Drug Labeling in Developing Countries

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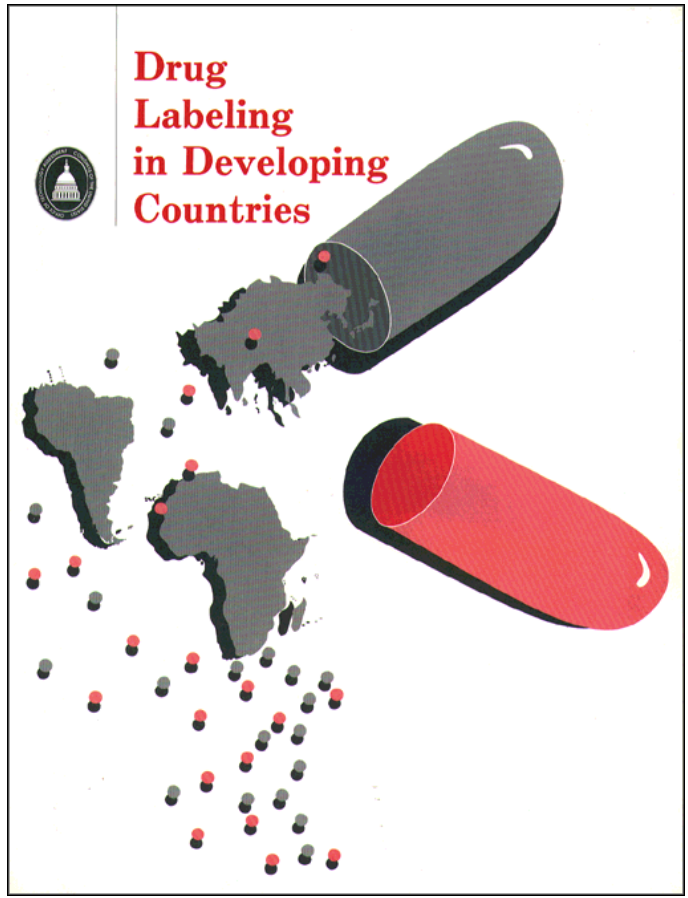

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Foreword

Pharmaceuticals developed in the latter part of this century have caused dramatic improvements in the quality of life for people around the globe. U.S. pharmaceutical companies can take credit for the largest number of new products and collectively maintain a share of the market larger than that of any other country. With this prominence comes the responsibility of informing the prescribers and consumers of pharmaceuticals of all the medically important information known about each one. In developing countries, where government resources to analyze and monitor drug labeling are severely constrained, companies operate with little oversight.

Prompted by the ethical imperative that U.S. pharmaceutical companies provide accurate and complete information with their products, and evidence from the past that they did not always do so, 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 M. Kennedy, then Ranking Minority Member and now Chairman of the Senate Committee on Labor and Human Resources, asked OTA to examine the status of drug labeling by U.S.-based multinational pharmaceutical companies in developing countries.

OTA developed a method for analyzing drug labeling, using a sample of several hundred labels from four developing countries-Brazil, Kenya, Panama, and Thailand. Unfortunately, serious problems were found. The policy options identified by OTA present Congress with possible ways to improve the situation.

The success of this project depended on a great deal of assistance to OTA. An Expert Working Group, which spent many days working with OTA staff, was key to the analytic process. The advisory panel, chaired by Dr. Bernard Mirkin, Professor of Pediatrics at Northwestern University Medical School, helped to guide the project. The cooperation and interaction with OTA of the 18 companies whose product labeling was evaluated was essential. Numerous individuals and organizations also provided information and assistance, including meeting with project staff in Kenya and Thailand and reviewing drafts of the report.

OTA is grateful for the contribution of each of these individuals and groups. As with all OTA reports, the final responsibility for the content of the assessment rests with OTA.



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NOTE: OTA appreciates and is grateful for the valuable assistance and thoughtful critiques provided by the advisory panel members. The panel does not, however, necessarily approve, disapprove, or endorse this report. OTA assumes full responsibility for the report and the accuracy of its contents.

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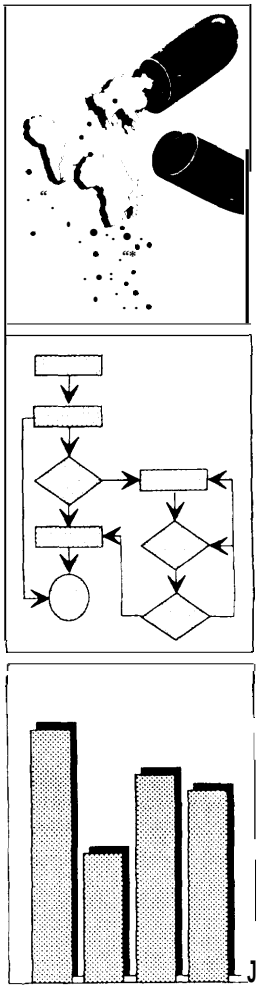

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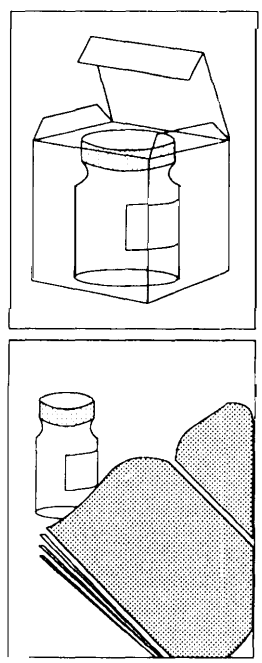


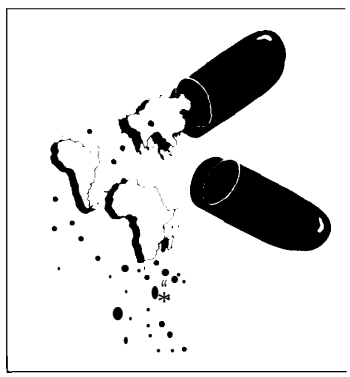
List of Abbreviations

ACE —angiotensin converting enzyme
AIDS —acquired immunodeficiency syndrome
AMA —American Medical Association
APED —Action Program on Essential Drugs (WHO)
BUKO —Federal Congress of Development Action Groups (Germany)
CIOMS —Council for International Organizations of Medical Sciences
DDA —Division of Drug Analysis (Thailand)
DEAC —Drug Export Act country
DESI —Drug Efficacy Study Implementation (FDA)
DHHS —Department of Health and Human Services
DIMED —Division of Drugs of the Ministry of Health (Brazil)
DIPROD-Division of Products (Brazil)
DMP —Drug Management and Policies (WHO)
EAA —Export Administration Act
FCPA —Foreign Corrupt Practices Act
FDA —Food and Drug Administration (DHHS)
FDCA —Food, Drug and Cosmetic Act
FR —Federal Register
GAO -General Accounting Office (U.S. Congress)
GATT -General Agreement on Tariffs and Trade
GPO -Governmental Pharmaceutical Organization (Thailand)
HAI —Health Action International
IAS —International Affairs Staff (FDA)
IBFAN —International Baby Food Action Network
ICI —Imperial Chemical Industries
ICJ —International Court of Justice (United Nations)
IEEPA —International Emergency Economic Powers Act
IFM —Infant Food Manufacturers
IFPMA —International Federation of Pharmaceutical Manufacturers Associations
ILO —International Labour Office (United Nations)
IMS —Index of Medical Specialties
IND —Investigational New Drug (FDA)
INN —international proprietary name
INRUD —International Network for the Rational Use of Drugs
IOCU —International Organization of Consumers Unions
IRB —Institutional Review Board
MaLAM-Medical Lobby for Appropriate Marketing
MIMS —Monthly Index of Medical Specialties
MNC —multinational corporation
MOPH —Ministry of Public Health (Thailand)
NAS —National Academy of Sciences
NATO —North Atlantic Treaty Organization
NDA —New Drug Application (FDA)
NIFAC —Nestle Infant Formula Audit Commission
OECD -Organization of Economic Co-operation and Development (United Nations)
OTA -Office of Technology Assessment (U.S. Congress)
OTC -over-the-counter
PAHO —Pan American Health Organization
PDR —Physicians' Desk Reference
PLM —Para los Medicos
PMA —Pharmaceutical Manufacturers Association
SEC -Securities and Exchange Commission
SMON —subacute myelo-optic neuropathy
SNVS —National Secretariat for Health Monitoring (Brazil)
TFDA —Thai Food and Drug Administration
UNCTC —United Nations Centre on Translational Corporations
UNICEF-United Nations Childrens Fund
USAID —United States Agency for International Development
USP DI —United States Pharmacopoeia Drug Information
WHO —World Health Organization (United Nations)

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

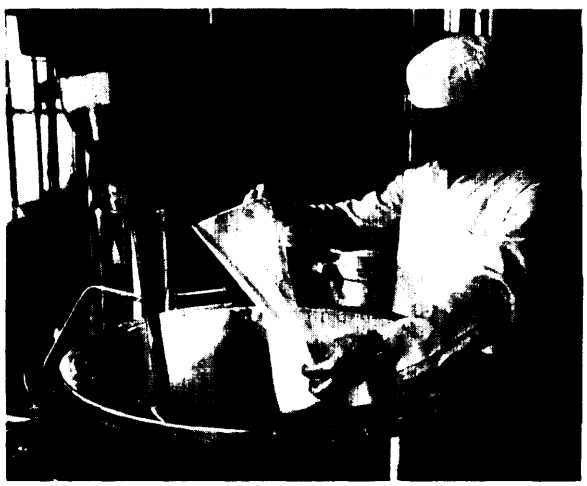


PHOTO CREDIT: P. MERCHEZ, WHO

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.

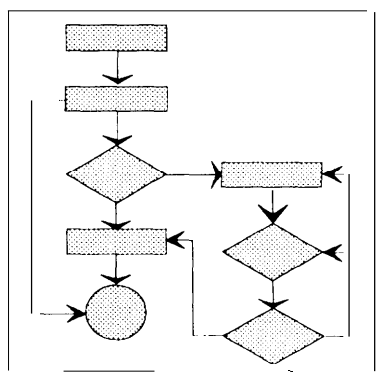
The OTA Survey and Evaluation Process 2

This study took a "snapshot" of drug labeling current between 1988 and 1990 and evaluated its medical appropriateness. Unlike previous drug labeling studies, which had approached the task by documenting problems with specific product labeling, OTA took a broader perspective and developed new methodology. This chapter describes the methods that were developed to select sample products, gather labeling material, and evaluate the information content of the labeling. The results of the analyses are presented in chapter 3.

SAMPLE SELECTION

Selection of Countries

The congressional requesters of this study stipulated that 8 countries be included from the 15 listed in their letter to OTA. OTA considered it important to represent different geographic areas and, to the extent possible, other country characteristics (e.g., level of development, cultural background). Panama and Brazil were selected for a pilot study based on OTA's judgment that they would be accessible for field visits and represented sizable markets for the products of U.S.-based pharmaceutical companies. As it turned out, it was not possible to arrange official visits to either country during the time of the pilot study. Product labeling was obtained from those countries, however, and procedures for evaluating the information were developed and tested.



In order to gauge the importance of field work to the project (visits to study countries were required by the request), a third country, Kenya, was chosen. Arrangements were made quickly for project staff to travel to Kenya in March 1988 for discussions with government, industry, and health sector representatives, and to collect labeling directly.

Experience with the evaluation process and the field visit made it clear that it would not be possible to carry out a thorough study in eight countries. The evaluation process is time-consuming and exacting of medical knowledge, both for OTA staff and for outside reviewers. Field visits require extensive planning and are expensive both in staff time and money. OTA therefore proposed to limit the study to four countries, including those already begun, adding one other in Southeast Asia, the other major market area. For reasons of market size and for the ease of conducting field work, Thailand was chosen. OTA staff visited Thailand in November 1989 to conduct interviews and collect labeling for a sample of products.

Identifying Relevant Companies

OTA identified the U.S.-based companies selling products in the study countries through the Pharmaceutical Manufacturers' Association (PMA). PMA was approached for this purpose after it had been determined that it was not possible to identify U.S.-based multinational pharmaceutical companies from any U.S. Government source, including the FDA and the Department of Commerce. In all, 19 companies were included. All are PMA members and are major research-based fins. Although it is possible that some companies were missed, based on examining prescribing guides and on scanning pharmacies for products, these 19 companies do account for the vast majority of U.S.-based pharmaceutical business in the study countries.

Selection of Sample Products

Over the course of the study, OTA asked each company to supply a complete list of their products marketed in Brazil, Kenya, Panama, and Thailand. Sampling of products for each country was carried out independently, and within each country, independent samples were drawn for each company. In total, 273 products were selected. The same sampling procedure was used for Panama and Brazil, and a slightly different one for Kenya and Thailand. Both procedures were designed to produce unbiased samples.

For Panama and Brazil, each company's complete list of products was first grouped by therapeutic category. The products within each category were alphabetized and numbered. Samples of between 20 and 25 percent of each company's products were selected by number within each therapeutic category using a random number generator.

For Kenya and Thailand, the lists of products were used as sampling frames in the order they were received from the companies. Again, samples of 20 to 25 percent were taken, using a "systematic sample." For each company, every fourth or fifth product listed was included. The companies had organized the lists in different ways, and OTA had specified no special order for them, so the systematic approach should not have introduced any bias.

No adjustments were made to the random or systematic samples to include or exclude specific products for any reason. No attempt was made to include "problem" products.

Throughout the course of the study and in this report, OTA has maintained as confidential the names of the sample products and the details of the evaluations. Only the Expert Review Group, OTA staff, and the companies themselves (each for their own products only) were privy to all the details. This was not done because the study involved privileged information, but because the particular products studied by OTA are a representative sample and do not themselves represent an important set of drugs.

OBTAINING PRODUCT LABELS

Early in the study, OTA asked the companies to send all labeling material (including packaging, package inserts, advertising, and promotional material) for all their products marketed in Panama and Brazil. This elicited a large volume of information, which was used to determine

what a reasonable sample size would be, and to examine the various types of material for their general content. Since there was no opportunity for field collection in Panama and Brazil, labels for the sampled products came directly from material submitted by the companies. Labeling material (packaging and inserts) for products in the Thailand and Kenya samples was obtained from pharmacies in those countries.

The original labeling sources were supplemented by the companies in response to queries sent to them after the original material (for Panama and Brazil, material provided by companies, and for Kenya and Thailand, the field-collected material) had been examined by the Expert Review Group (see below). Various updated inserts, inserts pending approval, and prescribing guide entries were submitted to OTA and these were used in subsequent analyses *providing they were in circulation or had been submitted to the country regulatory authority for approval at the time the Expert Review Group reviewed them. New* labels initiated after the relevant Expert Review Group workshop were not accepted for later review. This restriction was necessary because many changes were initiated by companies as a result of OTA'S initial queries. In a number of cases, companies sent their international product circulars, but these were not acceptable for the purposes of this study, as they would not be available routinely to practicing physicians.

OTA always evaluated the most comprehensive piece of labeling material that would be readily available to practicing physicians for each product in each country. Table 2-1 lists the information sources that were accepted for analysis, and each one is described briefly below.

Package Insert

Package inserts—fliers enclosed with each company-packaged bottle or box of product—generally contain more detailed information than other sources of labeling. In the United States, package inserts are virtually always included with over-the-counter (OTC) and prescription drugs. (See ch. 4 for the detailed requirements.) Their format is dictated by the U.S. Code of Federal Regulations, and their content must be approved by the FDA. Brazil, Kenya, and Thailand also require some type of package insert, but they are optional in Panama. In Thailand, many products contain both a Thai language and an English language insert, and others have English

Table 2-l—Sources of Labeling Material for OTA Analysis

Source	Description
Package insert pending approval	Insert submitted to local regulatory agency but not yet approved. Contains, on average, more complete information than insert then in current use.
Package insert	Fliers enclosed with each company-packaged bottle or box of product. Generally contains the most detailed information (when no new insert is pending approval).
Product label only	The composite of information printed on packages and bottle labels. Used only when no package insert was available.
Prescribing guide	A periodic publication distributed to physicians designed as a quick reference for availability y and prescribing information for pharmaceuticals. Used when no package insert was available.
Product datasheet	Also known as international product documents. This detailed source of product information is distributed to physicians and pharmacists by drug company representatives and is also available on request from the company.

SOURCE: Office of Technology Assessment, 1993.

or Thai inserts only. The Thai language inserts are often abridged compared with the English ones, so, when available, English inserts were used for analysis.

In some cases, companies informed OTA that they had submitted a request to the national drug regulatory authority for approval of updated labeling. In those cases, OTA asked the companies to document their claims, and when it was provided, the inserts pending approval were used for the analysis. In two instances, product documents were evaluated.[1]

Prescribing Guide Entries

Prescribing guides are periodic publications distributed to physicians in many countries, and often are the most readily available pharmaceutical reference. They are specific to individual countries or regions, and exist for each of the countries included in this study. The purpose of prescribing guides is stated by their publishers as being a quick reference to find out which drugs are available in a country or region and to provide brief prescribing information.

In most prescribing guides, general information about a class of drugs is given, followed by brief entries for each product in the class. A typical entry contains the trade name and generic name of the product, the manufacturer, a brief review of indications, contraindications, warnings, precautions, and dosing information, and a description of how the product is presented and packaged. The product-specific information is submitted to the publisher by the companies, but the publisher has editorial control, and may abridge the entry considerably. In this study, prescribing guide entries were used for just under half of the products from Panama and were also used as supplementary information when provided for drugs from Thailand and Brazil.

Package Labels and Boxes

When nothing else was available, the composite of information printed on packages and on bottle labels was used for analysis.

