq.). The* FDCA is implemented by the Federal Food and Drug Administration (FDA), whose role is that of health promoter and protector. One of FDA's primary functions is to approve drugs for marketing in the United States and to regulate the manner in which they may be marketed.

The FDCA regulates only those pharmaceuticals sold in or exported from the United States; its reach does not extend to pharmaceuticals that are manufactured, repackaged, and/or sold by the foreign subsidiaries of U.S. companies. Some companies do, however, use the U.S. labeling as a starting point for the development of labeling for other countries.

Labeling of Drugs in the United States

In approving new drugs, the FDA must also review and approve all labeling material. Labeling includes the "label;' which is the "display of any written, printed, or graphic matter upon the immediate container" of the drug, as well as any written, printed, or graphic matter that accompanies the drug, including package inserts, containers, and wrappers (21 U.S.C. § 321(k),(m)). It is not necessary that the labeling accompany the drug physically. The FDA has interpreted labeling to include brochures, reprints of scientific articles distributed by a manufacturer, index file

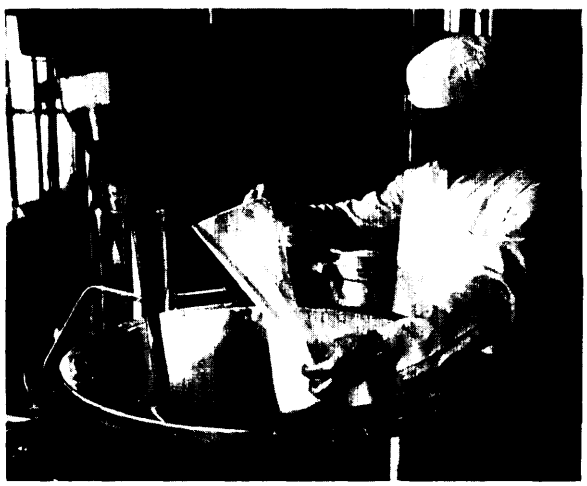


PHOTO CREDIT: P. MERCHEZ, WHO

Pharmaceutical formulation in Latin America.

cards distributed to physicians with information about a drug, and even press releases (170).

All prescription drugs in package form must have *labels* that include (21 U.S.C. § 352; 21 C.F.R. $$201.22,201.50,201.100 and 21 1.137):

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;
4. 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;
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 proper container.

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).

The package insert contains most of the information that the practitioner needs to use a drug safely and effectively in the care of patients (44 FR 37437). The following types of information are included (21 C.F.R. $5201.56, 201.57):

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 content of the label is guided by a requirement that all indications be supported by substantial evidence based on adequate and well-controlled studies, and that warnings be placed on the label if there is a reasonable association between a drug and a serious hazard (21 U.S.C. § 355(d); 44 FR 37434). Once the label for a prescription drug has been approved, all proposed changes by the manufacturer must be reviewed and approved by the FDA (21 C.F.R. § 314.70).

Consumers buy over-the-counter OTC) drugs without the assistance of physicians or pharmacists, so labeling information must be directed to consumers. This has required FDA to develop regulations for OTC labeling that differ from those for prescription drugs. The guiding principle for OTC labeling is that it must be "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" (51 FR 16259). The outside label of an OTC drug must include the name of the manufacturer, packer, or distributor; lot number; expiration date; and any special warning required by the FDA (e.g., presence of aspartame as inactive ingredient) (21 C.F.R. §§201.1, 201.17, 201.18, 201.20-21). Directions for adequate use, warnings, precautions, contraindications, dosage information, and other required information may be found on a package insert, the outside label, or both (21 C.F.R. §§ 201.1-201.20) (56).

Labeling for a number of OTC drugs is prescribed by FDA monographs (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).

The FDA also regulates prescription drug advertising and, to a lesser extent, advertising of OTC drugs (OTC drug advertising is regulated primarily by the Federal Trade Commission) (15 U.S.C. §§45, 52, 55). Advertising material for both prescription and OTC drugs must be based on the approved labeling and must not contain any exaggerated or misleading claims (21 U.S.C. § 352(n); 21 C.F.R. § 202.1; 44 FR 37437) (166). The FDA reviews prescription drug advertising, which must include a summary of the indications, contraindications, and side effects, consistent with the prescribing information contained in the package insert (21 C.F.R. Part 202.l(e)). The advertisement must present this information in a balanced manner; the warnings may not be minimized nor the effectiveness exaggerated (21 C.F.R. § 201.1).

EXPORT AND LABELING OF APPROVED DRUGS

All approved drugs may be exported freely from the United States provided they are accompanied by FDA-approved labeling, The FDCA prohibits export of pharmaceuticals in finished form that do not include a U.S. label, with some minor exceptions. Certain older drugs, those approved prior to 1938, may be exported without U.S. labeling provided the labeling complies with the importing country's requirements (21 U.S.C. § 381(e)), and certain antibiotics may be exported with labeling that differs from the U.S. labeling (21 C.F.R. § **432.9).**

The net result is that U.S. companies do not export drugs approved after 1938 with a label that differs from the U.S. labeling, even if the drug regulatory authority in the importing country requires different labeling. Most pharmaceutical products exported from the United States, however, are not in finished dosage form, but are in bulk form for repackaging and labeling abroad (178,243).

EXPORT OF UNAPPROVED DRUGS

For many years, drugs not approved in the United States could not be exported at all. This was changed in 1986, when Congress amended the FDCA to allow for limited export of unapproved pharmaceuticals. To be eligible for export, the pharmaceutical must be in the clinical trial stage of the drug approval process, and the company must be in active pursuit of U.S. approval. An unapproved drug may be exported only to an industrialized country named in the legislation, and only after it has been approved for sale in that country (21 U.S.C. § 382(b)(l)(B)). The current list of countries that may import unapproved drugs from the United States includes all the European Community countries (except Greece) plus Australia, Austria, Canada, Finland, Japan, New Zealand, Norway, Sweden, and Switzerland. These countries were selected because they have well-developed drug regulatory systems.