TRANSLATION OF FOREIGN LANGUAGE LABELING

All labeling to be evaluated from Panama and Brazil was translated into English by independent technical translators of Spanish and Portuguese, respectively, on contract to OTA. Labels from Kenya were all in English. Labels in Thai language were translated for OTA by a Thai pharmacy graduate student with English fluency. In a few cases, OTA asked the companies to provide translations from Thai.

THE LABELING EVALUATION PROCESS

The heart of the evaluation process was a review of the labels for "medically important" information by a group of outside experts. The sample drugs were discussed during the course of three 2-day meetings of this Expert Review Group. The "medical importance standard" was not applied by simply cataloging differences between the foreign labels and FDA-approved labels or some other standard. Each label was reviewed to determine whether it contained appropriate and sufficient information-essential medical information-for a physician to rely on to use the product safely and effectively. The process is described fully in the sections that follow.

Although details of each product evaluation are given in chapter 3, the products are not named, nor are the responsible companies or countries of sale. This presentation is meant to illustrate the nature of OTA's evaluation and rating system. Summary data from the sample are also presented in chapter 3.

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[1] At the beginning of the study, OTA agreed to evaluate the company product documents for two products that did not have package insert.% Later, however, OTA decided not to accept company product documents as a source of labeling for analysis be-cause product documents are not universally available to the physicians who use the product (they are often only available by request to the company or sometimes distributed by company detail men to physicians and pharmacists). Because OTA had previously agreed to evaluate the two product documents referred to, they remain in the analysis.

I OTA Preliminary Screen of Labels

OTA screened each label before the meeting at which it was to be discussed, as an aid to the Expert Review Group. The screen consisted of a section by section comparison of the sample label with some recognized standard, and the differences were listed on a summary form. Information is often organized differently on labels from different companies and in different counties, so the summaries were also useful in standardizing information groupings, regardless of where the information appeared on the foreign label. Labels were *not* considered divergent from the medical importance standard simply because information was organized differently, however.

The sources of comparison for screening are listed in table 2-2. For brandname products (or their components) available in the United States (or products with the same active ingredients), the *Physicians' Desk Reference* (PDR) (151) or the *Physicians' Desk Reference for Nonprescription Drugs (152) was* used as the reference. These annual volumes contain the complete FDA-approved labeling for most products sold in the United States; however, it is not mandatory that all products be included in the PDR volumes. One or a combination of other sources were used for products not included in the PDR, either because they are not sold in the United States or because entries for them did not appear in the PDR.

The screening summaries for each product were distributed to the Expert Review Group, along with the actual label (or translation) and a notation of the source used for the screen (less readily available sources, e.g., specific journal articles, were enclosed for the convenience of the members).

The Expert Review Group: First Review

The Expert Review Group consisted of academic and practicing physicians and pharmacologists and one physician consumer advocate (members are listed in the front of this report). All were highly qualified technically to make medical judgments on pharmaceutical information. It was OTA's intention to include technically qualified industry representatives in the group as well, but for legal reasons, this proved problematic for industry, so they chose not to be represented. The members listed all attended at least one meeting; about eight were present at each meeting.

Three 2-day meetings were held between 1988 and 1990 to review the sample labels. About 50

Table 2-2—References Used for Comparison With Sample Labeling

Source	Use in sample
Physicians' Desk Reference **(151)**	**Prescription drugs sold in the United States**
Physicians' Desk Reference for Nonprescription Drugs (152)	**OTC products sold in the United States**
Martingale: The Extra Pharmacopoeia **(184)**	**Drugs that are not approved for sale in the United States**
USP DI **(U.S. Pharmacopeial Convention) (247)**	**Commonly used generic products lacking full prescribing information in PDR.**
American Hospital Formulary Service **(8)**	**Generic products and products not available in the United States**
Goodman and Gilman's The Pharmacological Basis of Threrapeutics (75)	**Basic pharmacologic information.**
Search of medical literature	**Products with no other source of reference.**

SOURCE: Office of Technology Assessment, 1993.

products were reviewed each day. OTA's screening summaries were used as a guide, but discussion was not limited to the points mentioned in them, and the sources of comparison used by OTA were not considered "gold standards." Other references, from standard pharmacology textbooks (75) to specific journal articles, were referred to regularly during these meetings.

The standard of evaluation was "medical importance." The question OTA posed to the group was:

> Is the information provided on this label accurate and is it sufficient to allow a physician to use the product safely and effectively, given what we know about the drug from U.S. labeling and other sources?

The result was a focus on essential medical information, rather than a laundry list of all the "differences" between the foreign labels and either the U.S.-approved label or another comparison. In addition, each medically important deviation was given a relative importance ranking, which eventually was translated by OTA into a numerical ranking.

When the FDA-approved labeling was the screening source, there was general agreement that the *indications* listed were probably well supported, given FDA's strict standards of evidence. However, lack of an indication on the FDA-approved label was not taken as sufficient evidence that an additional indication on the sample label was inappropriate. Other references were often consulted to determine the evidence for and medical acceptability of "unlabeled indications" (see discussion in ch. 4). Most commonly used were the *USP DI (247),* AMA's *Drug Evaluations (7),* and *Drug Facts and Comparisons (46),* each of which routinely lists both labeled and unlabeled indications that are accepted by medical experts in the United States. Expert Review Group members were the final arbiters.

It was recognized by the Review Group and OTA that FDA-approved labeling contains a large number of warnings and precautions that represent rare cases, and may be of limited medical importance. When these were absent from foreign labels, they were not necessarily considered violations of the medical importance standard. Important divergences in warnings and precautions were identified only when the Review Group believed that their absence would hinder a physician's safe and effective use of the product, and might place a patient at undue risk.

After products were reviewed, each instance of a divergence from the medical importance standard, as determined jointly by the Expert Review Group and OTA staff, was formulated into a query to the manufacturer.

Queries to Companies

A summary query sheet was prepared for each product evaluated. If there were no divergences from the medical importance standard, a sheet was still prepared conveying that information, but not requiring a response. For the labels with divergences, queries were organized by category of labeling information. Companies were asked to provide justification or medical evidence to support the adequacy of the labeling as it existed, in relation to each query. The type of information to be submitted was left to the discretion of the companies.

It had been explained in correspondence with the companies that, except for issues requiring clarification, the request for information on the queries would not be reopened, so their responses should be as complete as possible. (OTA was to recant on this and allow further submissions late in the process. This is discussed later in this chapter.)

OTA Evaluation of Company Responses

Companies responded with varying degrees of completeness and with different types of infor-

mation (the types of responses received are described in table 2-3). The responses fell into two broad groupings: "evidence" and "explanations." Although some type of response was given for most queries, one company chose to respond to queries for only a "sample" of their products. Another company sent a list of general responses, and answered the queries with a numbered list of the general responses that applied in each case.

OTA evaluated each response using the criteria given in table 2-3. If the response provided sufficient justification for the existing labeling, or if the company indicated that a revised label had already been prepared that covered the point raised by OTA, the query was considered satisfied. (At the time of the first review for each product, OTA did not require documentary evidence that a revised label had been submitted to the foreign regulatory authority, but this was required later in the process, as discussed below.)

Many of the queries had referred to indications not appearing in the major references used by OTA, and which were considered inappropriate or questionable by the Expert Review Group. The issue in some cases was that the indications were overly broad or vague and might lead to inappropriate use of the product. In general, OTA required evidence from at least one adequately controlled, well-designed clinical trial as support for these additional indications. Submission of articles (or abstracts during the initial round of information seeking) or citations to articles describing the clinical trials were necessary for OTA to evaluate the studies and judge their acceptability as evidence. In some cases, however, companies stated that they had an application pending with the FDA to include the questioned indication on the U.S. labeling. OTA accepted those statements as adequate, as companies were deemed unlikely to go through the long and expensive application process without having carried out the necessary studies. Some of those applications would undoubtedly be approved, and some might be denied. OTA gave the benefit of the doubt to the companies that they did have evidence, and did not attempt to review submissions to FDA.

In many instances, companies stated that the questioned labeling had already been changed or that the changes were pending approval by the foreign drug authority. In some cases, companies

Table 2-3-Categories of Company Responses to OTA Queries

Explanations
- Product is no longer sold by this manufacturer.
- Other manufacturers have similar labeling for this product.
- OTA has misinterpreted information on the label.
- Inclusion of the requested information will be misleading or confusing to patients or practitioners.
- The local regulatory agency will not allow the requested information to be included on the label.
- This information is presented in datasheets that are distributed separate from the product, is included in a drug manual or prescribing guide, or is sent to physicians who request it.
- The information omitted is common medical knowledge.
- The questioned information appears in the label.
- OTA has not correctly translated the label or insert.
- The company will make or consider making the requested changes.
- The local regulatory agency has approved the labeling.
- The labeling complies with local practice customs.
- Regulatory agencies from sophisticated countries have approved the questioned labeling.
- The requested information has been approved for labeling for the same or a similar product marketed in the United States.
- The requested changes are pending with the local regulatory agency.
- The requested information is included in the current product insert (which supersedes the one reviewed by OTA).
- The requested changes are unnecessary for reasons other than noted above.

Evidence
- The questioned indication or lack of warning/adverse reaction/contraindication/precaution is supported by the data.
- The company cited U.S. FDA application materials for this indication.
- The company submitted results from controlled clinical trials as support for an indication.
- The company claimed that certain labeling was supported by studies in uncited literature.
- The company cited anecdotal evidence as support for an indication.
- The company provided support for indications with opinions of medical experts.
- The company provided abstracts of relevant studies as evidence.
- The company provided support with in vivo and in vitro experiments in animal models.
- The foreign labeling includes "unlabeled" indications that are widely accepted in the U.S. but the manufacturer has not obtained formal FDA approval.

SOURCE: Office of Technology Asssessment, 1993.

enclosed the revised labeling, but in many cases, they did not. If the changes had been made or were in process at the time the Expert Review Group had evaluated the particular product, OTA accepted these statements as sufficient evidence to dismiss the query, even if documentation was not included. Documentation for these instances was later sought, however (see below, *Provision of Scoring Sheets to Companies).*

OTA Scoring of Labels

After all company submissions had been evaluated, those queries that had been justified by data or explanations were eliminated from further consideration. The remaining unsatisfied queries formed the basis for calculating a "score" for each product. The scoring system was three-tiered: first, each individual unresolved query was assigned a score based on its seriousness; second, each information category was assigned a score; and third, an overall score for the product was calculated. All aspects of scoring are discussed here and shown in table 2-4.

Table 2-4-Scoring OTA Survey Drugs

Category scores (derived from scores for Individual queries)

score code	Definition
N/A	Not applicable (drug excluded from consideration)
—	No queries in category
0	All queries in category resolved
1	At least one query rated 1; no query rated 2
2	At least one query rated 2
R	Score of R (or 1) in "INGREDIENT' category specifically for failure to list inactive ingredients

Overall scores (derived from category scores)

score code	Definition
N/A	Not applicable (drug excluded from consideration)
0	No queries or all queries resolved
O/R	INGREDIENT Score = R; all other category scores = O
1	Score of 1 in one or more category; no category with score of 2
2	Score of 2 in one category only
3	Score of 2 in two or more categories

SOURCE: Offices of Technology Assessment, 1993.

Individual queries were assigned scores of "l" or "2," representing lesser or greater divergence from the medical importance standard. A score of 2 was generally defined as one for which there was:

> a substantial likelihood that a practitioner relying on the information would use the drug in a manner that could result in nontrivial harm to a substantial proportion of users or severe harm or death to some users.

All unsatisfied queries not fulfilling the criteria for a score of 2 were assigned a score of 1. Overall scores were calculated byexamining the individual query scores *by category of labeling information.*

For clarity, it should be noted that more than one divergence from the standard in a single category (e.g., two medically important adverse reactions missing) did not carry more weight than would one divergence in that category. This allowed OTA somewhat more freedom in stating the queries in the most concise manner. In some cases, similar divergences were grouped together within a category to avoid repeating the same phrase for each one. Whether these would be considered one or several divergences in the scoring was not important because scoring took into account the entire category, rather than the individual queries within each category.

PROVISION OF SCORING SHEETS TO COMPANIES

OTA sent each company the score sheets for their own products. These sheets included all the original queries, with a summary of OTA's evaluation of the evidence that had been submitted on each point. Scores for each remaining unsatisfied query and the overall scores were indicated.

OTA had informed the companies originally that there would not be a second opportunity to respond to the queries, and the scoring sheets were being provided for their information only. A number of companies and members of the Advisory Panel urged OTA to consider additional information submitted by the companies; for a

variety of reasons, complete information had not been submitted during the initial rounds.

In the interest of fairness and completeness, OTA invited the companies to submit additional information on the queries still remaining. Companies were asked to limit their submissions to information available at the time of the Expert Review Group meeting at which the particular product labeling was evaluated (e.g., a labeling change that had been made after OTA's initial review would not be accepted to satisfy the query). OTA also took the opportunity to request documentation for certain statements made in the companies' original responses. Table 2-5 lists the items for which documentation was requested, and the type of material that would be accepted.

This request to the companies also allowed OTA to gather information for an analysis recommended by the Advisory Panel and certain companies. There was some concern that OTA's standard (the "medical importance" standard) was an inappropriate one for products shipped to developing countries from developed countries, mainly European countries, other than the United States. The general feeling was that OTA should take into account the fact that labels rated deficient by OTA's standards might well be identical

Table 2-5-Responses for Which Documentation was Requested

Company response	Requested documentation
The company has applied for changes in labeling with the relevant regulatory authority.	Must be accompanied by dated documentary evidence. Official correspondence with the regulatory authority is acceptable.
The questioned information appears in the labeling pending approval.	The pending labeling must be submitted.
More complete labeling superseded the labeling that OTA reviewed.	Must be accompanied by a dated copy of that labeling, The label must be dated before the evaluation date indicated on the product evaluation sheets.
The questioned information appears in the superseding labeling.	The superseding labeling must be submitted.
The questioned information appears in the labeling that OTA reviewed.	Must be accompanied by a copy of the labeling.
A claim that the local regulatory authority has not required certain labeling.	This is sufficient justification for a deficiency if the manufacturer documents that the regulatory authority rejected more appropriate language. If the local regulatory authorities have devised standard package inserts for certain products, documentation must be provided that these standard inserts are mandated by local health authorities.
Particular labeling is approved in the developed country that the product is exported from.	Must be accompanied by the foreign label from that country accompanied by translation if the original is not in English. (OTA evaluation will still be based on the medical importance standard, however.)
Any questioned indications.	OTA will accept indications supported by adequately controlled clinical trials (excepting only a disease with a well known natural history, where there is evidence that a therapy consistently alters the natural history of that disease).

NOTE: If documentation was not provided, OTA relied on the label reviewed originally. OTA requested that copies of all studies cited for support be submitted, non-English studies translated into English, FDA submissions cited for support provided in summary form, and unpublished data include a clear statement of the study design and a summary of the findings.

SOURCE: Office of Technology Assessment, 1993.

to the approved labels in the developed countries of export.

It was agreed that a subsidiary analysis would be carried out on this point. OTA, therefore, asked companies to submit the approved labeling from the exporting countries for products in the sample. (In the end, this analysis was not carried out because companies did not submit the material, though one did a different subsidiary analysis, which is discussed in ch. 3.)

The new material submitted by the companies was evaluated using the same standards described earlier, and scores adjusted as appropriate. It *was only possible for scores to improve based on new information, except in cases where companies failed to document previous statements.*

Review of OTA Scoring by Expert Review Group

OTA did not routinely seek the advice of the Expert Review Group in evaluating evidence submitted by the companies. In most cases, the evidence either clearly did or did not respond adequately to the queries. The experts were consulted on an ad hoc basis, according to OTA's needs. Initially, therefore, they did not review OTA's scoring.

At the urging of the companies and members of the Advisory Panel, a subgroup of the Expert Review Group met to review the criteria for scoring and the scores themselves, based on the first submissions of the companies. The four members of the Expert Review Group who also served on the Advisory Panel constituted the subgroup, and they were joined by the Advisory Panel chairman, who had not been present at previous Expert Review Group meetings.

In nearly all cases, the Subgroup affirmed OTA's judgments. However, they believed OTA to have been lenient in its judgments, giving the benefit of the doubt to the companies in many more cases than they themselves were willing to do. Consequently, they recommended some changes in the original scoring. The changes were due to the Subgroup rating the absence of certain types of information (mainly adverse reactions) as more medically serious than had OTA. Of the 66 products to which OTA had given an overall score of 3 (greatest divergence from standard), it was recommended that 3 be considered less serious, lowering the scores to 2. Of the 66 originally scored as 2, they recommended lowering scores for 3 to less serious categories and raising 11 products to 3s. Of the 61 initially rated as 1, they recommended lowering 1 to a less serious category and raising 13 to a more serious one. Of the 39 products OTA rated as O initially, no changes were proposed. (The final figures reported in ch. 3 are different from these because they reflect the company's "additional responses." In the end, 59 products, rather than 74, were rated 3.)

By the time of the Subgroup meeting, OTA had already sent the companies evaluation sheets for their additional responses. In the cases where scores had been raised for individual queries from O (OTA's original evaluation) to 1 or 2 based on the Subgroup evaluation, revised evaluations were sent to the companies.

Provision of Summary Sheets to Companies for Additional Responses

In November 1991, the updated summary sheets were provided to the companies for their additional responses, which were received over the next several months. A massive amount of information was submitted by the companies overall, responding much more fully to the queries than they had originally. OTA staff analyzed the new information and rescored all the products. As a whole, the scores improved as a result of the additional responses. In a few cases they were worse, mainly because companies had originally stated that labels had been changed, or that applications for changes had been filed with the country regulatory authority, but the company failed to document these claims in the additional re-

sponse period. Table 2-6 shows the distribution of interim and revised overall scores.