To export an unapproved drug, the exporter must submit an application to the FDA 90 days before intending to export. Notice of the application, identifying the applicant, the product, and the country to which the product will be exported, is published in the *Federal Register. The ex*porter must certify that all other FDA requirements have been met and must obtain written agreement from each importer stating that the importer will not reexport the drug to a country not included on the list of countries to which unapproved drugs may be exported from the United States. The exporter must cease exporting if:

1. the receiving country withdraws approval of the drug or withdraws the drug from sale,
2. the drug is withdrawn from the U.S. approval process, or
3. the FDA rejects the drug for marketing in the United States (21 U.S.C. §§ 382(c)(1)(A)-(C)).

EXPORT OF TROPICAL DISEASE DRUGS

The FDA has special provisions to govern the export of unapproved new pharmaceuticals intended primarily for treatment of tropical diseases. 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 export of these drugs

PHOTO CREDIT: P. MERCHEZ, WHO

Pharmacy in Latin America.

is similar to those required to export other unapproved drugs. The main difference between the export of unapproved tropical disease drugs and all other unapproved drugs is that the former are exported primarily to developing countries, and need not be in the U.S. approval pipeline.

EXTRATERRITORIAL JURISDICTION UNDER U.S. LAW

The FDA's authority over drug labeling stops at the U.S. border. It has no authority to regulate the labeling of pharmaceuticals that are produced or finished, and subsequently marketed, by foreign subsidiaries of U.S. MNCs. And it is these products, not those exported in finished form from the United States, that constitute the overwhelming majority of U.S. products sold in other countries, including developing countries. Pertinent to this assessment is the question of whether the United States could regulate or otherwise influence the labeling of these products, an authority clearly beyond the reach of the FDCA as it stands today. The question is one of U.S. extraterritorial jurisdiction, and the answer comes from understanding the principles of international law.

INTERNATIONAL LAW

A decision to exercise extraterritorial jurisdiction is usually guided by two basic principles of international law: the territorial principle and the nationality principle. In addition, the United States has asserted a third basis for exercising extraterritorial jurisdiction, the effects doctrine. While this doctrine is generally accepted by the United States, it is not well accepted by other countries, and is the subject of debate (2,218).

The territorial principle is the primary doctrine of international law, holding that each nation has the exclusive right to regulate conduct within its borders. A corollary is that one country does not have the right to interfere in another country's internal affairs. Under a strict interpretation, the United States would never have the right to exercise jurisdiction over a foreign subsidiary of a U.S. company. The territorial principle is not absolute, however. The nationality principle recognizes a nation's interest in maintaining some degree of control over its citizens residing in other countries. An example is a U.S. citizen's obligation to pay U.S. income taxes even when residing

abroad, or the ability of the United States to demand child support payments from U.S. fathers or mothers residing abroad. The nationality principle also may be applied to corporations which are, in legal terms, "persons" (though there is some disagreement on how the nationality of a corporation is determined).

The effects doctrine is a modification of the territorial principle that is accepted by the United States, but not by all other countries. Under this doctrine, the United States claims the right to exercise jurisdiction over certain acts that occur outside the United States but that have a substantial, direct effect in the United States, This doctrine has been applied generally to economic laws.

By definition, the nationality principle and the effects doctrine conflict with the territorial principle, because they give a country the right to exercise jurisdiction within another country's borders. One framework for resolving these conflicts can be found in the "rule of reason" adopted by the American Law Institute in their *Restatement (Third) of the Foreign Relations Law of the United States (6),* a document influential in defining the U.S. interpretation of international law (but not necessarily reflecting international law as accepted by the majority of nations or even the U.S. Government).

Under the reasonableness approach, a country should not exercise extraterntorial jurisdiction if it would be an "unreasonable encroachment" on another country's sovereignty. Determining the reasonableness of a particular action requires balancing the competing interests of the countries directly involved in the situation, and examining the impact the decision will have on international economic and social discourse (136). The *Restatement* instructs that a country may not exercise jurisdiction over a foreign subsidiary merely on the basis that it is owned or controlled by citizens of the regulating state. But there are exceptions; for example, it allows countries to impose regulations that apply to all MNC subsidiaries requiring uniform accounting standards, disclosure of information to investors, and the preparation of consolidated tax returns. These financial reporting requirements may be important to the regulating nation and should not affect the internal affairs of the host country.

In exceptional cases, a nation might argue that an exercise of extratemitorial jurisdiction is vital to its national interests. Trade embargoes and export controls are typical extraterritorial actions used to protect national interests, or, more aptly, to further foreign policy objectives. In some cases, the extraterritorial law may conflict with the laws or policies of the foreign country. This type of action has been at the heart of extraterritorial conflicts between the United States and other countries (186),

U.S. LAWS ALLOWING EXTRATERRITORIAL ACTS

U.S. statutes authorizing extraterritorial actions include the Export Administration Act of 1977 (50 U.S.C. App. §§ 2401-2420) and the International Emergency Economic Powers Act of 1977 (50 U.S.C. App. §§ 1701-1706). Under these statutes, the President may assert Limited jurisdiction over foreign subsidiaries in times of war, national emergency, or when foreign policy considerations make such acts imperative. Other countries have opposed this authority, contending that the United States has overstepped the bounds of international law (59).

In the case of trade embargoes and boycotts, foreign subsidiaries are caught in a dispute between the United States and a foreign government. But the actions of the foreign subsidiary itself may also prompt action. The most pertinent example of this is the Foreign Corrupt Practices Act of 1978 (FCPA), passed to stop U.S. MNCs from bribing foreign officials. The FCPA might be seen as a precedent for regulation of drug labeling by foreign subsidiaries of U.S. pharmaceutical MNCs.

The Foreign Corrupt Practices Act

The FCPA was enacted after revelations of widespread secret payments to foreign officials

by U.S. companies. Most of the transactions occurred outside the United States and, according to some corporations, were necessary to compete in those countries. Congress concluded, however, that such bribery could lead to scandals with serious foreign policy implications, and that corporate bribery offended the moral expectations and values of the American public and distorted the competitive market. Revelation of these bribes could lead to lawsuits, cancellation of contracts, and even appropriation of company assets. These consequences would affect U.S. investors and destroy investor confidence in U.S. industry. The FCPA makes bribery of foreign officials by U.S. citizens and corporations a criminal act.

Despite the fact that the FCPA has such broad extraterritorial reach, it has encountered little international opposition. One reason may be that the statute captured the sentiment of the time, when the United Nations was considering a resolution condemning corrupt practices in international commerce, and the Organization for Economic Cooperation and Development had issued voluntary guidelines for MNCs forbidding bribery of public officials. There was international consensus that bribery of foreign officials by MNCs should be controlled, even if most countries were unwilling to act unilaterally against their own corporations,

EXTRATERRITORIAL REGULATIONS RELATING TO THE HEALTH AND SAFETY OF FOREIGN NATIONALS

The appropriateness of the FCPA as a precedent for extraterritorial regulation of pharmaceutical labeling should not be overstated. In contrast to the foreign and domestic policy implications of bribery by U.S. corporations, pharmaceutical labeling is viewed primarily as a domestic health and safety issue by each country. The *Restatement of U.S. Foreign Relations Law* leaves activities that affect primarily the health, safety, and welfare of the national population exclusively to national laws. Attempts to regulate these domestic issues would impinge on the sovereignty of the host country to control activities within its borders (6). There are few examples of U.S. legislation that force foreign subsidiaries of U.S. companies to comply with US. health, safety, and labor standards when operating abroad, and those that do exist are designed to protect U.S. citizens working for those companies (43, 293).

To justify an exercise of *unilateral* extraterritorial jurisdiction, the United States must have a strong foreign policy interest that cannot be served by any alternative action. Under the effects principle, the action the United States seeks to regulate must have an adverse effect within the United States. This is sometimes further limited to foreign actions that violate criminal or civil laws of countries with developed legal systems (59,73). In the case of the FCPA, Congress recognized that bribery of foreign officials could lead to scandals that, in turn, could both damage foreign relations and have domestic financial implications if investors lost faith in U.S. companies. In addition, bribery is almost universally seen as a crime.

The case for extraterritorial jurisdiction over labeling by U.S. companies and foreign subsidiaries is not so strong. This study assumes that U.S. corporations are, on the whole, in compliance with national laws and are providing at least as good or better information than other companies. There is no evidence that U.S. companies are violating laws or acting in a manner that could lead to sanctions or other actions that could erode investor confidence. The United States, therefore, has virtually no authority to regulate the subsidiaries under the effects principle. This leaves the nationality principle; however, the United States is virtually alone in its position that its foreign subsidiaries incorporated in foreign countries can be considered nationals of the United States for purposes of U.S. laws.

The justification for exercising extraterritorial jurisdiction over pharmaceutical labeling would be a moral interest in having U.S. pharmaceutical companies lead the way and provide the best and

most informative labeling of all companies. This does not reach the "major national interest" required by U.S. precedents and the *Restatement. In* addition, the United States' interest must be weighed against the factors that do not support U.S. jurisdiction, primarily the fact that developing countries have their own laws regulating pharmaceutical labeling, and that the U.S. law would primarily protect foreign citizens. These countervailing factors do not necessarily preclude all forms of extraterritorial jurisdiction, but they cannot be ignored.

This issue also raises practical considerations. Whereas most countries condemn bribery and agree generally on its definition, coming to agreement on proper labeling of pharmaceuticals would be more difficult. The fact that a developing country has limited labeling regulations or enforcement does not *necessarily* mean that it would welcome U.S. labeling, thought it might see this as desirable.

CODES OF CONDUCT AND PHARMACEUTICAL INFORMATION

International law is based on the consensus of nations. Sometimes international law is expressed in binding agreements, such as treaties. Treaties may address a single issue between two nations or may address a multitude of economic issues among many nations, as does the General Agreement on Tariffs and Trade (GATT'), Binding agreements are not entered into lightly, however, and those affecting primarily domestic commerce are generally avoided. At the same time, the increasingly international economy and the cross-border operations of MNCs present issues that cannot be addressed effectively by one nation's legal system. One way to promote the necessary cooperation is through codes of conduct and international guidelines,

Codes of conduct are voluntary agreements between nations in which countries endorse certain general principles that they may—though they are not required to-implement through national laws and other actions. Codes of conduct contain policies that nations agree are desirable, but do not force nations to uphold the embodied principles through specific actions. As one legal commentator explained, codes are "politically-agreed behavior which cannot be directly legally enforced but cannot either be legitimately infringed" (125),

Codes of conduct have been formulated by both governmental and nongovernmental organizations, including the United Nations and its agencies, the International Labour Office (ILO), the Organization of Economic Co-operation and Development (OECD), the International Chamber of Commerce, and regional organizations. The codes range from broad pronouncements of principles which multinationals should follow, such as the OECD Guidelines for Multinational Corporations, to specific guidelines for corporate operations, such as the United Nations Conference of Trade and Development Code of Conduct on Restrictive Business Practices, or the European Community's Code of Conduct for Companies Operating in South Africa (98).