Analysis of Final Results

The results of the evaluation process are presented in chapter 3. All discussion and presentation of scores, both for individual points and products overall refer to the final evaluations, after the material submitted by the companies during both rounds of review had been evaluated and queries were either resolved or not.

Table 2-6—Distribution of Interim and Final Scores

Overall score	Interim score count	Final score count
0	59	78
1	61	42
2	59	63
3	63	59
Not evaluated	31	31
Total	273	273

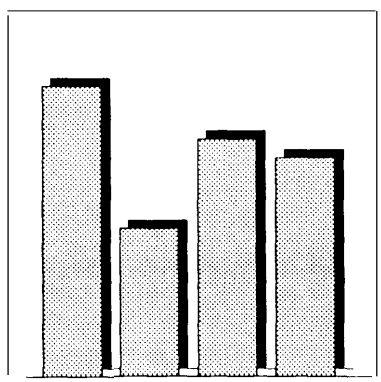
NOTE: Interim versus final scares were not cross tabulated, so this table cannot be used to determine how many scores changed during the process.

SOURCE: Office of Technology Assessment, 1993.

Results of the OTA Survey 3

The results presented here emerged from the process described in chapter 2. Quantitative results based on the product scores give a general picture of the quality of information found, but the detail behind the scores brings them into clearer focus. Detailed tables (addenda 3-1 to 3-6) at the end of this chapter catalogue every divergence from the medical importance standard that OTA scored for each of the products, but does so using only the type of drug as an identifier, and not the name. The rest of this chapter describes the types of problem encountered and gives quantitative results by section of the label, by overall scores, by company, and by country. Also included is an analysis provided by one of the survey companies, pitting OTA's evaluation against labeling in other industrialized countries; and an OTA analysis comparing our own evaluation against the information included in World Health Organization (WHO) monographs of drug prescribing information.

QUALITATIVE RESULTS: ADDENDA



The particular products evaluated in the survey are not listed by name in this report. These drugs constitute a representative *sample* and were not singled out as being potentially problematic; by themselves, they do not constitute a meaningful universe for action. It was realized, however, that with no detail on the types of divergences from OTA's standard that contributed to the scores and the results in general, it would be difficult to judge the fairness and consistency of the OTA process. To remedy this, the addenda to this chapter consist of tables listing each product, identified by therapeutic class and type of drug (where appropriate), and the divergences that contributed to its score. Illustrations are drawn from the addenda in the discussion that fol-

lows, but readers are encouraged to delve into the tables themselves to understand the nature of the OTA analysis, which cannot be judged adequately on the basis of numeric scores and averages.

QUANTITATIVE RESULTS

Overall Analysis

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 rest were scored, as described in chapter 2, taking into account all the information the companies sent in response to OTA queries.

The scale for *overall scores* ranges from O to 3, with O signifying no important divergence from OTA's medical importance standard, and 3 signifying the **greatest** divergence. Labeling was assigned an overall score of 3 if two or more sections of labeling information were found to have the most medically serious divergence scores. (The scoring system is explained in detail in ch. 2.) The overall scores use the FDA-approved labeling as **a ceiling.** This means that labels were never held to a higher standard than what is required by FDA in U.S. labels.

Table 3-l-Summary of Overall Scores

Overall score	Number of products (%)
o	78 (32%)
1	40 (17%)
2	64 (27%)
3	59(24%)
All fully evaluated	241 (1 00%)
Not fully evaluated	32
Total in original sample	273

Degree of divergence from medical importance standard:
O: 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= O or 1
3: At least two category scores. 2

NOTE: See text for details of scoring.

SOURCE: Office of Technology Assessment, 1993.

In this analysis, about half the products had labels that were either completely in accord with OTA's medical importance standard, a score of O, 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 3-l).

Analysis by Category of Labeling Information

INTRODUCTION

The sections listed below, which OTA used to categorize divergences from the medical importance standard, were adopted from the U.S. label format as a matter of convenience. Labels from other countries, developed and developing, are organized differently, and OTA did not require that specific items of information appear in the sample labels in sections of the same name. The labels were evaluated as whole entities, and the appearance of the appropriate information, as judged against the medical importance standard, was all that was required, regardless of the label's organization.

The scale for category scores ranges from O (no divergence) to 2 (the most serious category of divergence). The numbers and percentages reported in each section, below, and in table 3-2, 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 clinical pharmacology* sections of the labels, most of them (45) rated 1, and 6 rated 2. The most common 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).

For example, a manufacturer of an antihistamine did not provide information about the half-life of the product, even though the half-life was particularly long (l-2 weeks).

INGREDIENTS

The *ingredients* section contributed to a divergence in the final scores in only four cases. This

contrasts markedly with OTA's interim scores, in which the lack of an inert (inactive) ingredient list was scored as an unsatisfied query. In the final analysis, lack of an inert ingredient list did *not* contribute to overall divergent scores, except in the few cases where a particular inert ingredient was known to be particularly sensitizing. A specific exception is failure to note alcohol as an ingredient of drugs that might be given to children, in whom even small amounts may cause serious adverse reactions, including central nervous system depression and seizures. For all the rest, lack of inert ingredient lists elicited a score of "R," which was tracked separate from the rest of the scores. In all, 17 of the products with a primary score of O lacked inert ingredient lists (scored "R"), as did 57 (24%) of those with scores of 1, 2, or 3. The "R" itself did not contribute to the score, however.

OTA and the Expert Review Group did consider it medically important to include a list of inert ingredients, and, in fact, all manufacturers in the OTA survey list them voluntarily on U.S. labels. By regulation, they are required to list inert ingredients only for injectable products, and to note the presence of only a small number of specific ingredients in oral products. In the past, countries of the European Community have not required a complete listing, but this is changing with the new harmonization efforts, and inert ingredient lists will be required. Japan first required inert ingredient disclosure for injectable drugs and those applied to mucous membranes in 1988. For drugs for internal use, however, listing is required only for particular ingredients. An independent drug bulletin in Japan has, however, assembled a database of all inert ingredients for about 6,000 products. Sales of the database are reported to be good (18).

These developments suggest that it is medically important for physicians to know what nonpharmacologic ingredients are in the preparations they prescribe. Nearly one-third of the labels evaluated by OTA lacked this information.

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. These scores resulted from:

1. indications that did not appear in the U.S. label or 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.

Table 3-2—Summary of Category Scores

Category score	DCP	ING	IND	CI	WP	AR	DA	OD
1	45 (19%)	1 (O%)	20 (8%)	12 (5%)	49 (20%)	25 (10%)	17 (7%)	8 (3%)
2	6 (2°/0)	3 (1%)	43 (18%)	15 (6°/0)	79 (33$40)	37 (15%)	11 (5%)	37 (15%)
R		74 (31 %)						

Categories:
DCP = Description/Clinical Pharmacology
ING = Ingredients
IND - Indications
- 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.

In the first situation, the Expert Review Group and OTA recognized that products are used and effective for some indications other than those approved by FDA, so the mere fact that an indication did not appear on the FDA-approved label did *not* automatically call it into question. For example, OTA accepted the indication of a beta-blocker for prophylaxis of migraine headache, even though it is not an indication on the FDA-approved label. OTA did not however, accept the indication of an androgenic steroid in frigidity therapy, in menopause, as therapy for benign mammary disturbances, or in suppression of lactation.

The second situation, vague or general indications, is illustrated by an injectable corticosteroid indicated for "arthritis in general" and "dermatitis in general" with no qualification.

The third type of divergence was failure to note that the product, although effective for a specific indication, was not the drug of choice. For example, an antidiarrheal combination with an aminoglycoside antibiotic did not note that oral dehydration therapy is considered first-line treatment for childhood diarrhea. This information is particularly important for drugs with relatively more common or more severe adverse effects compared with other choices, or which are less effective than alternatives, In general, labeling was considered deficient if it failed to note when a product was not first-line therapy. However, if the manufacturer provided some justification and supporting evidence for first-line use, it was accepted, even if it did not agree with U.S. labeling or other reference information.

CONTRAINDICATIONS

Contraindications diverged from the medical importance standard for 27 labels (11 percent), including 15 rated 2, the most serious category. Contraindications describe situations in which a drug should not be used because, for one reason or another, the risks of taking it are likely to outweigh the benefits. The reasons include:

1. the patient has another medical condition that could be made worse by the drug (e.g., failure to contraindicate an anthelminthic known to induce seizures in patients with epilepsy);
2. the patient is taking another drug known to interact with the product in an unacceptable way (e.g., failure to contraindicate the use of a monoamine oxidase inhibitor with the antidepressant fluoxetine);
3. the drug may harm a fetus in a pregnant woman (e.g., failure to contraindicate use of an androgenic steroid in pregnancy) or pass through a nursing mother's breast milk, potentially harming the child;
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; and
5. the patient has known sensitivity to the drug itself or related products.

There is some disagreement about the last point, the need to contraindicate a drug specifically for hypersensitivity to the drug itself or to the class of drugs. Some people consider this self-evident. Silverman, Lydecker, and Lee, in their recent book, *Bad Medicine: The Prescription Drug Industry in the Third World (212),* comment:

> No attention is paid hereto statements that a particular agent is contraindicated in patients who may be allergic or hypersensitive to that product or related substances—advice that would be as useless and irritating as a warning that "this drug should not be used by a patient who should not use it. "

This view is not held universally, however. The WHO monographs of prescribing information, which are relatively brief, and were developed by a consensual process, do contain these statements, where appropriate.

In OTA's survey, five of the divergence scores in contraindications were for failure to mention

hypersensitivity to the product itself (in two cases, this was the only problem in contraindications, and in three, there was at least one other); and in two cases, the score was given for failure to contraindicate for hypersensitivity to the drug class (in one case, this was the only problem; in the other, it was one of several). Five labels had unresolved queries for having no contraindication section at all, and presumably, some of those might have specified hypersensitivity as a problem.

WARNINGS AND PRECAUTIONS

The greatest number of problems, and the greatest number rating a 2, was found in *warnings and precautions* sections. More than half the labels (128) evaluated 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 that divergences were common 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 about 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 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.

Specific problems in warnings and precautions include:

- an antiepileptic that failed to warn about the increased risk of fatal hepatotoxicity in children under 2 years of age;
- a magnesium-containing antacid indicated for infant feedings "to prevent milk from souring and forming curds in the stomach" that did not warn about the risk of hypermagnesemia in infants from chronic administration;
- an antihypertensive that stated that hypotension is an "infrequent secondary reaction," whereas in the United States, hypotension is not considered infrequent, and potentially serious consequences of hypotension are noted in the labeling;
- an antihypertensive known to increase blood sugar levels that did not include information about appropriate use in diabetic patients; and
- an antihypertensive that failed to warn about interactions with other drugs, most notably other antihypertensive medications, which may lead to additive or synergistic effects in decreasing blood pressure.

ADVERSE REACTIONS

Widespread divergences were also noted in *adverse reactions* sections of the labels. Just over a quarter (62) had unresolved queries, of which 37 (59 percent) were rated 2, the most serious category. Adverse reactions noted as absent ranged from some that are possibly worrisome to patients though not medically serious (e.g., discoloration of urine or other body fluids) to life threatening (e.g., agranulocytosis, the complete absence of a type of blood cell; and Stevens-Johnson syndrome, an extremely severe skin manifestation), 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 the seriousness of it was not conveyed. In one case, for example, granulo-

cytopenia-low numbers of blood cells known as granulocytes-was listed, but the product had, in rare cases, caused agranulocytosis, the complete absence of these cells, a potentially fatal condition. The company argued that the distinction was not essential, as physicians know the relationship between the two conditions. OTA, however, scored this and other similar instances as divergences, either a score or 1 or 2, depending on the seriousness of the reaction.

DOSAGE AND ADMINISTRATION (EXCLUDING OVERDOSAGE)

Most problems in *dosage and administration* had to do with regimens that included 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 and other material supplied by the companies. 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 maximum 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 for its management was common. Forty-five (19 percent) 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 (score of 2) if there were specific measures, as opposed to just general monitoring and supportive measures, recommended for treatment of the overdose. An example was a combination phenothiazine antipsy chotic and tricyclic antidepressant that did not include detailed information on the symptoms and management of overdose.

I Analysis by Company and Country

ANALYSIS BY COMPANY

The number of fully evaluated products (out of 241) per company ranged from 4 to 25, reflecting in part the number of products each company sells in the sample countries, and also the varying number of products not evaluated. OTA calculated average overall 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, including one with a score of O, and two were more than 2. For the reasons discussed below, it was not considered appropriate to rank companies by their scores.

In general, the samples sizes for individual companies are not large enough to sustain rigorous statistical manipulation, particularly because most of the scores fall into a relatively small range.

A major factor affecting company scores is the mix of products in the OTA sample. Many companies emphasize products for one or several clinical conditions, so their products tend to clump in particular therapeutic categories. 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 berated as 3, diverging greatly from the medical importance standard, regardless of the labeling. Products fitting this description do, in fact, dominate in the sample from the company with the lowest overall score and form varying proportions of other company's products.

ANALYSIS BY COUNTRY

The average overall scores for the four 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 With Other Industrialized Countries

Several survey companies criticized OTA's medical importance standard for adopting a U.S. perspective on labeling, to the exclusion of established standards in other industrialized countries. This is true in that FDA-approved labeling was used as a guide for evaluating sample labeling and that labels were not held to a standard higher than FDA requirements, OTA also required evidence of efficacy from formal clinical trials for questioned indications and documentation to justify the omission of warnings, adverse reactions, etc., that do appear in U.S. labels, so in this sense, the medical importance standard borrows from FDA standards of evidence.

Some companies believed the OTA standard to be particularly inappropriate when the sample label was based directly on labeling from the country of export. They stated their belief that it is important to consider European country labeling because former colonies have often patterned their drug regulatory systems after their colonizers. Some companies noted that, from a business perspective, it may be most practical to include the export country's label.

OTA recognizes that labels in other industrialized countries often contain different information from their U.S. equivalents. Some of the reasons for these differences are discussed in chapter 4, having to do with the history of drug regulation in different countries. In view of these concerns, OTA asked the companies to indicate the country of export for each sample product and to provide sample labeling from the exporting country so that a direct comparison could be made. No company responded systematically to this request.

One company did respond, however, by comparing OTA's interim evaluations against labeling for the same or similar products in each of the 21 countries named in the Drug Export Act of 1986 (see ch. 4 for a discussion of the Act) and documenting the labeling from those countries. During the final draft review, 16 other companies conducted similar analyses, which they provided to the Pharmaceutical Manufacturers Association (PMA) and which were included in PMA's comments to OTA. The PMA comments contained only the companies summaries of the comparison, and not the corroborating labeling from the other countries, so it was not possible for OTA to fully evaluate those analyses. These latter results are not discussed in this report, but the analysis of the first company is presented in detail in table 3-3 and summarized below.

The 21 countries included in the one company's "composite standard" are cited in the Drug Export Act as having regulatory systems adequate to allow the export to them of drugs not yet approved in the United States. The company takes this a step further, reasoning that Congress should then accept labeling from any of those countries as being adequate in developing countries (although his conclusion is not supported by the legislative history of the Act).

The company analysis took each *unsatisfied query* that OTA had scored 1 or 2 and checked the labeling of the 21 Drug Export Act countries (DEACs) to see whether they were similar to the original survey country label on the point OTA had questioned. If they found a correspondence in at least one of the 21 countries, they considered OTA's score invalid and rescored the query as O. They then retallied the overall scores.[1]

Nineteen of the company's products had been included in the survey and of those, 10 received *interim overall scores* of 1, 2, or 3; the rest scored O (no medically important divergences from the OTA standard). The company conducted their analysis on these 10 products. For two of them,

[1] The company was working with OTA'S *interim* evaluations. The material they submitted during their second opportunity to supply information resulted in changes reflected in OTA'S final scores. These instances are noted in table 3-3. The changes made by OTA occurred only in response to *medical evidence* supporting the original label, not the mere correspondence of the sample label to a label in a third country.