Codes of conduct often address the operations of MNCs; however, MNCs are not parties to the agreements negotiated by international governmental organizations, such as the United Nations, As a result, government-negotiated codes do not bind MNCs to take any specific action unless the code is implemented into national law. But MNCs may feel pressure to comply with codes in order to maintain good political relations, or they may find it advantageous to comply so that the host country is more likely to fulfill its obligations to the MNC. Most codes of conduct include an implementing body that may provide interpretations of the code and assess its implementation. This organization may also provide a forum for further debate and may identify code violations that can be addressed at a national level.

Currently, no single code addresses pharmaceutical labeling. A draft United Nations Code for Translational Corporations, which has been under negotiation for more than 12 years, gener-

ally addresses consumer issues, including the provision of safety information for consumer products. The language of the consumer protection provisions is very general and the Code, if passed, may not have a significant impact on drug labeling.

There is an International Code for the Marketing of Breast-Milk Substitutes (Breast-Milk Substitutes Code), which was negotiated under the auspices of WHO. This code addresses promotional practices of companies that sell infant formula and other breast-milk substitutes. The Breast-Milk Substitutes Code addresses a single industry and focuses on preventing marketing practices that have potentially harmful effects on consumers. It has, therefore, been viewed as a precedent for a pharmaceutical code.

WHO rejected a proposal to draft a pharmaceutical code in the 1980s when the pharmaceutical industry developed its own code of conduct for promotional practices. Unlike a code adopted by governments, industry's code was adopted by IFPMA member associations, so it is a self-imposed standard. WHO did, however, issue guidelines on advertising and promotion of pharmaceuticals. Although similar to the industry code, WHO's guidelines are more specific, and WHO would like governments to implement them at the national level.

INTERNATIONAL CODE OF MARKETING OF BREAST-MILK SUBSTITUTES

The WHO International Code of Marketing of Breast-Milk Substitutes was passed in 1981 in response to specific marketing practices of MNCs and, at the time of drafting, it was seen as a possible precedent for a pharmaceutical marketing code, The Breast-Milk Substitutes Code, which sets forth standards for the promotion and labeling of infant formula, has been used by a number of countries as a basis for national regulation or national codes of conduct.

Consumer groups have used the Code to generate public pressure against companies that fail to comply, and have educated governments and health officials about the meaning of the Code (281). Industry also has responded. The International Association of Infant Food Manufacturers (IFM), an industry group with 35 member companies in 15 countries, has instituted a complaint procedure and is developing an arbitration mechanism to address Code violations that cannot be dealt with by direct negotiations between the company and the complainant (281). Finally, the Code's requirement that each country report annually to WHO on the actions it has taken toward implementation has been instrumental in keeping attention on the issue. It appears that the more egregious promotional practices have ceased since the Code came into existence, though violations still are being reported (188, 281).

WHO'S ETHICAL CRITERIA FOR MEDICINAL DRUG PROMOTION

In 1968, before interest became strong in a pharmaceutical code of conduct, WHO adopted "Ethical and Scientific Criteria for Pharmaceutical Advertising" (267). This document was revised and expanded in 1988, The revised document, now called the "Ethical Criteria for Medicinal Drug Promotion" (referred to as the "Ethical Criteria"), provides "guidelines" for a broad range of "informational and persuasive activities by manufacturers and distributors" (273).

Guidelines are weaker policy pronouncements than are codes of conduct. The language of the Ethical Criteria merely "urges Member States to take into account the Ethical Criteria in developing their own appropriate measures" and "appeals to pharmaceutical manufacturers and distributors" to use these Criteria (264). The document also states that the Ethical Criteria "constitute general principles that could be adapted by governments. . .as appropriate to their political, economic, cultural, social, educational, scientific and technical situation, their national laws and regulation s." They do not constitute legal obligations (264,265).

The primary target of the Ethical Criteria is advertising, but they also instruct companies to comply with national laws with respect to other information, and if no national laws pertain, or if the laws are rudimentary, the company should provide information consistent with that required by another reliable drug authority. The Ethical Criteria state that all text and illustrations on the drug package and label should provide only reliable, truthful, informative, and current information, supported by scientific data. Companies are instructed not to use information that is likely to induce medically unjustifiable drug use or give rise to undue risks (264).

The Ethical Criteria specify information required in advertisements as: the name and quantity per dosage of active ingredients, the brand name of the drug, the name of other ingredients that patients might be sensitive to, the approved therapeutic use, the proper dosage, the side effects and major adverse drug reactions, precautions, contraindications, warnings. major drug interactions, name and address of manufacturer and distributor, and references to scientific literature as appropriate.

No formal body oversees the implementation of the Ethical Criteria, and WHO recently found that few developing countries have the capacity to oversee advertising and promotion of pharmaceuticals. The International Federation of Pharmaceutical Manufacturers Associations (IFPMA), an association of national pharmaceutical manufacturers associations, has not adopted the guidelines of the Ethical Criteria, but believes its own code of conduct is consistent with them.

IFPMA CODE OF PHARMACEUTICAL MARKETING PRACTICES

The IFPMA is an association of 50 pharmaceutical associations (e.g., the U.S. Pharmaceutical Manufacturers Association) *from 51* countries. In **1981, the** IFPMA adopted its Code of Pharmaceutical Marketing Practices, industry's statement on promotional practices. The Code addresses drug labeling only generally, stating **that all** information provided with a pharmaceutical should be scientific and be presented with "objectivity and good taste, with scrupulous regard for truth and with clear statements with respect to indications, contraindications, tolerance and toxicity" (111). In addition, pharmaceutical companies are expected to provide essential information on safety, contraindications, side effects, and toxic hazards of their products, "subject to the legal, regulatory and medical practices of the country."

The phrase, "subject to the legal, regulatory and medical practices of the country," has been the source of controversy among consumer advocates. The IFPMA claims that decisions of national drug regulatory authorities on indications and precautionary information take precedence over decisions made by more sophisticated drug regulatory agencies, such as the FDA (1 11). (As a point of information, no evidence surfaced in the OTA survey to suggest that opposition to U. S.-type labeling by regulatory authorities in study countries accounted for the divergences that were found.) In addition, for products that have been evaluated and registered by an established regulatory authority, the approval itself is accepted as evidence that the drug is efficacious (9). Certain consumer groups argue that the point of a code of conduct is to set standards that are higher than the legal minimum, and that deference to regulatory bodies in developing countries, which the IFPMA admits may be rudimentary, essentially defeats the purpose of a code (9). Consumer groups have also been critical of the IFPMA Code because it uses very general language, lending itself to varying interpretations.

Enforcement of the Code

Alleged violations of the Code maybe reported to IFPMA or to member associations that have developed their own dispute resolution systems. For complaints made to IFPMA, the local member organization where the company is located will issue a decision on whether the company violated the Code. Over the past 10 years, the

IFPMA has reviewed 72 complaints, consisting of 962 separate cases, of which 56 percent were found to be violations of the Code.

The IFPMA cannot force a company to change its advertising, but instead uses the threat of adverse publicity to encourage change. According to the IFPMA, most companies take remedial action as soon as they are informed of a complaint.

A contentious issue in interpreting the Code has been the definition of "reminder advertisements," which require less information than must be provided with full advertisements. According to WHO's Ethical Criteria, reminder advertisements must not make therapeutic claims for drugs. But the IFPMA Code defines reminder advertisements more loosely, so that some relatively long advertisements (more than 200 words) have been classified as reminders, exempting them from the more inclusive requirements of full advertisements (130,196).

PHOTO CREDIT: PAHO

Health workers examining essential drugs.

Over the past 2 years, the number of complaints brought to the IFPMA has dropped significantly. It is not known whether this drop signifies that pharmaceutical advertising is improving, consumer groups are bringing a larger proportion of complaints directly to national associations, or if complaints are no longer being filed for other reasons, such as frustration with earlier experience.

INTERNATIONAL PROGRAMS TO IMPROVE PHARMACEUTICAL LABELING

The most effective way to insure that adequate prescribing information is available in developing countries is to strengthen existing regulatory systems within the countries. WHO is the primary international governmental agency providing direct support to developing countries for all aspects of health care. One of WHO's major initiatives is the Action Program on Essential Drugs (APED), whose aim is to improve access to and the rational use of pharmaceuticals. The provision of accurate prescribing information is a key component. The majority of APED's activities are in the form of direct country support. However, the WHO's Division of Drug Management and Policies (DMP) is responsible for developing standards and systems for drug safety, efficacy and quality, as well as drug regulation. Relevant WHO activities are reviewed briefly below and are discussed more fully in chapter 7.

Distribution of Prescribing Information

WHO's Division of Drug Policies and Management (DMP) has developed training materials designed to improve prescribing practices. Among those relevant to drug labeling are: the *Model Guide to Good Prescribing,* developed in conjunction with the Groningen University in the Netherlands, and designed to be used in undergraduate medical education (286); and the *Manual for Rural Health Workers: Diagnosis and Treatment with Essential Drugs (47).* In addition, APED distributes the *The Essential Drugs Monitor,* a quarterly newspaper that discusses all aspects of essential drug programs, to 28,000 subscribers worldwide (286).

DMP's ongoing work includes a series of publications entitled *WHO Model Prescribing Information* for drugs on the essential drugs list and which are of particular interest to developing

countries (280,282,283,284,288,289). Recognizing that prescribing guides from industrialized countries provide useful information, WHO also provides national drug regulatory authorities in developing countries with official prescribing guides from France, the United Kingdom, and the United States (10,15 1,249).

WHO Certification Scheme

Nearly all countries have a process for registering new drugs, and it is at the point of registration that labeling is reviewed and approved. For pharmaceuticals imported into a country, the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (Certification Scheme) provides developing countries with a mechanism for obtaining information on their quality, whether they are approved for use in the country of export and, if approved, what labeling is used there.

Under the Certification Scheme, an importing country may request that the exporter provide a WHO certificate for the product to be imported. The exporter must ask the regulatory authority in the country in which the drug is manufactured to issue one of three certificates.

The most comprehensive is the certificate for a pharmaceutical product, which may be used when the importing country is deciding whether to register the product for sale in the country, or when administrative action is necessary to renew, extend, or vary an existing license for import or sale (285). The certificate includes the following: a statement that the product was manufactured in accordance with current good manufacturing practices and information on when the plant was last inspected, confirmation that the product is approved for sale in the country in which it is manufactured or an explanation of why it has not been approved, and a copy of the labeling approved in the country of manufacture.

In lieu of a certificate for a pharmaceutical product, a country may request the statement of licensing status, a short certificate attesting that the product is licensed for sale in the country of export. This might be used when bidding on an international contract to supply pharmaceuticals. The third type of certificate is a batch certificate to be issued by the manufacturer (except for vaccines, sera, and other biological products for which governments issue batch certificates). Batch certificates provide the importing country with information on the expiration date and the results of any analyses undertaken on the batch (285).