Table 3-3-Company Comparison of OTA Evaluation With Labeling in DEAC Countries

Product type	OTA Interim evaluation: divergence from standard	Company reevaluation	OTA final evacuation
Nonsteroidal anti-Inf lammatory drug	indication for pain and fever associated with acute respiratory tract inflammation. (IQS = 2)	indication accepted in Finland and Japan and for "competitor products" in several other countries. (CQS = O)	Company provided insufficient medical evidence to support efficacy for this indication. (FQS = 2)
	Labeling recommends a higher dosage than approved in U.S.(IQS = 2)	Higher dosage approved in 16 other countries. (CQS = O)	Company documented safety and efficacy of higher dose. (FQS = O)
Overall scorn	*OTA Interim score* = 3	*Company rescore = O*	*OTA final score*= 2
Nonsteroidal anti-inflammatory drug	Overly broad indication for conditions "requiring anti-inflammatory and/or analgesic activity, such as rheumatoid arthritis. . ."'(IQS= 2)	**Company stated that all labeling for this product contains specific indication state-'rents. Because specific conditions are mentioned, indication cannot be considered over-iy broad. (CQS = O)	Specific conditions are given in the nature of examples, not delimiting the appropriate use of the-product. (FQS =2)
	Labeling recommends a higher dosage than approved in U.S. (IQS =2)	Higher dosage is approved in 17 other countries. (CQS _O)	Company documented safety and efficacy of higher dose. (FQS = O)
Overall score	*OTA interim score = 3*	*Company rescore = O*	*OTA final score= 3t*
Asthma drug	No information on signs and treatment of overdosage. (IQS = 2*)	information not included in labeling in 2 comparison countries in which drug is marketed. (CQS = O)	This information is not required by FDA. (FQS = O)
Overall Score	*OTA interim score = 2*	*Company rescore = O*	*OTA final score= O*
Oral hypoglycemic agent	Labeling does not state that product is considered second-line treatment for one indication. (IQS = 1)	information not included in 10 of 17 countries in which drug is marketed. (CQS = O)	The company provided no medical evidence to modify this evaluation. (FQS = 1)
	No contraindication in patients with history of hypersensitivity. (IQS = 1)	Company agreed with this evaluation. (CQS = 1)	No change in OTA evaluation. (FQS . 1)
	No warning about increased cardiovascular mortality associated with this type of drug. (IQS = 2)	Labels in 15 other countries do not have this warning. (CQS = O)	OTA accepted company's additional argument that the study on which this warning is based is controversial and its results not widely accepted. (FQS. O)
	No information about use during pregnancy or by nursing mothers. (IQS = 1)	Company agreed with this evaluation, (CQS = 1)	No change in OTA evaluation. (FQS = 1)
	No warning about possible loss of blood glucose control when used with certain other drugs. (IQS = 2)	Company agreed with part of this evacuation, but not with mention of one specific drug. (CQS = 2)	No change in OTA evacuation. (FQS = 2)

	No advice about dosages for patients with impaired hepatic or renal function. (IQS = 2)	Company agreed with this evaluation. (CQS = 2)	No change in OTA evaluation. (FQS = 2)
	No information about safety and efficacy of another drug when used with this product. (IQS = 1)	Company agreed with this evaluation. (CQS = 1)	No change in OTA evaluation. (FQS = 1)
Overall *score*	***OTA interim score = 2***	***Company rescore = 2***	***OTA final score= 2***
Antibiotic	No susceptibility testing information. (IQS = 1)	Information not included in 9 of 12 countries in which drug is marketed. (CQS = O)	OTA accepted company's additional contention that sufficient information is included in label. (FQS = O)
Overall score	***OTA interim score = 1***	***Company rescore = O***	***OTA final score= O***
Antinausea antihistamine combination product	No rationale for the combination. (IQS = 1)	Product not marketed in U.S. or other DE-ACs. Company states that "comparable products" with similar labeling are available in 5 countries. (CQS = O)	Company provided no medical evidence that combination was more effective than any single ingredient. (FQS = 1)
	Indication for pyloric spasm and infant colic. (IQS = 2)	● *Company agreed with OTA evaluation but not with score of 2. (CQS = 1)	Company provided some evidence of efficacy in infant colic, but not for pyloric spasm. (FQS = 2)
	Indication for all types of vertigo, including vertigo of vestibular origin. (IQS = 1)	Indication appears in labeling for 1 component in 1 DEAC. (CQS = O)	Company provided evidence of efficacy in vertigo of vestibular origin. (FQS = O)
	No warning about use of product: a) with alcohol orb) by children under 12 years. (IQS = 2)	Labels in one DEAC and in other countries for "comparable products" do not include these warnings. (CQS = O)	Company provided no medical rationale for not including these warnings. (FQS = 2)
	No warning that antihistamines can cause excitability in children. (IQS = 1)	Labels in one DEAC and in other countries for''comparable products" do not include this warning. (CQS = O)	Company provided no medical rationale for not including this warning. (FQS = 1)
	Dosage recommendations for children (OTA requested evidence of safety and efficacy). (IQS = 2)	Dosage recommendations for children are similar to those in some DEACs. (CQS = O)	OTA found that dosages for children were significantly higher than in other countries, according to material supplied by company. However, this was rescored to O because it addresses the same concern as the warning about use in children under 12, above. (FQS = O)
	No information on signs and treatment of overdose. (IQS = 2*)	● *Company pointed out that FDA-approved labeling does not include this information. (CQS = O)	This information is not required by FDA. (FQS = O)
Overall score	***OTA interim score = 3***	***Company rescore = 1***	***OTA final score= 3***

(Cent/nued on next page)

Table 3-3-Company Comparison of OTA Evaluation With Labeling in DEAC Countries-(Continued)

Corticosterold	**No information about drug interactions. (IQS = 1)**	**Company agreed with this evaluation** (cm =1)	**No change in OTA evaluation. (FQS = 1)**
	No information on monitoring long-term therapy. (IQS = I*)	**This information does not appear in labeling for "comparable products" in DEACs.** (CQS = o)	**This information is not required by FDA. (FQS = O)**
	No information on risk of dermal and subdermal atrophy. (IQS = 1")	**This information does not appear in labeling for "comparable products" in DEACs.** (cm = o)	**This information is not required by FDA. (FQS = O)**
	No specification of maximum prescribing limits, pediatric doses, or doses for intra-articular administration. (IQS = 1)	**This information does not appear in labeling for "comparable products" in DEACs.** (CQS = o)	**No change in OTA evaluation. (FQS = 1)**
	No description of procedure for intra-articular administration. (IQS = 1•)	**This information does not appear in labeling for "comparable products" in DEACs. (CQS = O)**	**This information is not required by FDA. (FQS = O)**
Overall *score*	***OTA interim score = 1***	***Company rescore = 1***	***OTA final score= 1***
Antibiotic	**No description of allergic reaction to sodium formaldehyde sulfoxylate (an antioxidant). (IQS = 2*)**	● ***FDA-approved labeling at time of OTA review did not contain this warning. Product was discontinued in survey country 1 year before OTA review. (CQS = O)**	**Company documented discontinuation of product during second review. (FQS. NA)**
Overall score	***OTA interim scorn = 2***	**Company rescore = O**	**OTA final *score = NA***

"* Denotes company response based on rationale other than labeling in other countries.
1• and 2*:A single asterisk denotes a query that deals with information not required by FDA. All such queries were rescored to O in the final evaluation, so no label was held to a standard higher than that of FDA-approved labeling.
tThree additional queries concerning warnings and precautions with interim scores of O had final scores of 1 (one case) or 2 (two cases) because the company failed to document statements made in their first responses to the effect that they had initiated changes in the labeling before the OTA review. The final score remained a 3.

ABBREVIATIONS:
IQS=Interim Query Score (OTA)
CQS. Company Query Score (Company)
FQS - Final Query Score (OTA)
DEAC - Drug Export Act Country (i.e., the 21 countries named in the Drug Export Act of 1986)

NA = Not applicable (product was dropped from analysis because it has been withdrawn from market before OTA review).

SOURCE: Office of Technology Assessment, 1993.

the only outstanding query concerned a listing of inactive ingredients. OTA's final scoring excludes consideration of inert ingredients (see ch. 2), leaving eight of the company's products with queries of other types.

Using the company's "DEAC" standard, five products had overall scores of O, two had scores of 1, and one had a score of 2. After taking into account additional material submitted by the company during the second round of review, OTA final scores were two scores of O, two scores of 1, two scores of 2, and two scores of 3.

Comparison of OTA Evaluation With WHO Prescribing Information

OTA compared its final product evaluations with an independent standard, WHO model prescribing information monographs. These monographs are being prepared as part of WHO's revised drug strategy, adopted by the World Health Assembly in 1986 to complement their "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 representing relevant areas of medicine and nongovernmental professional and business organizations with official relations with WHO (including the International Federation of Pharmaceutical Manufacturers Associations, the International Pharmaceutical Federation, the International Union of Pharmacology, and the World Federation of Proprietary Medicine Manufacturers) (282).

Six monographs, organized by area of medicine, were available as of mid-1992. The entries for individual drugs are relatively short compared to FDA-approved labeling, and are intended to contain only essential medical information. For all drugs in the OTA sample that also were in the monograph, OTA compared the monograph entries with OTA's final evaluations of those products. This was done by checking each of the problems identified by OTA ("unresolved queries") with the monographs to see if the monograph agreed with OTA's evaluation. "Agreement" with OTA's evaluation in this case means that the monograph contained information OTA queried as missing from the sample label or did not include information OTA queried as not belonging in the label (mainly indications). Details of the comparisons are given in table 3-4 and summarized here.

Twenty-three products in OTA's sample are included in the six WHO monographs. Excluding queries about inactive ingredients,[2] there were 52 queries relevant to this analysis. Of these, the monographs "agreed" with OTA's evaluation in 40 cases. In 5 cases, the monographs were consistent with some, but not all, aspects of the query, and in 7 cases, the monographs agreed with the sample label and not with the OTA evaluation. This analysis suggests strongly that the majority of unresolved queries in OTA'S product evaluations represent significant problems in the content of the label, as measured against an independent standard.

Summary of Comparisons

The composite standard used by the participating company in its reanalysis resulted in great discrepancies with OTA scoring. The "DEAC standard," however, does not represent a particular set of guiding principles, so the meaning of the results is difficult to interpret. It could be seen as a "least common denominator"—labeling pieced together from the least rigorous points of each of 21 labels would be acceptable under this standard.

OTA's evaluations are generally consistent with the judgments of WHO for those products included in model prescribing information mono-

[2] Inactive ingredients vary among product formulations and, therefore, are not listed in these monographs dealing largely with generic products.

Table 3-4-Comparison of OTA Evaluations With WHO Model Prescribing Information

WHO monograph	WHO monograph agrees with OTA evaluation	WHO monograph does not agree with OTA evaluation
Drugs Used in Anesthesia (280)		
Product 1: Barbiturate anesthetic	No information on clinical pharmacology. (query score = 1) No contraindication for patients hypersensitive to barbiturates, in status asthmatics, or with porphyria. (query score =2) No recommendation for special care in patients with advanced cardiac disease, asthma, and endocrine insufficiency. (query score =2) No information about use in pregnancy and nursing mothers. (query score =1) No mention of following adverse reactions: respiratory depression, myocardial depression, prolonged somnolence, hypersensitivity reactions. (query score = 2) Too little information on use of product (advises physicians to consult the literature). (query score = 2) No information about management of overdose. (query score= 2)	No contraindication for patients without suitable veins for iv. administration. This was part of the overall query on contraindications, so had no individual query score. No recommendation for special care in patients with increased intracranial pressure. This was part of the overall query on patients requiring special care, so had no individual query score. No mention of the following adverse reaction: bronchospasm during recovery. This was part of the overall query on adverse reactions, so had no individual query score. No information about preparation of solutions and incompatibility of product with compounds that may acidify the solution. (query score = 1)
Product 2: Analgesic	No warning about allergic reactions to product. (query score= 1) No information about symptoms and management of overdose. (query score =2)	
Product 3: Anesthetic	inadequate data about safe use of product in pregnancy. (query score =1) No discussion of psychological manifestations during emergence and their avoidance. (query score = 1)	No information about several aspects of clinical pharmacology, including biotransformations, elimination, and half-life. (query score. 1)
Drugs Used In Epilepsy (288)		
Product 1: Antiepileptlc	No warning about use in children under *2* years. (query score. 2) No mention that acute pancreatitis associated with this antiepileptic may be fatal. (query score= *2)*	
Product 2: Antieplieptlc	No mention that acute pancreatitis associated with this antiepileptic may be fatal. (query score= 2)	

Product 3: Antiepllileptic	No warning that sudden withdrawal of this drug can precipitate absence (petit mat) status. (query score = 2) No information on Stevens-Johnson syndrome, a serious adverse reaction. (query score = 2)	
Product 4: Antieplieptic	No information on clinical pharmacology. (query score= 1) No information on indications and usage. (query score= 2) No information on contraindications. (query score = 2) No information on warnings and precautions. (query score =2) No information on drug interactions. (query score =2) No information on adverse reactions. (query score =2) Specific doses for initiation and maintenance not given. (query score =2)	
Product 5: Antieplieptic	No information on clinical pharmacology. (query score = 1) No precaution to discontinue drug if serious forms of dermatitis (bullous, exfoliative, or purpuric), lupus erythematosus, orStevens-Johnson syndrome are suspected. (query score =2) No information on drug interactions. (query score =2) No information on symptoms and management of overdose. (query score =1)	
Drugs Used in ParkInsonIsm (283)		
Product 1: Antiparkinsonism drug		No mention of interaction with tricyclic antidepressants. (query score =1)
Product 2: Antiparkinsonism drug	No information on symptoms and management of overdose. (query score = 2)	
Drugs Used In Mycobacterial Diseases (284)		
Product 1: Antituberculosis drug	No statement that this drug should not be used as monotherapy in light of rapid development of resistance. (query score = 2)	
Product 2: Antltuberculosis drug'	No warning about fatalities associated with hepatic dysfunction. (query score =2)	No warning about increased incidence of hepatomas in mice exposed to this drug. This was part of the warning about hepatic dysfunction, so had no separate query score. No mention that this drug may induce elevations of BUN and serum uric acid. (query score = 1)

(Continued on next page)

Table 3-4-Comparison of OTA Evaluations With WHO Model Prescribing Information-(Continued)

WHO monograph	WHO monograph agrees with OTA evaluation	WHO monograph does not agree with OTA evacuation
		No mention of a number of CNS effects (drowsiness, fatigue, ataxia, dizziness, mental confusion, inability to concentrate, pains in extremities, and generalized numbness). (query score = 1)
		No detailed description of hypersensitivity reaction. (query score =2)
Product 3: Antituberculosis drug		No discussion of the syndrome of CNS depression in infants who receive this drug. (query score = 2)
Drugs Used in Parasitic Diseases (282)[2]		
Product 1: Anthelmintic drug	No statement that other drugs are preferred for dracontiasis and no qualification of effectiveness in trichinosis. (query score= 1)	
	incomplete information on carcinogenesis and mutagenesis. (query score =1)	
	No information on pharmacokinetics. (query score = 1)	
Product 2: Anthelmintic drug	No specific warning about potential neurotoxicity of drug, especially in children. (query score = *2)*	No information on certain precautions (e.g., appropriate caution should be exercised for use in patients with severe malnutrition or anemia). This was part of the overall query on precautions, so had no individual query score.
	Nonformation on certain precautions (e.g., discontinue use if CNS, gastrointestinai, or hypersensitivit y reactions occur). (query score =2)	
	No information on adverse reactions. (query score = 2)	
	No statement that maximum cure rate is usually obtained with multiple-dose regimen. (query score =2)	
Product 3: Anthelmintic drug	No information on clinical pharmacology. (query score = 1)	
	No contraindication for patients with epilepsy. (query score =2)	
	No information on side effects, including transient neurological effects and urticarial reactions, (query score = 2)	
	No information on toxicity. (query score= 2)	

Drugs Used in Superficial Fungal Infections (289)[3]	
Product 1: Topical antifungal drug	No microbiology data. (query score= 1) No warning about possible irritation or allergic contact dermatitis. (query score =1) No precaution against contact with eyes. (query score = 1)
Product 2: Topical antifungal drug	No statement that this drug is not indicated for trivial infections. (query score =2) No warning regarding prophylactic use, tumorigenicity, use in pregnancy, teratogenicity, and suppression of spermatogenesis. (query score =2) (WHO monograph includes all except warning about suppression of spermatogenesis.)

[1] One of OTA's queries, related to use of this drug for indications other than mycobacterial diseases, was not addressed in the WHO monograph. That query is not included in this table.
[2] Four products in OTA's sample were included in this monograph: 1 had a final overall score of O. Only the remaining 3, with unresolved queries, are included in this table.
[3] Six products in OTA's sample were included in this monograph: 4 had final overall scores of 0. Only the remaining 2, with unresolved queries, are included in this table.

graphs. The monographs contain relatively short entries for products, containing only the most essential information. This analysis provides validation of OTA's method and evaluation standard.

EXPLANATION OF ADDENDUM TABLES 3-1 THROUGH 3-6

Addenda tables 3-1 through 3-6 detail the results of drug labeling analyses for each product in OTA's sample. The products are arranged in six tables based on their overall scores, and are arranged alphabetically by type of drug within each table. Products with labeling that was not fully evaluated are designated by the overall score "NA."

The column labeled Type of drug" gives a brief description of each drug, rather than the specific generic or brand name. (OTA agreed early on in the study that it would not include the specific generic or brand names of drugs in this report.)

The third column, labeled "Source," describes the source of labeling information that was evaluated. In most cases, the package insert was evaluated (indicated by the abbreviation pi). In other instances, the package insert pending approval by the local regulatory agency was evaluated (abbreviated pipa). Where package inserts were not available, other sources of information were used, including prescribing guide entries (pg) and package labels (pl), and in two instances, product documents (pals) were evaluated.[34]

The fourth column, labeled "Category," lists the category of labeling information in which each of the unresolved queries falls. Categories of information include: description and clinical pharmacology (abbreviated "dcp"), ingredients (ing), indications (ind), contraindications (ci), warnings and precautions (wp), adverse reactions (ar), dosage and administration (da), and overdose information (od).

A description of each unresolved query appears in the fifth column, labeled "Nature of problem." The queries are listed by the category of information to which they refer. Where several queries for a product fall in the same category of information, they are listed in succession.

The sixth column, "Query score;' lists the medical importance score assigned to each unresolved query.

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[3] At the beginning of the study, OTA agreed to evaluate the company prod@ documents for two products that did not have package inserts. Later, however, OTA decided not to review company product documents because they are not universally available to the physicians who use the product (they are often only available by request to the company or sometimes are distributed by company detail men to physicians and pharmacists). However, because OTA had previously agreed to evaluate the documents for these two products, these evaluations appear in the sample.

[4] In several instances, the package insert for a product did not include some medically important information that was included in the product's prescribing guide entry. In these instances, indicated "pi, pg," credit was given both for medically important information included only in the prescribing guide entry and for information appearing in the package insert.

Addendum 3-I—Products With Adequate Labeling (Overall Score = O)

Type of drug	Source	Type of drug	Source
Absorbable hemostatic sponge	pi	Emollient dental paste	pi
Adrenergic decongestant for ocular administration	pi	Folic acid antagonist antineoplastic	pi
Aminocyclitol antibiotic	pi	Hair growth stimulant	pi
Aminoglycoside for ophthalmic administration	pi	Injectable corticosteroid with anesthetic	pipa
Antacid	pi	Injectable postmenopausal estrogen	pi
Antibiotic	pi	Insulin preparation	pi
Antiestrogenic drug	pg	Ion exchange resin	pi
Antifungal agent	pi	Monotropic cardiac drug	pi
Antifungal polyene antibiotic suspension	pg	Macrolide antibiotic	pipa
Antihistamine	pg	Nonsteroidal anti-inflammatory drug	pi
Antihistamine	pi	Nonsteroidal anti-inflammatory drug	pipa
Antihistamine, barbiturate, and methylxanthine combination	pi	Nonsteroidal anti-inflammatory drug	pi
Antineoplastic	pi	Nonsteroidal anti-inflammatory drug in suppository form	pg
Cephalosporin antibiotic	pi	Oral contraceptive	pi
Cephalosporin antibiotic	pi	Penicillin-derivative antibiotic	pi, pg
Cephalosporin antibiotic	pi	Penicillin-derivative antibiotic	pi
Cephalosporin antibiotic	pi	Progestin used for oncologic indications	pi
Cholinergic agonist for urologic indications	pi	Pyrimidine analogue antineoplastic	pi
Combination analgesic, antihistamine, and adrenergic decongestant	pi	Quinolone antibiotic	pi
Combination antifungal and antiprotozoal antibiotic	pg	Quinolone antibiotic	pi
Combination aspirin, antihistamine, caffeine, and adrenergic decongestant	pi	Selective alpha-ad renergic blocking agent	pg
Combination sulfa antibiotic and corticosteroid for ophthalmic administration	pi	Sulfonylurea oral hypoglycemic	pi
Combination sulfa antibiotic and corticosteroid for ophthalmic administration	pi	Sympathomimetic decongestant	pi
Combination topical anesthetic and antacid	pi	Systemic corticosteroid	pi
Combination topical decongestant and analgesic for otic administration	pi	Systemic corticosteroid	pi
Combination xanthine-derivative bronchodilator and expectorant	pg	Tetracycline antibiotic	pi
Dopamine antagonist antiemetic	pi	Tetracycline antibiotic	pi
Electrolyte dehydration solution	pi	Tetracycline antibiotic	pi
		Thioxanthene-derivative antipsychotic	pi
		Thyroid hormone synthesis inhibitor	pi
		Topical antifungal and steroid combination	pi
		Topical nonsteroidal anti-inflammatory drug	pi
		Tricydic antidepressant	pi

SOURCE KEY: pi - package insert; pg - prescribing guide entry; pipa - package insert pending approval.

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Addendum 3-2-Products With an Overall Score of 1

overall score	Type of drug	Source	Category	Nature of problem	Query score
1	Aminoglycoside antibiotic	pi	wp	Labeling does not have information about some drug-laboratory test interactions.	1
1	Aminoglycoside antibiotic	pi	wp	Insert has no information about carcinogenesis.	1
1	Antihistamine	pi	wp	Insert has no information about use of this product in patients with liver disease.	1
1	Antihistamine indicated for appetite stimulation	pi	dcp	Insert omits information on pharmacokinetics and metabolism.	1
			ing	Insert does not list inactive ingredients.	R
1	Antiparasitic drug	pi	dcp	Insert does not include information about pharmacokinetics.	1
			ind	Insert does not state that niridazole and metronidazole are preferred treatments for dracontiasis; insert does not adequately qualify effectiveness of this drug in trichinosis (the drug is not effective in altering the course of the infection once established, i.e., once the infection has reached the invasive stage).	1
1	Antiparkinsonian agent	pi	wp	Insert omits interaction with tricyclic antidepressants (resulting in hypertension, dyskinesia).	1
1	Beta blocker	pi	ing	Insert does not list inactive ingredients.	R
			ind	Product broadly indicated for symptomatic treatment of hyperthyroidism (rather than for adjunctive therapy for thyrotoxicosis).	1
			ar	Insert does not list among adverse reactions depression, hailuanations, visual disturbances, and emotional lability.	1
1	Combination analgesic, antihistamine, opioid, and methylxanthine	pi	dcp	Manufacturer did not provide adequate rationale for this drug combination.	1
1	Combination antacid	pi	dcp	Insert contains promotional language (e.g., “the preferred dosage”).	1
			da	Insert does not include the maximum daily dosage.	1
1	Combination antihistamine and adrenergic decongestant	pg	a	Entry lacks a specific contraindication for children under 2 years of age. Product should be contraindicated in infants, who may have unpredictable reactions-e. g., central nervous excitation rather than sedation.	1
			od	Entry does not include information about overdose management.	1
1	Combination antihistamine, adrenergic decongestant, and antitussive	pg	dcp	Manufacturer did not provide data demonstrating the additive therapeutic actions and minimal potential for toxicity of this combination.	1
1	Combination centrally acting antiadrenergic agent and thiazide diuretic	pipa	ind	Insert has no warning that this fixed combination drug is not indicated for initial therapy for hypertension.	1

1	Combination methylxanthine bronchodilator, barbiturate, and adrenergic agonist	pi	ing	Insert does not list inert ingredients.	R
			ci	Insert has no contraindication for patients with prostatic hypertrophy.	1
1	Folic acid analogue	pi	dcp	Insert does not have section describing clinical pharmacology,	1
			wp	Insert does not have information about drug interactions (with neuroleptics).	1
			da	Insert does not specifically advise monitoring methotrexate levels to ensure that the dose of this folic acid analogue is adequate for rescue.	1
1	H-2 receptor antagonist	pipa	wp	Labeling omits mention of the pharmacologic interaction of this H-2 receptor antagonist and some other drugs, such as propranoloi, tricydic antidepressants, and lidocahe.	1
1	Long-acting nitrate vasodilator	pi, pg	ci	insert does not include contraindication for hypersensitivity or idiosyncrasy to other nitrates or nitrites.	1
			wp	Insert has no warning about the following: risks inherent in concurrent with calcium channel blockers; risk of paroxysmal bradycardia; risk of aggravation of angina.	1
				Insert has no information about use in pregnancy, use in nursing mothers, or pediatric use.	1
1	Macrolide antibiotic	pl, pg	ing	Entry does not list inactive ingredients.	R
			ind	Entry indicates this macrolideantibiotic for treatment of *Giardia lamblia, Clostridium tetanii*, and *Ureaplasma urealyticum*.	1
			ar	Entry does not note that rare reports of pseudomembranous enterocolitis have been reported with therapy with this antibiotic; entry does not list adverse reactions for which a cause and effect relationship has not been established, including isolated reports of central nervous system side effects, cardiovascular symptoms, and, in persons with renal insufficiency and/or who are receiving high doses of this antibiotic, reversible hearing loss,	1
1	Multivitamin and multimineral	pi	ing	Insert does not list inactive ingredients.	R
			ind	Product indicated for "undernourishment."	1
1	Multivitamin with iron	pi	ing	Insert does not list inactive ingredients.	R
			da	Insert does not have appropriate dosage information for infants less than one year of age.	1
1	Non-barbiturate anesthetic	pi	dcp	Insert does not provide information about several aspects of clinical pharmacology, including biotransformation, elimination, and half-life.	1
			ing	Insert does not list inactive ingredients.	R
			wp	Manufacturer provided inadequate data about safe use of this product in pregnancy (this product may induce uterine contractions during the first trimester of pregnancy),	1
				Insert does not have a detailed discussion about psychological manifestations during emergence and its avoidance.	1

Continued on next page

Addendum 3-2—Products With an Overall Score of I-Continued

overall score	Type of drug	Source	Category	Nature of problem	Query score
1	Nonsteroidal anti-inflammatory drug	pi	dcp	Insert does not have clinical pharmacology information, including half-life, onset and duration of action, and route of elimination.	1
			ing	Insert does not list inactive ingredients.	R
1	Nonsteroidal anti-inflammatory drug	pi	ing	Insert does not list inactive ingredients.	R
			wp	Insert does not contain a precaution regarding NSAID-induced aseptic meningitis.	1
1	Ophthalmic aminoglycoside antibiotic	pg	ind	Manufacturer did not provide data supporting efficacy against certain strains of mycoplasma	1
1	Ophthalmic tetracycline analogue antibiotic	pi	ind	Insert does not limit indications to ophthalmic infections that are superficial.	1
1	Opioid-derivative antidiarrheal	pi	ind	Labeling does not note that pediatric use for treating chronic diarrhea has not been established.	1
1	Oral contraceptive	pi	ind	Insert indicates product for menstrual irregularities in general without specifying causes.	1
1	Oral contraceptive	pi, pg	ind	Insert indicates product for correction of certain menstrual irregularities, without specifying causes.	1
1	Penicillin-derivative antibiotic	pi, pg	wp	Insert does not warn about possible development of pseudomembranous colitis (merely warns about the possibility of superinfection).	1
1	Potassium-sparing diuretic	pg	dcp	Entry does not describe chemical properties or pharmacokinetics.	1
			ing	Entry does not list inactive ingredients.	R
			ind	Entry does not state that the product is not first-line therapy for congestive heart failure.	1
				Entry includes indications for “idiopathic edema,” myasthenia gratis, and malignant hypertension.	1
				Indication for malignant hypertension contradicts the contraindication in acute renal dysfunction.	1
			wp	Entry has no warnings about drug interactions with indomethacin and captopril.	1
			da	Entry does not recommend adding another diuretic if adequate response is not obtained with the product alone.	1
1	Substituted benzamide antipsychotic	pi	ing	Insert does not list inactive ingredients.	R
			wp	Insert does not caution about use in patients with cardiovascular disease, CNS depression, blood dyscrasias, hepatic impairment, and in comatose patients.	1
			ar	Insert does not warn about the following adverse reactions: blurred vision, pigmentary retinopathy, difficulty with urination, photosensitivity, rash.	1

1	Substituted benzamide antipsychotic	pi	wp	Insert does not include a precaution about the potentiating effect of alcohol.	1
				Insert omits precautions about use in patients with respiratory disease or cardiovascular disease; no warning about use in patients with liver dysfunction or a history of jaundice.	1
				Insert does not have information about drug-lab test interactions.	1
1	Systemic corticosteroid	pi	ing	Insert does not list inert ingredients.	R
			wp	Insert has no information about drug interactions.	1
			da	insert does not give pediatric dosages.	1
1	Systemic corticosteroid	pi	ing	Insert does not list inactive ingredients.	R
			od	Insert does not have information on overdose.	1
1	Systemic corticosteroid	pds	wp	Insert does not warn that this drug may prolong coma in cerebral malaria.	1
1	Systemic corticosteroid	pi	wp	Insert does not warn about enhanced effect of steroids in patients with hypothyroidism or cirrhosis.	1
1	Topical analgesic	pg	ind	Indications not appropriately limited to minor wounds.	1
1	Topical antifungal	pi	dcp	Insert does not provide microbiology data.	1
			wp	Insert does not warn about possibility of irritation or allergic contact dermatitis.	1
				Insert does not have precaution against contact with eyes.	1
1	Topical bacteriostatic agent	pi	ind	Product is indicated for cleansing of infants in certain circumstances.	1
			wp	Insert does not note that detectable blood levels of this topical bacteriostatic agent have been found after repeated cleansings.	1
				Insert provides no information on use in nursing mothers or about carcinogenesis and impairment of fertility,	1
1	Topical combination corticosteroid and 8-hydroxyquinolone antibiotic	pg	ing	Entry does not list inactive ingredients.	R
			wp	There are no precautions about interference with thyroid function tests and interference with laboratory assays for phenylketonuria.	1
				Entry does not note potential for adrenal suppression with substantial systemic absorption and other adverse effects of systemically absorbed steroids.	1
1	Topical corticosteroid	pi	dcp	Insert has no information about pharmacokinetics of topically absorbed corticosteroids.	1
			wp	Insert does not note that patients receiving large doses of a potent topical steroid applied to a large surface area should be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests.	1

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Addendum 3-2—Products With an Overall Score of l-Continued

overall score	Type of drug	Source	Category	Nature of problem	Query score
1	Tricydic antidepressant	pi	ing	Insert does not list inert ingredients.	R
			wp	Insert does not warn about cross sensitivity with other tricyclic antidepressants.	1
				Insert does not warn about the following: concurrent use with antithyoid agents may increase the risk of agranulocytosis; delirium has been reported with concurrent administration of the tricyclic antidepressant and disulfiram.	1
				Insert does not warn that paralytic ileus may occur in patients taking tricyclic antidepressants with anticholinergics; schizophrenic patients may have increased symptoms of psychosis; patients with paranoid symptoms may have an exaggeration of such symptoms.	1
				Insert does not note that withdrawal symptoms of nausea headache, and malaise may occur with abrupt cessation of therapy.	1
			ar	The following adverse reactions are not listed: drowsiness, dizziness, and neuroleptic malignant syndrome.	1
1	Urinary tract antiseptic	pi	wp	Insert does not state that urine pH should be monitored to maintain urine acidity.	1

SOURCE KEY: pi= package insert; pg - prescribing guide entry; pipa. package insert pending approval; pl= package label; pds - product document.

CATEGORY KEY: dcp= description/clinical pharmacology; ing. ingredients; ind - indications; ci - contraindications; wp= warnings and precaution; ar= adverse reactions; da. dosage and administration; od = overdose information.

Addendum 3-3-Products With an Overall Score of 2

overall score	Type of drug	Source	Category	Nature of problem	Query score
2	Aminocyclitol antibiotic	pi	dcp	Insert does not mention need for susceptibility y testing of isolates associated with treatment failure.	1
			wp	Insert does not have warning about the benzyl alcohol content of the product's diluent.	1
				Insert does not include precautions regarding development of resistance to ***Neisseria*** *gonorrhoeae.*	1
				Insert has no warning about risk of anaphylaxis or anaphylactoid reactions.	2
2	Aminoglycoside antibiotic	pi, pg	ind	Insert indicates product for methicillin-resistant S. *aureus* and gonococcal infections without noting that this aminoglycoside antibiotic is not drug of choice for these infections.	2
			Wp	Although labeling states that safety of this aminoglycoside antibiotic during pregnancy has not been established, the insert fails to warn specifically about the risk of total irreversible bilateral congenital deafness to children whose mothers receive aminoglycosides during pregnancy.	1
2	Aminoglycoside antibiotic	pi	dcp	Insert states that this aminoglycoside antibiotic is effective *in vitro* against *Neisseria meningitidis, Neisseria gonorrhoeae,* and *Streptococcus pyogenes.*	1
			wp	Insert does not include a discussion of the syndrome of CNS depression in infants who receive this aminoglycoside antibiotic.	2
2	Analgesic	pi	ing	Insert does not list inactive ingredients.	R
			wp	Insert does not warn about allergic reactions to this product.	1
			od	Insert does not have information about the symptoms and management of overdose.	2
2	Anesthetic for ophthalmic administration	pi	dcp	Insert does not describe clinical pharmacology.	1
			ing	Insert does not list inactive ingredients.	R
			wp	Insert does not warn about risk of corneal opacification with prolonged use.	2
				Insert does not warn about risk of systemic toxicity.	1
				Insert does not caution that the patient should protect eyes from irritants during the period of anesthesia.	2
			ar	Insert does not list among adverse reactions systemic hypersensitivity, pupillary dilatation, or cycloplegic effects.	1
2	Antacid	pi	ing	Insert does not list inactive ingredients.	R
			wp	Insert fails to warn about risk of hypermagnesemia in patients with renal disease.	2
				Insert omits information about the interaction of aluminum in this antacid with tetracycline.	2
2	Antacid combination	pi	wp	Label omits warning concerning use in patients with renal dysfunction.	2
				Label omits warning about known drug interaction with tetracycline.	1

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Addendum 3-3-Products With an Overall Score of 2-Continued

overall score	Type of drug	Source	Category	Nature of problem	Query score
2	Antidiarrheal combination with aminoglycoside antibiotic	pi	ind	Product is broadly indicated for "bacterial diarrhea" (rather than specifically for preoperative suppression of intestinal bacteria and treatment of diarrhea due to enteropathogenic *Escherichia coli).*	2
				Insert does not note that oral dehydration therapy is considered first-line treatment for childhood diarrhea.	1
			ci	Insert does not contraindicate use in children.	1
2	Antidopanergic antiemetic and gastrokinetic	pi	ind	Product is indicated broadly for gastrointestinal motility disturbances (rather than for symptomatic gastroesophageal reflux, diabetic gastroparesis, prevention of nausea and vomiting associated with cancer chemotherapy, and small bowel incubation).	2
			wp	Insert has weak warning about tardive dyskinesia.	1
			da	Insert does not include information about admixture compatibilities of intravenous solution.	1
2	Antiepileptic drug	pg	ar	Entry does not note that acute pancreatitis associated with use of this antiepileptic drug may be fatal.	2
2	Antiepileptic drug	pg	dcp	Entry does not include information about clinical pharmacology.	1
			wp	Entry does not include precaution to discontinue this antiepileptic if more serious forms of dermatitis (bullous, exfoliative, or purpuric dermatitis), or if lupus erythematosus or Stevens-Johnson syndrome are suspected.	2
				Entry does not have information about drug interactions, including drugs which may increase levels of this antiepileptic (e.g., chloramphenicol, acute alcohol intake, estrogens, sulfonamides, cimetidine); drugs which may decrease levels of this antiepileptic (e.g., chronic alcohol abuse, reserpine, antacids containing calcium); drugs which may either increase or decrease serum levels of this antiepileptic (phenobarbital, valproic acid, sodium valproate); and drugs whose efficacy is impaired by this antiepileptic (corticosteroids, quinidine, digitoxin, rifampin, doxycydine, estrogens).	2
2	Antihistamine	pi	ing	Insert does not list inactive ingredients.	R
			ar	Insert does not mention among adverse reactions the following: nervousness, weakness, appetite increase, cough, angioedema, hypotension, photosensitivity, seizures, prolonged QT interval on EKG, and ventricular arrhythmias.	2
			od	Entry does not have information on symptoms and management of overdose.	1
2	Antiparkinsonian agent	pipa	od	Insert does not include information on signs and management of overdose.	2
2	Antituberculosis drug	pi	ind	Insert does not state that this antituberculosis drug should not be used as monotherapy in light of rapid development of resistance.	2