Despite the fact almost all industrialized countries have agreed to participate in the scheme and most exports to developing countries are from industrialized countries, the Certification Scheme has apparently not been used extensively by developing countries. Expanding use of the Certification Scheme remains one of WHO's priorities and with financial support from the U.S. Agency for International Development (USAID) and the assistance of the U.S. FDA, the DMP will evaluate the Certification Scheme and make recommendations to improve its implementation (259, **286).**

Access to New Safety and Efficacy Information

In both developing and industrialized *countries*, registration may be effective for defined periods (e.g., 5 years in Panama) or indefinitely (as in the United States). Regardless of the registration period, most countries require pharmaceutical companies to amend their registration in response to new information on the safety and efficacy of the drug. In industrialized countries, this requirement often is supplemented by a mandatory adverse drug reaction reporting system. Since most developing countries do not have a surveillance system of this type, WHO attempts to provide them with equivalent information. WHO does this by gathering information from around the world on restrictive regulatory decisions and voluntary actions taken by manufacturers in response to concerns about the safety of

their products. This information is distributed monthly to the drug regulatory authorities of member countries through the *WHO Pharmaceutical Newsletter (285). WHO Drug Information,* a quarterly journal, provides discursive commentaries on the more important actions of national drug regulatory bodies (258,285). Finally, WHO has established collaborating centers in each of its five regions for the purpose of information dissemination, training, and operational research (274). APED's documentation center distributes more than 20,000 publications a year (286).

International Activities of the U.S. FDA

The U.S. FDA is primarily a domestic agency, but as the drug regulatory agency for the largest pharmaceutical market in the world, it is often called on for advice. FDA's primary international activity is disseminating information about its own regulatory actions. FDA sends WHO and the European Community monthly updates on important regulatory developments, which include: proposed regulations and policies; reports of serious adverse reactions from pharmaceuticals; lists of approvals for new drugs, medical devices, and biologics; and other public information (95). Information on important regulatory decisions is sent on an as-needed basis to WHO and to 62 foreign embassies in Washington, DC (32). This information focuses on decisions that FDA believes are important, and which may or may not be of critical importance to developing countries. The FDA also distributes its newsletter, *Medical Bulletin,* to over 800 government and academic organizations all over the world, mostly in industrialized countries, but also in developing countries. The *Medical Bulletin also* focuses on new FDA policies and findings on particular drugs and devices.

The FDA also hosts many international visitors. In the year ending September 1991, FDA was visited by 603 representatives from 61 countries. In 1990, they were visited by 789 foreign officials representing 65 countries and multinational organimations (168).

FDA cooperates with WHO in various activities. In 1980, the FDA and WHO cosponsored the first International Conference of Drug Regulatory Authorities, which has continued biannually, bringing together regulatory authorities from all over the world. FDA representatives have provided advice and other assistance to various WHO programs (166), and FDA is a WHO Collaborating Center for Monitoring of Adverse Drug Reactions, providing WHO on a monthly basis with an automated data processing tape of all serious domestic adverse reaction reports (168).

Most recently, the FDA agreed to assume a small role in the collaborative effort of USAID with WHO to evaluate the Certification Scheme. The FDA will also assist WHO in its evaluation of the "Guiding Principles for Small National Authorities" (24,278). (The Guiding Principles outline some of the key elements for establishing a drug regulatory system.)

The U.S. Agency for International Development

USAID has recently begun assisting WHO with evaluations of the Certification Scheme and the "Guiding Principles for Small National Authorities;' and it also is collaborating on research projects to facilitate the rational use of drugs in developing countries. The research will be carried out by the International Network for the Rational Use of Drugs (INRUD), a nonprofit research organization.

USAID has a 5-year cooperative agreement with the U. S. Pharmacopoeia to assess and facilitate the distribution of pharmaceutical information in developing countries, including information provided to both drug regulatory authorities and health workers. Finally, USAID will be sponsoring a 5-year project to assist developing countries address the following pharmaceutical issues: drug regulation and registration; ration-

alization of procurement strategies; and the development of pharmaceutical information for prescribers, consumers, and drug regulatory authorities (24).

Consumer Groups

Consumer groups and academic researchers have helped bring to the public's attention the problems of improper drug labeling in developing countries. Most consumer groups use public opinion and pressure as instruments of change, so distribution of newsletters, journals, and books are key activities. Some of the major studies of drug labeling supported by these groups are summarized in appendix A, and their ongoing activities are discussed in chapter 7.

A number of the individual health and consumer groups in developing and industrialized countries are part of the larger international network, Health Action International (HAI), which itself works closely with the International Organization of Consumers Unions, a large and active umbrella group that helps promote consumer issues and consumer advocacy in many countries.

Consumer groups often confront pharmaceutical companies directly, demanding explanations for behavior. One influential group is the Medical Lobby for Appropriate Marketing (MaLAM), an international network of physicians that acts as a watchdog for pharmaceutical advertising (199) (results of some of MaLAM's work are discussed in ch. 4 and ch. 6).

Finally, some groups function as research consultants to developing countries. One such group in the United States is the International Network for the Rational Use of Drugs (INRUD). INRUD is a cooperative organization of health professionals, administrators, and researchers whose aim is to devise and implement innovative programs to improve the use of pharmaceuticals in developing countries. According to INRUD, there has been little evaluation of a number of strategies developing countries have tried to improve the rational use of drugs, including development of standard treatment protocols, provision of drug information and drug bulletins, implementation of changes in health training curricula, restriction of drug advertising, and use of public education. These strategies are merely assumed to have a positive impact. However, studies in industrialized countries have revealed that some of these same interventions have not been very effective, and INRUD believes similar research needs to be done in developing countries (127).

CONTENT OF THIS REPORT

The remainder of this chapter presents options for Congress to consider that could improve the state of drug labeling in developing countries. Chapter 2 lays out OTA's labeling survey and evaluation process, and chapter 3 presents the survey results, both in summary form and in a table giving the details of each product evaluation. Chapter 4 contains a discussion of drug labeling and registration requirements in the United States and, in less detail, in other countries. It also talks about sources of prescribing information other than drug labeling. Basic information about the structure and functioning of multinational pharmaceutical corporations within the international legal community is covered in chapter 5, along with a discussion of extraterritorial jurisdiction. Various types of international agreement, focusing on codes of conduct and voluntary guidelines, are explored in chapter 6. Chapter 7 reviews efforts being made to improve drug labeling in developing countries by WHO, consumer organizations, and other private groups. It also discusses the role of the U.S. FDA and USAID in these efforts.