2	Benzodiazepine	pg	dcp	Company provided no adequate rationale for description of this product as a "tranquilizer."	1
			ci	Entry does not include a contraindication against use by patients with hypersensitivity to this product.	1
			wp	Entry does not include warnings against use in psychotic states and psychiatric disorders in which anxiety is not a prominent feature; no warning about use in addiction-prone patients, such as drug addicts and alcoholics; no information about withdrawal symptoms.	2
				Entry does not include information on drug interactions.	1
				Entry does not note the need for frequent patient reassessment; insert does not warn about use in depressed patients in case of suicidal tendencies; does not warn that this benzodiazepine may increase depression; no evidence of safety and efficacy of this benzodiazepine in patients below age 18; no information on long-term use.	2
			od	Entry does not have information on treatment of overdose.	1
2	Benzodiazepine hypnotic	pi	ing	Insert does not list inactive ingredients.	R
			wp	Insert claims that this benzodiazepine hypnotic has no withdrawal effects (omits mention of daytime anxiety and rebound insomnia).	2
				Insert does not state that fetal damage may occur if drug is used in the first trimester (insert merely states that the safety of drug during pregnancy has not been established).	1
				Insert does not warn that hypnotics can increase depression in patients who are already depressed, and may therefore increase risk of attempted suicide.	1
			ar	Insert does not mention common (greater than 4 percent incidence) adverse reactions, including nervousness, nausea and vomiting.	1
2	Cephalosporin antibiotic	pg	ind	No adequate support for indication for use in treatment of endocarditis.	2
			wp	Entry does not have information about potential for superinfection with prolonged use of this antibiotic.	1
2	Cephalosporin antibiotic	pi	ind	No adequate support for indication for use in treatment of endocarditis.	2
2	Combination "hepatic protector"	pg	dcp	Entry does not have description and information about clinical pharmacology.	1
				Company did not provide adequate justification for this drug combination and the ratio of its components.	2
			ind	Product is indicated for treatment of "hepatobiliary dysfunction" but also includes a warning about use in persons with jaundice.	1
			wp	Entry omits precautions for an amino acid component of this combination (nausea and vomiting; may precipitate hepatic encephalopathy in patients with established liver disease; concurrent use with MAO inhibitors could superimpose symptoms of intoxication, such as delirium, visual hallucinations, ataxia, speech disturbances, increased salivation, and hyperhidrosis).	1
			ar	Entry omits adverse effects associated with one component of this combination (nausea, vomiting, gastrointestinal discomfort and diarrhea, incontinence, depression, and an unpleasant fishy odor).	1

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Addendum 3-3-Products With an Overall Score of 2-Continued

Overall score	Type of drug	Source	Category	Nature of problem	Query score
2	Combination analgesic and centrally acting muscle relaxant	pi	ing	insert does not list inactive ingredients.	R
			dcp	Insert does not describe chemical properties of this combination.	1
				Insert does not describe the clinical pharmacology of this combination.	1
			ind	Company failed to provide evidence of efficacy and safety of this centrally acting muscle relaxant in humans.	2
			wp	Insert has no warning about cross-sensitivity with aspirin.	1
				Insert has no information about carcinogenesis, mutagenesis, or impairment of fertility.	1
2	Combination antiflatulent and antacid	pg	wp	Entry omits mention of a drug interaction with tetracycline.	2
			da	Entry omits maximum dosage.	1
2	Combination antihistamine and adrenergic decongestant	pl	ing	Label does not list inactive ingredients.	R
			wp	Label provides no warning about use in patients with cardiac disease, diabetes, or asthma.	2
				Label has no information about use in pregnancy.	1
				Label has no warning about use with MAO inhibitors or with antihypertensive drugs.	1
			ar	Labeling does not warn about sleeplessness, dizziness, and nervousness.	1
2	Combination antihistamine, analgesic, and adrenergic decongestant	pi	ing	Insert does not include alcohol content of product.	2
2	Combination antihistamine, antitussive, and adrenergic decongestant	pi, pg	ing	Insert does not list inactive ingredients.	R
			ind	No evidence that components of this product are effective as expectorants.	1
			wp	Insert does not caution about using antihistamines inpatients with narrow angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, symptomatic prostatic hypertrophy, bladder neck obstruction, and ventricular tachycardia.	1
			ar	Insert does not note adverse effects associated with antihistamines (such as dry mouth, dizziness, disturbed coordination, confusion, epigastic distress, thickening of bronchial secretions), adrenergic decongestants (such as tachycardia palpitations, headache, nervousness, tremor), and the antitussive in this preparation (such as confusion, nervousness, or irritability).	2
			od	No information is provided about overdose.	1
2	Combination aspirin with antacid	pi	ing	Label does not list inactive ingredients.	R
			od	No information about management of overdose.	2

2	Combination bismuth, anesthetic and corticosteroid for topical administration	pi	ing	Insert does not list inert ingredients.	R
			wp	Insert does not have a precaution concerning systemic absorption and development of HPA axis suppression and the need for monitoring; use over large areas; caution against ophthalmic contact; and warning to discontinue use if irritation develops.	1
				Insert does not warn against using tight-fitting diapers or plastic pants on children being treated in the diaper area (these garments may constitute occlusive dressings).	2
				Insert has no information on use in nursing mothers.	1
			ar	Insert does not list the following adverse reactions: skin atrophy, itching, irritation, dryness, folliculitis, hypertrichosis, acneform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of skin, secondary infections, and striae.	1
			da	Insert does not provide information on duration of therapy.	1
2	Combination cortcosteroid, antifungal polyene antibiotic, and aminoglycoside antibiotic for topical administration	pg	wp	Entry contains no warning against ophthalmic use.	1
				Entry Contains no warning about the following: nephrotoxicity and ototoxicity of aminoglycoside antibiotic, risk of HPA axis suppression and Cushing's syndrome with systemic absorption of topical corticosteroids, and risk of overgrowth of nonsusceptible organisms.	2
				Entry contains no recommendation to perform appropriate microbiological studies if there is a lack of therapeutic response.	2
				Entry has no information about carcinogenesis, mutagenesis, and impairment of fertility.	1
				Entry does not mention precautions about the following: use in pediatric patients, use in pregnancy, use in nursing mothers, risk of systemic absorption of topical carticosteroids, and types of conditions that augment systemic absorption.	2
			ar	Entry does not mention the following adverse effects: ototoxicity, nephrotoxicity, burning, itching, dryness, folliculitis, hypertrichosis, acneform eruptions, hyperpigmentation, perioral dermatitis, allergic contact dermatitis, maceration of skin, secondary infection, skin atrophy, and striae.	1
			da	Entry does not advise against use of this product under occlusive dressings.	1
2	Combination urinary tract antiseptic and analgesic	pi	wp	Insert omits precaution against use in prepubertal children and pregnant women just prior to labor.	1
			od	Insert omits overdose treatment information for this combination.	2
2	Combination xanthine bronchodilator, barbiturate, and adrenergic agonist	pi	ing	Insert does not list inactive ingredients.	R
			wp	Insert does not state that acute or severe asthma attacks may necessitate supplemental therapy with other inhaled or parenterally administered drugs.	2
			da	Dosages are not adjusted for the weight of the patient.	1
				Insert recommends dosing three times a day rather than every eight hours.	1

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Addendum 3-3-Products With an Overall Score of 2

overall score	Type of drug	Source	Category	Nature of problem	Query score
2	Corticosteroid for ophthalmic and otic administration	pi	ing	Insert does not list inactive ingredients.	R
			ind	Insert indicates this topical corticosteroid for treatment of herpes zoster ophthalmia, without noting that other topical steroid preparations are preferred.	2
				Insert indicates this topical corticosteroid for neovascularization, keratoconjunctivitis (without qualification), phiyctenularkeratitis (other references recommend a combination topical corticosteroid-antibiotic combination).	2
			wp	Insert lacks information about use in pregnancy, in pediatric patients, and in geriatric patients.	1
			ar	Insert does not list the following adverse reactions: globe perforation, exacerbation of glaucoma or ocular hypertension, Posterior subcapsular cataracts, and burning or stinging of ears.	1
2	Direct-acting arterial vasodilator	pg	wp	Weak warning about hypotension (listed as an "infrequent" serious secondary reaction).	2
				Entry omits precaution that product is for use in closely monitored settings, such as in the hospital.	2
2	Hypolipidemic drug	pi	ind	Insert does not note that diet is the initial therapy of choice for hyperlipidemias, and that drug therapy should not be used for routine treatment.	1
			ci	Labeling does not include a contraindication for patients with preexisting gallbladder disease and for patients with hypersensitivity to this drug.	1
			wp	No warning that this drug maybe associated with cholelithiasis.	1
				insert does not state that adequate studies on caranogenicity have not been done in humans, and that hepatic carcinomas have been found in rats that have been exposed to this drug.	2
				Insert does not include the following precautions: insert does not state that treatment should be discontinued if response is inadequate after 3 months; labeling omits rare hematologic changes; no information on impairment of fertility (based on animal studies); labeling has no statement about pediatric use.	1
2	Injectable progestin	pi	a	Insert does not contraindicate use in carcinoma of the breast and missed abortions.	1
			wp	Insert states that "[n]o teratogenic effects were observed in mice and rats" although progestins have been shown to have teratogenic effects in animals and humans.	2
				Insert does not address evidence of development of mammary nodules in monkeys.	1
2	Lincosamide antibiotic	pi	ind	Insert indicates antibiotic for use in upper respiratory infections, although most upper respiratory infections are non-bacterial.	1
			wp	Insert has weak warning about association between antibiotic use and the development of pseudomembranous colitis.	1
				Insert does not warn that this antibiotic should not be used for treatment of meningitis (due to poor penetration of the blood-brain barrier).	2

			ar	Insert does not note that eosinophilia, agranulocytosis, and thrombocytopenia have occurred with use of this antibiotic.	1
2	Macrolide antibiotic	pi	ind	Insert includes indication for respiratory tract infections due to staphylococci, streptococci, and haemophilus.	2
				Insert does not limit the treatment of Staphylococcus *aureus* with this antibiotic to skin and soft tissue infections.	2
2	Multivitamin with calcium and iron	pg	wp	Entry does not note that iron absorption is inhibited by the concurrent ingestion of eggs and milk.	1
				Entry does not mention interactions with other drugs, including antacids, tetracycline, and levodopa	1
			od	Entry does not include information about the signs, symptoms, and management of overdose.	2
2	Multivitamin with iron	pg	ing	Entry does not list inactive ingredients.	R
			ind	Product is indicated as an appetite stimulant.	2
			wp	Entry does not have recommendation for pregnant women and nursing mothers to seek medical advice before using this product.	1
2	Multivitamin with minerals	pi	ing	Insert does not list inactive ingredients.	R
			ci	Insert does not have contraindication for patients with hemochromatosis.	1
			wp	Insert does not warn that the presence of pernicious anemia should be excluded before initiating therapy because folic acid may mask symptoms of pernicious anemia, allowing untreated necrologic deficits arising from vitamin B-1 2 deficiency to progress.	2
				Insert does not have the following precautions: calcium content should be considered before prescribing for patients with kidney stones, do not exceed recommended dosage, need for periodic hematologic tests to monitor therapy.	1
			ar	Insert does not list adverse reactions such as allergic reactions, skin rashes, gastrointestinal disturbances, nausea vomiting, diarrhea, constipation, generalized flushing and feeling of warmth with niacinamide, allergic sensitization following administration of folic acid.	1
			da	Dosage of iron inadequate for pregnant women.	1
			od	Insert does not have information on management of iron overdose.	1
2	Multivitamin with protein and minerals	pg	ing	Entry does not list inactive ingredients.	R
			wp	Entry does not state that product is merely supplemental and not a replacement for oral food intake or for treatment of protein-calorie deficiency states.	2
2	Nitrosourea antineoplastic	pi	wp	Insert does not note that past history of lung disease is a risk for pulmonary toxicity.	2
				Insert has no information about the relation of pulmonary toxicity to total cumulative dose.	2
				Insert fails to recommend monitoring of complete blood count for hematologic adverse reactions for at least six weeks after receiving a dose of this antineoplastic agent.	1
			da	Insert has no warning about use of this product with glass containers.	1

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Addendum 3-&Products With an Overall Score of 2-Continued

Overall score	Type of drug	Source	Category	Nature of problem	Query score
2	Nonsteroidal anti-inflammatory drug	pi	wp	insert does not have a warning about the pharmacologic idiosyncratic type of anaphylactic reaction to anti-inflammatory drugs.	1
				Insert does not mention that the usefulness of fever and inflammation as diagnostic signs of infection in patients on nonsteroidal anti-inflammatory drugs is reduced.	1
			ar	insert does not mention that this nonsteroidal anti-inflammatory drug has been associated with skin reactions, including erythema multiform; insert also does not note that agranulocytosis (which may be fatal) may occur (insert only mentions granulocytosis which suggests a less serious effect).	2
2	Nonsteroidal anti-inflammatory drug	pi	dcp	Insert does not have full information on clinical pharmacology.	1
			ar	insert does not warn specifically about the following adverse reactions: risk of erythema multiforme and StevensJohnson syndrome, ulcers, renal effects, fluid retention, and use in cardiac patients.	2
2	Nonsteroidal anti-inflammatory drug	pds	dcp	Document does not include medically important pharmacokinetic information, including half-life and route of elimination.	1
			ing	Document does not list inactive ingredients.	R
			wp	Document does not warn that there are known effects of this class of drug on the human fetus, including closure of the fetus, arteriosus, platelet dysfunction with resultant bleeding, renai dysfunction or failure with oiigohydramnios, gastrointestinal bleeding or perforation, and myocardial degenerative changes.	1
				Document states that concomitant administration of this drug and sulindac results in a substantial, "but not statistically significant," lowering of plasma levels of sulindac, despite the fact that plasma levels in the 13 male volunteers included in the study dted had plasma levels of sulindac lowered by one-third.	1
				Document has no recommendation against use in children.	1
			ar	Document does not include proteinuria among adverse reactions.	1
			od	Document has no information on the management of overdose.	2
2	Nonsteroidal anti-inflammatory drug	*pg*	od	Entry does not have information about signs and treatment of overdose.	2
2	Nonsteroidal anti-inflammatory drug	pi	wp	Insert has no information about proteinuria or the nephrotic syndrome.	1
				Insert does not state that this drug is a known teratogen in animals.	2
2	Nonsteroidal anti-inflammatory drug	pi	ing	insert does not list inactive ingredients.	R
			ind	Manufacturer did not provide adequate evidence of efficacy for relief of pain and fever associated with acute upper respiratory tract inflammation.	2
2	Opioid analgesic used in anesthesia	pi	wp	insert does not include information about use in nursing mothers.	1
				Insert does not warn about the euphoria and miosis that may occur with narcotic analgesics.	1

			ar	Insert does not contain information on secondary rebound respiratory depression or about a number of other adverse reactions that may occur when this narcotic analgesic is used in combination with droperidol.	2
2	Penicillin-derivative antibiotic	pi	ind	Insert lists indications by types of susceptible pathogen and site of infection separately rather than listing indications by site of infection, qualifying each by type of susceptible pathogen.	1
				Insert includes the following indications: ear, nose, throat, and oral cavity infections; endocarditis.	2
2	Penicillin derivative antibiotic	pi	wp	Insert fails to warn about risk of anaphylactic reactions.	2
				Insert has no information about several drug-lab test interactions (e.g., fake positive glucose reactions with Clinitest, Benedict's solution, or Fehling's solution).	1
			ar	Insert does not include information about the following adverse reactions: gastrointestinal system (e.g., pseudomembranous colitis), liver function (enzyme elevations), hemato-poietic system (anemia, eosinophilia, agranulocytosis).	1
2	Postmenopausal estrogen	pi, pg	ing	Insert does not list inactive ingredients.	R
			wp	Insert has no information on carcinogenesis, mutagenesis, use in nursing mothers, and pediatric use.	1
			ar	Insert does not list gallbladder disease among adverse effects.	1
			da	No justification for recommendation on insert to increase dosage to 2.5 mg/day in 3-4 days if no improvement occurs at a dosage of 1.25 mg/day.	2
2	Progesterone-derivative oral contraceptive	pi	ing	Insert does not list inactive ingredients.	R
			ind	Product is indicated for treatment of pelvic pain and mastodynia; company provided no adequate evidence of efficacy for these indications.	2
			wp	Insert does not caution about the use of oral contraceptives in patients with impaired liver function.	1
				Insert does not warn about the increased risk of pyridoxine and folate deficiency in oral contraceptive users.	1
2	Sulfonylurea oral hypoglycemic	pg	ing	Entry does not list inactive ingredients.	R
			ind	Entry indicates oral hypoglycemic for diabetes insipidus, but does not note that desmopressin is the preferred treatment.	1
			ci	Entry does not contraindicate use by patients with known hypersensitivity to the drug.	1
			wp	Entry does not have information about use in pregnancy and nursing mothers.	1
				Entry does not describe the following: loss of control of blood glucose when drugs which produce hyperglycemia are used; interaction of oral miconazole and oral hypoglycemic.	2
				Entry does not advise conservative doses in patients with impaired hepatic or renal function.	2
				Entry does not provide data on the safety and efficacy of use of phenformin with sulfonylurea oral hypoglycemic in patients who are unresponsive to sulfonylurea oral hypoglycemic alone.	1

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Addendum 3-&Products With an Overall Score of 2-Continued

overall score	Type of drug	Source	Category	Nature of problem	Query score
2	Synthetic androgen	pi	ing	Insert does not list inactive ingredients.	R
			wp	Insert lacks warning regarding decreased HDL and increased LDL in patients receiving this synthetic androgen.	1
			ar	Insert does not list the following adverse effects: pancreatitis, carpal tunnel syndrome, prolonged post-therapy amenorrhea thrombocytopenia, Stevens-Johnson syndrome, cataracts, bleeding gums, fever, nipple discharge, and Guillain-Barre syndrome.	2
2	Systemic corticosteroid	pi	ing	Insert does not list inactive ingredients.	R
			wp	Insert does not warn about prolongation of coma in cerebral malaria risk of activation of latent amebiasis, and steroid inducement of glaucoma, cataracts, or secondary ocular infections.	2
				Warnings about enhanced effects of corticosteroids in patients with hypothyroidism and cirrhosis, and warnings about fat embolism are not included.	1
				Insert has no specific warnings about use of this systemic corticosteroid in cases where there is a probability of abscess, pyogenic infection, and in patients with intestinal anastomoses; insert does not have warning about use in patients with myasthenia gravis.	2
			ar	Cutaneous reactions, convulsions, pseudotumor cerebri, vertigo, headache, ophthalmic disorders, nausea and malaise were not mentioned in the insert.	1
2	Systemic corticosteroid	pi	ing	Insert does not list inactive ingredients.	R
			wp	Insert does not have warning about increased calcium excretion associated with systemic corticosteroids.	1
				No warning about enhanced effect of steroids in hypothyroidism and cirrhosis.	1
				No warning about need to monitor growth and development of infants and children on systemic corticosteroids.	2
				No warning about need for gradual reduction of dosage following prolonged therapy.	2
				No outline of routine tests to monitor therapy.	1
2	Thyroid hormone supplement	pg	ing	Entry does not list inactive ingredients.	R
			wp	Entry does not include the following: recommendations about monitoring thyroid status when receiving this product; information about drug interactions (only interactions with anticoagulants and hypoglycemics are mentioned in entry); information about drug-laboratory test interactions; information about use in nursing mothers, infants, and children.	2
2	Topical antifungal agent	pi	ind	Company did not provide adequate justification for indicating this topical antifungal for treatment of staphylococcal and streptococcal skin infections.	2
			wp	Insert has no warnings and precautions.	1
				Insert has no information about use in pregnancy and in nursing mothers.	1
			da	insert lacks information on duration of therapy.	1

2	Tricyclic antidepressant	pipa	wp	Insert has no information about drug interactions.	1
			od	Insert does not describe signs and symptoms of toxicity.	2
2	Uninary anticholinergic and antispasmodic	pi	dcp	Insert does not have pharmacokinetic information, including mode of excretion, time of onset of action, or peak effect.	1
			wp	Insert has no information about use in pregnancy and nursing mothers.	1
			ar	Insert does not list among adverse reactions the following: vertigo, mental confusion, nervousness, leukopenia, tachycardia, palpitations, urticaria, eosinophilia, hyperpyrexia, disturbances of eye accommodation, and dysuria.	2
2	Urinary tract analgesic	pi	ing	Insert does not list inactive ingredients.	R
			ci	Insert does not include contraindication for use by patients with hypersensitivity to this product.	1
			wp	Insert does not note that the use of this urinary analgesic should not delay the definitive diagnosis and treatment of causative conditions.	1
				Insert does not note that this urinary analgesic may interfere with urinalysis based on spectrometry or color reactions.	1
				Insert does not have section on carcinogenesis, mutagenesis, or impairment of fertility. (U.S. labeling notes that long-term use of this product has induced neoplasia in rats.)	1
			od	Insert does not have information on management of overdose, including treatment of methemoglobinemia.	2
2	Urinary tract analgesic	pi, pg	ing	Insert does not list inactive ingredients.	R
			wp	Insert does not note that this urinary tract analgesic may stain all body fluids, not just urine; insert does not note that the use of this agent for symptomatic relief should not delay definitive diagnosis and treatment of causative organisms.	1
				Insert does not caution that this urinary tract analgesic may interfere with urinalysis based on spectrometry or color reactions.	1
				Insert has no information about use in pregnancy and by nursing mothers.	1
				Insert has no information on caranogenesis, mutagenesis, or impairment of fertility.	1
			ar	Insert does not list the following adverse reactions: headache, rash, gastrointestinal disturbances, renal toxicity, hepatic toxicity.	1
			od	Insert does not provide information on management of overdose.	2
2	Urinary tract antiseptic	pg	ind	Entry does not note that the same degree of effectiveness against susceptible organisms is achieved by a related agent with a lower incidence of CNS side effects.	1
			wp	Insert does not state that this urinary tract antiseptic may enhance the effects of oral anticoagulants, warfarin, or bishydroxycoumarin.	2
2	Urinary tract antiseptic	pi	ing	Insert does not list inactive ingredients.	R
			ind	Product is indicated for pyelonephritis and intestinal bacterial diarrhea.	2
			da	Children's dosages are adjusted by age rather than weight of the patient.	1

SOURCE KEY: pi= package insert; pg - prescribing guide entry; pipa - package insert pending approval; pl - package label; pds = product document.

CATEGORY KEY: dcp = description/clinical pharmacology; ing = ingredients; ind = indications; ci = contraindications; wp = warnings and precautions; ar = adverse reactions; da = dosage and administration; od - overdose information.

Addendum 3-4-Products With a Primary Overall Score of 3

Overall score	Type of drug	Source	Category	Nature of problem	Query score
3	Adrenergic drug	pi	ing	Label does not list inactive ingredients other than alcohol.	R
			ind	Label does not include information on indications and usage.	2
			ci	Label does not include information about contraindications.	2
			wp	Label does not list warnings and precautions.	2
			ar	Label does not list adverse reactions.	2
			od	Label does not have overdose information.	2
3	Analgesic and proteolytic enzyme combination	pi	dcp	Company did not provide adequate evidence of efficacy for this drug combination in human beings.	1
			wp	insert omits precautions regarding use inpatients with severe hepatic insuffidency, renal damage, or pulmonary hemorrhage.	2
			od	insert does not have information about signs and treatment of overdose.	2
3	Analgesic, decongestant, and antihistamine combination	pi	ing	insert does not list inactive ingredients.	R
			ci	insert does not list contraindications.	2
			wp	insert does not list warnings and precautions.	2
				insert does not have information about use in pregnancy and by nursing mothers.	2
			ar	insert does not list adverse reactions other than drowsiness.	2
			od	insert has no information about management of overdose.	2
3	Androgenic steroid	pi	ind	No adequate support for use of this androgenic steroid in the following: in menopause, in benign mammary disturbances, in suppression of lactation, and in frigidity therapy.	2
			a	important contraindications (such as use in pregnancy) are omitted.	2
			wp	Warnings are omitted regarding use in children and development of hepatic adenomas.	2
				insert does not describe laboratory test interactions (decreased levels of thyroxine-binding globulin) and drug interactions (may decrease blood glucose in diabetic patients).	1
3	Antacid	pi	ind	Product is indicated for infant feedings to "prevent milk from souring and forming curds in the stomach," to aid in digestion, and to prevent constipation; company provided no adequate evidence of efficacy for these indications.	2
			Wp	Label does not warn about use of magnesium containing compounds in renal disease.	2
				Label does not warn about risk of hypermagnesemia in infants subject to chronic administration.	2
3	Antacid combined with bismuth and digestive enzyme	pi	dcp	Company did not provide rationale for this combination.	1
			d	insert does not note that magnesium containlng compounds are contraindicated in severe renal impairment or that calcium-containing compounds are contraindicated in hypercalcemia	2

			wp	Insert does not warn about the following: risk of hypermagnesemia in very young children, bismuth may cause impaction in elderly patients, do not take this antacid if symptoms of appendicitis are present, do not take within 1-2 hours of other oral medication, do not take with large amounts of milk or milk products.	2
				Insert has no information about drug interactions, including: cellulose sodium phosphate, ketoconazole, mecamylamine, methenamine, oral tetracydines, and sodium polystyrene sulfonate resin.	2
				Insert has no information on drug-test interactions, such as with gastric acid secretion test, and assessments of serum calcium, phosphate, potassium, and gastrin.	1
				Insert does not note that bismuth may cause black discoloration of feces.	1
			ar	Insert does not list the following adverse effects: constipation or diarrhea metabolic alkalosis (in renal insuffidency), hypercalcemia, renal calculi, hypermagnesemia, nausea, vomiting, and stomach cramps.	2
3	Anthelmintic	pl	wp	Label omits specific warning about potential neurotoxicity of the drug, especially in children.	2
				Label omits precautions for use (e.g., discontinue use if CNS, gastrointestinal, or hypersensitivity reactions occur; appropriate caution should be exercised for use in patients with severe malnutrition or anemia).	2
			ar	Label omits reported adverse reactions (e.g., gastrointestinal system and central nervous system adverse reactions).	2
			da	Label does not state that the maximum cure rate is usually obtained with a multiple-dose regimen.	2
3	Anthelmintic	pl	dcp	Label does not have information on clinical pharmacology.	1
			ci	Label has no contraindication in patients with epilepsy.	2
			ar	Label has no information on side effects, Including transient neurological effects and urticarial reactions.	2
			od	Label has no information on toxicity.	2
3	Antibiotic	pi	ind	Insert does not note that this antibiotic is not indicated for treatment of the carrier state of *Salmonella typhi.*	2
			da	Company did not provide adequate support for intramuscular injection as an effective method of administration.	2
				No adequate support for pleural lavage as an effective method of administration.	2
				Company did not provide support for dosage intervals of 8 hours for adults and 12 hours for children (U.S. labeling recommends dosages at 6-hour intervals).	1

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Addendum 3-4-Products With a Primary Overall Score of Continued

Overall score	Type of drug	Source	Category	Nature of problem	Query score
3	Anticholinergic antispasmodic	pg	dcp	Entry does not include information on pharmacology.	1
			ing	Entry does not list inactive ingredients.	R
			ind	Entry includes indications for symptomatic treatment of irritable bowel syndrome and renal colic, and as adjunctive therapy in ulcerative colitis, diverticulitis, cholecystitis, and pancreatitis.	2
			wp	Entry does not note that this anticholinergic drug may potentate the sedative effect of phenothiazines.	1
			ar	Entry does not note that mental confusion, bloating, suppression of lactation, and anaphylaxis may occur.	1
			od	Entry does not note that, with overdose, a curare-like action may occur.	2
3	Antidiarrheal combination containing an aminoglycoside antibiotic	pi, pg	w p	Manufacturer claims that the components of this product have synergistic action, but did not provide evidence that this was the case.	1
				Insert is promotional in tone (e.g., through use of adjectives “powerful,” “extraordinary,” and “extremely effective”).	1
				Insert states that one component of the product can eliminate toxins, bacteria and add from the gastrointestinal tract; manufacturer did not provide evidence that this was the case.	1
			ind	Insert states that oral aminoglycoside antibiotic is effective in bacterial diarrhea; manufacturer did not provide evidence of efficacy.	2
				Insert broadly indicates product for symptomatic treatment of diarrhea implying that it is indicated for nonbacterial diarrheas.	2
			wp	Insert states that the aminoglycoside antibiotic orally “has never provoked reactions that are generally presented with its parenteral administration.”	2
				Insert does not caution about the following: administration of other nephrotoxic drugs should be avoided; respiratory parafysis from neuromuscular blockade may occur; monitoring for development of ototoxicity (insert recommends discontinuation of therapy if tinnitus develops); CNS depression syndrome has occurred in infants; encephalopathy has developed from high doses of one component of the product in patients with renal failure.	2
			ar	The following adverse reactions were not listed: nausea, vomiting, paraesthesias, rash, fever, urticaria, angioneurotic edema, eosinophilia, deafness, exfoliative dermatitis, Stevens-Johnson syndrome, dermatitis, anaphylaxis, urticaria, azotemia, leukopenia, thrombocytopenia, pancytopenia, hemolytic anemia, muscular weakness, amblyopia, vestibular dysfunction, visual disturbances including blindness.	2
			od	Insert provides no information about the management of overdose.	2
3	Antiepileptic drug	pi	wp	Insert omits specific warning about use in children under 2 years of age.	2
			ar	Insert does not note that acute pancreatitis associated with use of this antiepileptic may be fatal.	2

3	Antiepileptic drug	pl	dcp	Information on clinical pharmacology is not included in the label.	1
			ind	Label does not have indications and usage information.	2
			ci	Label does not provide information about contraindications.	2
			wp	Label does not provide information on warnings and precautions.	2
				Label provides no information on drug interactions.	2
			ar	Label does not provide information on adverse reactions.	2
			da	Label gives no specific doses for initiation and maintenance.	2
3	Antiepileptic drug	pi	wp	Insert does not warn that sudden withdrawal of this antiepileptic drug could precipitate absence (petit real) status.	2
			ar	Insert does not include information on Stevens-Johnson syndrome, a serious adverse effect of treatment with this antiepileptic.	2
3	Antiestrogenic drug	pg	dcp	Entry does not include a section on clinical pharmacology.	1
			ind	Entry broadly indicates drug for anovulatory women, without emphasizing need to diagnose the cause of anovulation first.	2
			wp	Entry does not include warning about use of this drug in pregnancy.	2
				Entry does not recommend endometrial biopsy in all patients with ovulatory disorders to rule out endometrial carcinoma as a cause.	2
			ar	Entry does not mention among adverse reactions abnormal uterine bleeding, breast tenderness, increased urination, weight gain, and rare incidence of massive ovarian enlargement.	1
3	Antihistamine	pi	dcp	Insert does not include distribution and elimination half-life of drug and its metabolizes (the half-life is particularly long).	2
			ing	Insert does not list inactive ingredients.	R
			ind	Insert broadly indicates this antihistamine for allergic conjunctivitis and “other allergic conditions.”	2
			a	Insert does not contraindicate this drug in patients with hypersensitivity to the drug or any of its inactive ingredients.	1
			wp	Insert does not have precaution about use in patients with hepatic impairment.	1
				Insert has no information about use in nursing mothers.	1
3	Antihistamine	pg	ing	Entry does not list inactive ingredients.	R
			ind	Entry includes indications for use in pregnancy, electroconvulsive therapy, anesthesia, surgery, disease due to radiation, post-fenestration syndrome, and migraine headaches.	2
			wp	Entry does not caution against use in patients with conditions that maybe aggravated by anticholinergic therapy.	1
			ar	Entry does not warn about dizziness, dry mouth, dry nose, dry throat, blurred vision, difficult or painful urination, headache, anorexia, nervousness, restlessness, insomnia, skin rash, thickening of bronchial secretions, tachycardia, epigastric distress, lassitude, excitation, and nausea.	2

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Addendum 3-4-Products With a Primary Overall Score of 3