Appendix A reviews the major studies of pharmaceutical labeling in developing countries that were carried out in the 1970s and 1980s by academic researchers and consumer organizations. These studies sparked interest in the issue of pharmaceutical labeling by multinational corpo-

rations and, in part, congressional interest in this assessment. Finally, appendix B provides summary information on drug regulations in the countries that were studied, focusing on drug labeling requirements.

OPTIONS FOR CONGRESSIONAL ACTION

Option 1: Require that all pharmaceuticals sold in developing countries by U.S. multinational corporations and their controlled subsidiaries be accompanied by the FDA-approved label in an appropriate language.

Congress could extend the existing requirements for labeling of drugs exported from the United States by making them applicable to all pharmaceuticals approved in the United States and sold in developing countries by U.S. pharmaceutical corporations or their foreign subsidiaries, regardless of where they are manufactured. This requirement could be limited to countries without well-developed drug regulatory systems. Such a limitation would recognize that the intent of the legislation would be to assist countries that do not have adequate resources to evaluate and regulate pharmaceutical labeling, and not to impose U.S. regulations on other nations. The law could require that the labeling be in English only, or in both English and the language required by the laws of the country in which the drug is sold.

Exceptions to labeling requirements under this option should be permitted when the regulatory authority of the host country affirmatively rejects the U.S. label. Deference to conflicting national laws of the importing country would ensure that this legislation would not interfere with the importing country's national sovereignty.

Under this proposed legislation, penalties would apply only to the offending U.S. corporation and not to its foreign subsidiaries, which usually are considered "citizens" of the host country. It would have to be established initially that the U.S. corporation had "control" over the labeling of pharmaceutical products sold by the foreign subsidiary that had "mislabeled" a product. In the case of a corporation, control over the labeling standards could be presumed if there is a corporate policy that requires the foreign subsidiary to obtain approval for labeling from the parent corporation, or if there is evidence of corporate control as demonstrated by a majority equity ownership of the subsidiary, a shared Board of Directors, or some other indicator,

However, even indirect regulation of the actions of foreign subsidiaries may be seen as an encroachment on the sovereign right of developing nations to regulate the labeling of pharmaceuticals marketed within their borders, especially since most developing countries already exercise jurisdiction over pharmaceutical labeling. To address this concern, a company would be exempt from this law if it is affirmatively required to follow contrary national laws of the importing country.

The legislation may require a company that uses this exemption to provide evidence that it was required to follow contrary national laws. This might, however, put U.S. companies at a disadvantage when competing for pharmaceutical contracts in developing countries because the company would need a ruling on the issue by the developing country before it is able to submit a contract bid. The U.S. State Department would consult with developing countries before legislation is enacted and provide them with the option of being included in the legislation. This would also provide Congress with feedback on whether developing countries favored the legislation.

This legislation would, in some ways, be analogous to the Foreign Corrupt Practices Act (FCPA), which, with respect to bribery, requires that foreign operations of U.S. multinational corporations comply with the same standards for corporate behavior that govern domestic companies.

One significant difference between this legislation and the FCPA is that it would apply only to corporations and not to individuals. Penalties under the FCPA apply to U.S. citizens as well as

U.S. corporations. However, the rationale for applying civil or criminal penalties to citizens is more compelling under the FCPA than it would be under a drug labeling statute, because bribery is an act that may be perpetrated by one or several individuals. By contrast, labeling of pharmaceutical products is generally a matter of corporate policy, and it is unlikely that a single individual would be responsible for product labeling.

Another significant difference between this legislation and the FCPA is that under the FCPA, the United States is essentially assisting in the enforcement of antibribery acts, which already exist in most other countries. The labeling legislation, however, would require U.S. MNCs to include information beyond the minimum required by the local drug labeling authorities.

The agency charged with monitoring and enforcement of this legislation would logically be the FDA, or possibly the Federal Trade Commission, which has responsibilities in other areas of international regulation. A surveillance mechanism could be established by the responsible agency to review samples of labeling periodically. The legislation might also permit a private reporting mechanism (i.e., by private citizens, including public interest groups) to supplement agency efforts.

It might be argued that the cost of compliance with this legislation could put U.S. pharmaceutical manufacturers at a competitive disadvantage relative to other manufacturers. Any new requirement is likely to necessitate an internal review of current labeling, and companies would have to bear the cost of this review. Most companies would also have to print new packages and labels. These costs could be minimized by allowing a grace period for compliance.

Option 2: Endorse a voluntary international code of conduct for pharmaceutical labeling and press for adoption of the draft United Nations Code of Conduct for Translational Corporations.

Codes of conduct are voluntary agreements among nations, associations, or other entities to comply with certain standards of behavior. Codes of conduct among nations often address the behavior of MNCs as well, although MNCs are not legally bound by the codes because technically they are not parties to the agreements. Nevertheless, the codes can be used by host countries and consumer groups to pressure multinationals into voluntary compliance. In addition, codes of conduct may become the basis for national laws.

In the late 1970s and early 1980s, a WHO code of conduct for labeling of pharmaceuticals was debated in the World Health Assembly. By 1983, it was no longer on WHO's agenda, in part because of opposition by the U.S. Government to codes of conduct by WHO to control specific industries. Interest in a code maybe renewed, however. In addition to promoting expansion of the Ethical Criteria, the United States could take an active role in revitalizing the move toward an international code.

An international code of conduct would provide a universal standard for pharmaceutical labeling that would apply to manufacturers from every country and could be adopted into national legislation. Endorsement of a pharmaceutical code could be coupled with U.S. assistance to WHO or directly to developing countries to establish and maintain administrative and legal mechanisms to implement the scheme.

The code could also establish an international entity to provide interpretations of the code and to monitor its implementation. Such an entity would provide a locus for the exchange of information and debate between signatories. The entity could also serve as a place for public interest groups to report violations and exert pressure for change. It could also arbitrate between companies and those that allege violations of the code. As experience with the Breast-Milk Substitutes Marketing Code suggests, implementation of a labeling code could lead to education of officials, adoption of country-specific codes of conduct,

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adoption of legislation implementing provisions of the code, and public education on the issue.

This code of conduct would be the result of an agreement among nations, and would differ from the International Federation of Pharmaceutical Manufacturers Associations' (IFPMA) Code, which was established by agreement among the manufacturers associations themselves. Under the IFPMA Code, the IFPMA itself determines whether a violation has occurred.

Codes of conduct are usually very crude tools for addressing technical areas. A code might set general parameters for labeling, such as the categories of information to be included, but is unlikely to provide specific standards for judging the adequacy of information for each product. The amount of opposition mounted against making the Ethical Criteria stronger and more specific suggests that successful negotiation of a very specific code is unlikely.

The United States could press for adoption of the U.N. Code of Conduct for Translational Corporations (UNCCTC). This draft code instructs MNCs to go beyond the requirements of national law by disclosing complete information on product risks, through accurate and honest promotion of products, and through active participation in the development of consumer protection policies. If the UNCCTC is passed by the U.N. General Assembly, it could be used to pressure MNCs to properly label and promote their drugs sold in developing countries. The UNCCTC provides much less specific labeling standards than would a code that directly addresses drug labeling.

Option 3: Endorse strengthening and expanding WHO's "Ethical Criteria for Medicinal Drug Promotion" to set standards for pharmaceutical labeling.

In 1968, WHO adopted the "Ethical Criteria for Pharmaceutical Advertising." This document was revised and significantly expanded in 1988, and currently covers a number of areas of pharmaceutical promotion, including drug labeling. The new "Ethical Criteria for Medicinal Drug Promotion" (the Ethical Criteria) provide general guidelines for package inserts and drug labels, requiring that they comply with national laws, and if national laws are rudimentary, that they provide information consistent with that required by a more developed drug authority.

The Ethical Criteria also require that all text and illustrations on the drug package and label provide only reliable, truthful, informative, and current information, supported by scientific data. Pharmaceutical companies are instructed to refrain from using information that is likely to induce medically unjustifiable drug use or give rise to undue risks.

Guidelines are a weaker pronouncement of policy than codes of conduct and, to date, it appears that few developing countries have implemented the Ethical Criteria. At the 1992 World Health Assembly, WHO member countries agreed to endorse a collaborative meeting of WHO and the Council for International Organizations of Medical Sciences (CIOMS) to discuss strategies for further advancing the Ethical Criteria. The United States could support activities that could help developing countries implement the Ethical Criteria. In addition, more specific labeling guidelines could be supported.

Option 4: Continue to support and expand direct assistance to developing countries for projects to improve pharmaceutical regulation, and provide additional information on pharmaceuticals to regulatory authorities.

The FDA and USAID now provide some assistance to developing countries for improving pharmaceutical regulation and for other related activities. FDA currently provides limited information about its regulatory actions to developing countries. These efforts could be systematized and expanded.

The FDA could be required to provide drug regulatory authorities in developing countries with information about the pharmaceuticals approved by their agency, including information on

the safety and efficacy of approved drugs, and the approved U.S. labeling. This would apply to newly approved products and to products with amended labels. However, providing information alone may not be sufficient to improve pharmaceutical regulation in developing countries. Efforts must be made to improve the legal and technical drug regulatory infrastructure in developing countries so that the information provided can be used effectively.

Option 5: Mandate ongoing surveys of pharmaceutical labeling in developing countries.

Congress could designate an agency to conduct periodic surveys of pharmaceutical labeling in developing countries. The results of these surveys would be presented to Congress and could serve as a basis for further investigation and action. In addition, the results could be made public and would serve as a source of information about the status of drug labeling by U.S. pharmaceutical manufacturers in developing countries.

This option does not necessarily require that Congress charge a Federal agency with the responsibility for monitoring the pharmaceutical labeling situation in developing countries. Congress could require that a joint public-private commission, comprising pharmacists, FDA representatives, academics, consumers, and industry representatives, be appointed to conduct the surveys. By appointing a commission with diverse membership, the survey could give a measure of impartiality that may not be achieved by similar surveys conducted by consumer activist groups or by industry. The design of the surveys could be similar to that employed in this OTA study, with the selection of several countries for review, the selection of a sample of products, and an assessment of the adequacy of their labeling. Advertising and promotional material could also be studied.

Industry may object to the adverse publicity that is generated about U.S. manufacturers, which may place them at a disadvantage in international markets. To address this concern, the survey could also include an evaluation of the labeling of products manufactured by multinational pharmaceutical corporations of other countries and by domestic manufacturers in developing counties. However, such a survey could also be politically sensitive as other countries may oppose a U.S. Government sponsored audit of their pharmaceutical companies' labeling.

The difference between this option and previously listed options is that compliance with the labeling standards that are established is purely voluntarily, i.e., no criminal or civil penalties would attach to manufacturers whose products were found to have inadequate labeling. Motivation for improvement among manufacturers would be based on their concern about the safety of consumers, about adverse publicity that would arise from inadequacies in labeling that are discovered, and about the threat of further regulation, should Congress find this necessary.

One advantage of this option is that it avoids possible objections of the international community to the extraterritorial application of laws and resultant threats to national sovereignty. In addition, this option has no provision for criminal or civil penalties, so the burden of the judicial proceedings and trial-type administrative procedures that arise from enforcement of criminal or civil penalties would be avoided.