Overall score	Type of drug	Source	Category	Nature of problem	Query score
3	Antihistamine	pi	dcp	Insert does not list mechanism of action.	1
			ing	Insert does not list inactive ingredients.	R
			ind	Insert adds indications for nausea and vomiting associated with electroshock therapy, anesthesia and surgery, labyrinthine disturbances, radiation sickness, and post-fenestration syndrome; company did not provide adequate evidence of eff icacy for these indications.	2
			wp	Insert does not have precautions regarding use in conditions that maybe aggravated by this product's anticholinergic actions, such as gallbladder obstruction, asthma, narrow angle glaucoma, emphysema, and prostatic hypertrophy.	2
				Drug interactions, such as with alcohol and other sedatives, are not listed.	1
			ar	Insert does not note that this product may cause anticholinergic effects.	2
			od	Insert does not have information about symptoms and management of overdose.	1
3	Antihistamine and vitamin B-6 combination	pg	dcp	No evidence was provided to justify this combination.	1
			ind	Manufacturer submitted no adequate well-controlled studies demonstrating the efficacy for use in pyloric spasm.	2
			wp	Entry does not include warnings about use of this antihistamine with alcohol or for children under 12 years of age.	2
				Entry does not include warning that use of antihistamines in children can cause excitability.	1
3	Antinausea and antivertigo drug	pg	ing	Entry omits mention of tartrazine, a particularly sensitizing agent.	2
			ind	Entry includes indication for motion sickness (i.e., any disorder caused by unaccustomed motions), despite potent side effects; entry indicates product for nausea caused by renal disease, but does not qualify use by noting that renal function impairment may increase the risk of side effects due to decreased excretion.	2
			wp	Entry fails to warn physicians to use this product in closely monitored settings.	2
			da	Company did not provide evidence of safety and efficacy of this drug in children weighing less than 22.8 kg.	2
3	Antitubercuiosis drug	pi	ing	Insert does not list inactive ingredients.	R
			ind	No adequate support for indication for enterococci and Proteus sp.; no statement that rapid development of resistance to Neisseria *gonorrhoeae* can occur.	2
			wp	Insert does not warn about fatalities associated with antibiotic-induced hepatic dysfunction and about increased incidence of hepatomas in mice exposed to this antibiotic.	2
				Insert does not mention that this antibiotic may induce elevations of BUN and serum uric acid.	1

			ar	Insert does not list a number of CNS effects, including drowsiness, fatigue, ataxia, dizziness, mental confusion, inability to concentrate, pains in extremities,and generalized numbness.	1
				Insert does not describe in detail the types of hypersensitivity reactions, including urticaria, pemphigoid reactions, eosinophilia, sore mouth, sore tongue, exudative conjunctivitis, and fever.	2
3	Barbiturate anesthetic	pg, pi	dcp	Entry does not include information on clinical pharmacology.	1
			a	Entry does not contraindicate this barbiturate anesthetic in patients without veins suitable for intravenous administration, patients hypersensitive to barbiturates, patients in status asthmatics, and patients with porphyria.	2
			wp	Entry has no recommendation for special care in administering this barbiturate anesthetic to patients with advanced cardiac disease, increased intracranial pressure, asthma, myasthenia gravis, and endocrine insufficiency.	2
				Entry does not have information about use in pregnancy and in nursing mothers.	1
			ar	Entry does not include among adverse reactions respiratory depression, myocardial depression, prolonged somnolence and recovering bronchospasm, and hypersensitivity reactions.	2
			da	Entry does not provide detailed information about the use of this barbiturate anesthetic; the entry only advises physicians to consult the literature.	2
				Entry does not provide information on preparation of solutions and the incompatibility of this barbiturate anesthetic with other compounds that may acidify the solution.	1
			od	Entry has no information about management of overdose.	2
3	Beta blocker	pl	dcp	Description, actions, and indications are not included in the label.	2
			wp	Label does not have information about warnings and precautions.	2
			ar	Label does not have information about adverse reactions.	2
			da	Label does not have information on dosage and administration.	2
			od	Label does not have information on overdose management.	2
3	Beta blocker	pg	ing	Entry does not list inactive ingredients.	R
			ind	No adequate support for broad indication for thyrotoxicosis (rather than as adjunctive therapy for thyrotoxicosis).	1
			wp	Entry has no section on drug interactions.	2
				Entry does not include the following warnings about the use of beta blockers: the signs and symptoms of acute hypoglycemia and thyrotoxicosis may be masked, the risks of general anesthesia and surgical procedures may be increased.	2
				Entry does not have information about use in nursing mothers or pediatric use.	1
			ar	Entry does not warn about some adverse effects, including impotence and depression.	1
			da	Specific dosing recommendations for patients in renal failure are not provided.	1
			od	Entry has no information about management of overdose.	2

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Addendum 3-4-Products With a Primary Overall Score of 3—Continued

Overall score	Type of drug	Source	Category	Nature of problem	Query score
3	Butyrophenonederivative antipsychotic	pi	ing	Insert does not list inactive ingredients, including tartrazine.	2
			wp	Insert has no precautions about the following: risk of extrapyramidal symptoms with concomitant discontinuation of antiparkinsonian medications; and risk of increased intraocular pressure.	1
			od	For management of overdose, insert recommends supportive care rather than gastric lavage, induction of emesis, charcoal slurry, and other specific measures.	2
3	Calcium channel blocking agent	pg, pi	dcp	Insert does not have information on pharmacokinetics.	1
			ci	Insert incorrectly relates contraindication regarding hypersensitivity to the products teratogenicity (i.e., insert states that the product "should not be administered to patients with known sensitivity to the treatment since teratogenic effects in animals have been reported").	1
			wp	Insert has no warning about the potential of this calcium channel blocker to induce hypotension.	2
				Insert does not note that this calcium channel blocker interacts with digoxin by prolonging AV conduction.	1
			da	Company did not provide adequate support for the long-term dosage regimen suggested in the insert.	1
			od	Insert does not have information on management of overdose.	2
3	Cephalosporin antibiotic	pi	ind	Product indicated for use in treatment of typhoid fever; company did not provide adequate evidence of efficacy for this indication.	2
				Insert does not state that penicillin is the drug of choice in the treatment and prevention of streptococcal infections.	1
			wp	Insert does not make specific reference to risk of pseudomembranous colitis.	2
3	Combination aminoglycoside antibiotic, opiate, antispasmodic, and bulk-forming agents	pg	dcp	Company did not provide rationale for this drug combination and the ratios of its ingredients.	1
			ind	Company did not support the safety of this combination in children and infants.	2
				Company provided no adequate rationale for indicating use as a general treatment for "diarrhea"	2
			wp	Entry does not state that oral dehydration therapy is the primary treatment for acute diarrheal disease.	2
				Entry does not warn against the risk of nephrotoxicity and ototoxicity associated with the use of an aminoglycoside antibiotic.	2
			od	Entry recommends an outdated treatment of overdose (in the U.S., activated charcoal rather than the "universal antidote" is recommended treatment of overdose).	2

3	Combination analgesic	pi	dcp	Company did not provlde justificatlon for this combination.	1
			wp	Insert does not include a warning about the association between aspirin and Reye's syndrome in children.	2
				Insert does not have the following precautions for opiate analgesics: use in pregnant women; use in patients with ulcerative colitis; increase in biliary tract pressure may result in biliary spasm or relic; combination may cause urinary retention and oliguria; combination drug may cause impotence or decline in libido; combination has a prolonged duration and cumulative effect in patients with hepatic or renal dysfunction; use with extreme caution in patients with seizures, acute alcoholism, delirium tremens, shock, untreated myxedema, cor pulmonale, bronchial asthma and chronic pulmonary disease; tolerance, psychological dependence, and physical dependence may occur in patients receiving opiate agonists.	2
			ar	Insert omits certain adverse effects associated with opiate analgesics including respiratory depression and circulatory depression; respiratory arrest, shock, and cardiac arrest; dizziness; visual disturbances; mental clouding or depression; sedation; coma; euphoria; dysphoria; weakness; faintness; agitation; restlessness; nervousness; seizures; delirium; insomnia; dizziness; nausea; vomiting; hypotension; pruritis; urticaria.	2
			da	Insert omits dosage recommendations for children.	2
			od	Insert omits information about overdose signs and management.	2
3	Combination antihistamine, adrenergic decongestant, and anticholinergic	pi	ing	Insert does not list inactive ingredients.	R
			wp	Insert does not note the anticholinergic effects that are associated with antihistamines.	1
				Insert lacks information about numerous drug interactions.	2
				Insert has no information on use in nursing mothers, caranogenesis, mutagenesis, or impairment of fertility.	1
				Insert does not state that in children antihistamines can produce paradoxical reactions, such as irritability and excitation.	1
			ar	Insert does not warn that antihistamines may cause confusion, excitement agitation, severe memory impairment, and that geriatric patients in particular are susceptible to the anticholinergic side effects of antihistamines, especially when they are receiving other drugs that also have anticholinergic effects.	2
				Insert omits mention of numerous adverse reactions associated with antihistamines and/or sympathomimetic amines.	2
			od	Insert does not warn that, in children, overdose of antihistamines can cause hallucinations or death.	2
				Insert does not mention that deaths have been associated with overdose.	2

Continued on next page

Addendum 3-4-Products With a Primary Overall Score of 3

overall score	Type of drug	Source	Category	Nature of problem	Query score
3	Combination antihistamine, corticosteroid, and phenothiazine antipsychotic	pi	dcp	The manufacturer has not provided justification for this fixed combination product over each of the components individually.	2
			wp	Insert does not include the following warnings regarding the corticosteroid in this product: since mineralocorticoid secretion may be impaired, salt and mineralocorticoid may need to be administered; corticosteroids may cause psychic derangements, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations; corticosteroids can cause elevation of blood pressure, salt and water retention, and increased calcium excretion.	1
				Insert does not have specific warnings about phenothiazine use: development of tardive dyskinesia associated with phenothiazine antipsychotics,	2
				Insert does not have warning about neuroleptic malignant syndrome; no precaution about cross-sensitivities to other phenothiazines; no warning about the possibility of liver damage; no warning about pigmentary retinopathy, lenticular deposits, and corneal deposits.	2
				Insert does not have the following warnings for antihistamines: overdoses of antihistamines may cause hallucinations, convulsions, or death, especially in infants and children; products containing antihistamines have additive effects with alcohol and other CNS depressants.	1
			ar	Adverse reactions associated with each of the components of this product are not listed with specificity.	2
			od	Insert does not have information about overdose and treatment.	2
3	Combination expectorant and analgesic	pl	wp	Label provides inadequate information about the enclosed free sample.	2
			od	Label does not contain information on the management of overdose.	2
3	Combination opioid analgesic, aspirin, and acetaminophen	pi	dcp	Insert does not have section describing clinical pharmacology.	1
			ing	Insert does not list inactive ingredients.	R
			ind	Company did not provide evidence of additive analgesic effects of this compound and decreased toxicity compared with the individual components.	1
			ci	Insert does not have contraindication for persons with hypersensitivity to the components of this combination analgesic,	1
			wp	Insert does not warn about the following: potential for drug dependence for this opiate analgesic-containing compound; possibility of Reye's syndrome and the need to avoid giving this product to children with flu-like symptoms; warning about giving this combination to children with asthma; warning about the potential of this drug to cause drowsiness, and a warning about driving or operating machinery after taking this drug; warning about the potential for gastric ulceration and gastrointestinal blood loss in this aspirin-containing combination; precautions about use in patients with head injury, acute abdominal conditions, or in elderly or debilitated patients; precaution advising to avoid using this combination in patients with bleeding disorders or in those patients receiving anticoagulants.	2

				Insert does not have information about use in pregnancy, use in nursing mothers, and pediatric use.	1
				Insert does not have information about drug interactions with CNS-active drugs.	1
			od	Insert does not have information about management of overdose.	2
3	Combination phenothiazine antipsychotic and tricyclic antidepressant	pi	wp	Insert does not have warnings about risk of tardive dyskinesia, cardiovascular concerns, and interaction with guanethidine-like drugs.	2
				Insert does not warn that patients with high suicide potential should not be given large supplies of this drug.	2
			ar	Insert does not list specific adverse reactions associated with this combination phenothiazine antipsychotic and tricyclic antidepressant.	2
			od	Insert does not mention some signs of toxicity (e.g., plasma levels associated with overdose, widening of the QRS complex on ECG, oculomotor paresis).	1
3	Combination phenothiazine antipsychotic and tricyclic antidepressant	pi	ind	Product is indicated for "anxiety" generally, rather than only for those patients for whom anxiety and depression cannot be clearly differentiated.	2
			wp	Insert does not warn about risk of neuroleptic malignant syndrome; insert does not warn specifically about risk of cardiac arrhythmias, myocardial infarction, and stroke.	2
				Insert does not warn that this combination can lower the convulsive threshold in susceptible individuals.	1
				Insert does not warn that prolactin levels maybe elevated, and that galactorrhea, amenorrhea, gynecomastia, and impotence may occur; also, an increase in mammary neoplasms has occurred in rodents.	1
				Insert does not warn about photosensitivity; insert does not warn about risk of paralytic ileus when product is taken with other anticholinergics.	1
			ar	Insert does not mention the following adverse reactions: persistent tardive dyskinesia, cerebral edema, abnormal CSF proteins, neuroleptic malignant syndrome, increased psychotic symptoms, lethargy, paradoxical excitement, restlessness, hyperactivity, nocturnal confusion, bizarre dreams, and insomnia.	2
			od	Insert does not describe symptoms and management of overdose in detail.	2
3	Combination phenothiazine, anticholinergic, and antispasmodic	pi	dcp	No adequate clinical data were provided supporting rationale for this combination.	2
			ind	No adequate clinical data were provided to support indication for "digestive disorders produced or intensified by psychic tension."	2
			wp	Insert has relatively weak warning on tardive dyskinesia.	2

Continued on next page

Addendum 3-&Products With a Primary Overall Score of 3-Continued

overall score	Type of drug	Source	Category	Nature of problem	Query score
3	Corticosteroid for intramuscular administration	pi	ing	Insert does not list inactive ingredients or preservatives.	R
			ci	Insert does not have contraindication for use in systemic fungal infections, idiopathic thrombocytopenic purpura, and septic arthritis.	2
			wp	Insert does not warn about masking signs and symptoms of infection, elevation of blood pressure, avoidance of vaccinations, and potential for local atrophy at injection site.	2
				There are no precautions about enhanced effects of this corticosteroid in hypothyroidism and cirrhosis, caution for use in ocular herpes simplex, risk of psychic derangements, impairment of growth and development in children, muscle wasting, and menstrual irregularities.	2
			ar	Insert does not have comprehensive list of adverse reactions by organ system.	2
3	Methylxanthine bronchodilator	pg	dcp	Entry does not include bioavailability data, including information about differences in half-life for different types of patients (e.g., patients with renal deficiency, alcoholics, smokers, newborns).	1
			wp	Entry does not have the following precautions: use with caution in patients with severe hypoxemia, hypertension, hyperthyroidism, acute myocardial injury, cor pulmonale, or liver disease; use with caution in the elderly and in neonates; use cautiously in patients with history of peptic ulcer.	2
				Insert does not mention drug interactions with lithium carbonate, propranoiol, furosemide, hexamethonium, reserpine, chlordiazepoxide, troleandomycin, erythromycin.	2
				No support for statement in entry that when the drug is taken with foods, its absorption will be slowed, but complete.	1
			od	Labeling omits information about symptoms and management of overdose.	2
3	Monoamine oxidase inhibitor	pi	ci	Insert does not contraindicate use of this monoamine oxidase inhibitor with fluoxetine, buspirone, or dextromethorphan.	2
			wp	Insert does not note that this monoamine oxidase inhibitor should be administered with caution to patients receiving disulfiram (Antabuse) because severe toxicity, including convulsions and death, have been noted in animals who had received this combination of drugs.	1
				Insert does not note incidence of hematologic disorders with use of this drug.	1
				Insert has no information on risk of developing dependency (particularly in patients with a history of drug abuse) or information about withdrawal symptoms.	2
			da	Insert notes that if no response occurs with 30 mg per day “continued administration will probably not be beneficial” (compare U.S. labeling, which notes that dosage maybe increased to 60 mg per day).	1
3	Neuroleptic tranquilizer	pi	dcp	Language in the properties section of the foreign labeling appears to be promotional in tone (e.g., “notably favorable therapeutic index” and “an excellent neuroleptic”).	1
			ind	Company provided inadequate data to support use in shock patients.	2

			wp	Insert omitted several warnings (e.g., reduce concomitantly-administered opioids, monitor patient closely, and have available treatments for hypotension induced by this drug).	2
				Insert omits precautions about use in patients with impaired liver function, use in pregnancy, and use in labor and delivery.	1
			ar	Insert does not list hallucinations among adverse effects.	1
			da	Insert omits information about dosage and administration.	2
			od	Insert omits information about signs of overdose and treatment.	2
3	Nonsteroidal anti-flammatory drug	pi	ind	Product is indicated broadly for conditions "requiring] analgesic or anti-inflammatory activity," as opposed to just osteoarthritis and rheumatoid arthritis.	2
			wp	insert does not warn about the following: severe hepatic reactions, serum-sickness-like syndrome, anaphylaxis, and bronchospasm.	2
				Insert does not have a section on drug interactions.	1
				Insert does not warn about the markedly increased ulcer risk with doses above 20 mg per day.	2
3	Nonsteroidal anti-inflammatory drug	w	ci	Contraindications are omitted for use in pregnant women, based on animal studies of fetotoxicity, minor skeletal malformations, and delayed ossification.	2
			wp	Entry omits mention of drug interactions with aspirin and other nonsteroidal anti-inflammatory drugs.	1
			ar	Several important adverse reactions are not included in the entry (e.g., edema, urticaria, pruritis, tinnitus).	1
			od	Insert does not have information on symptoms and management of overdose.	2
3	Nonsteroidal anti-inflammatory drug	pi	ind	Product is indicated for minor ailments (such as headaches) despite potent side effects; insert does not note that safer alternatives are available.	2
			wp	Insert does not caution about use in patients with acute porphyria.	2
				Insert has no information about use in pregnancy or in nursing mothers.	1
				Insert does not note that agranulocytosis and death have occurred with use of product (notes only that granulocytopenia rarely occurs).	1
			ar	Insert does not mention the following adverse effects: skin reactions, allergic reactions, fever, anaphylactic shock, brochospasm, gastrointestinal symptoms, and drug-induced toxic epidermal necrolysis.	2
			od	Insert has no information about management of overdose.	2
3	Ocular sympathomimetic decongestant combination	pi	dcp	Company did not provide evidence of efficacy of combination over individual components alone.	1
			wp	Insert does not list warnings and precautions.	2
			ar	Insert does not list adverse reactions.	2

Continued on next page

Addendum 3-4-Products With a Primary Overall Score of Continued

overall score	Type of drug	Source	Category	Nature of problem	Query score
3	Oral contraceptive	pl	dcp	Label does not include section on clinical pharmacology.	1
			ing	Label does not list inactive ingredients.	R
			ind	Label has no information on indications and usage.	2
			a	Label does not list contraindications.	2
			wp	Label has no warnings about cardiovascular disorders, myocardial infarction, other thromboembolic and thrombotic diseases, and other risks associated with oral contraceptives.	2
				Label does not include precautions.	2
			ar	Label does not list adverse reactions.	2
3	Phenothiazine antipsychotic	pi	ind	Insert does not note that this phenothiazine antipsychotic is not drug of choice for generalized nonpsychotic anxiety because of the risk of tardive dyskinesia.	2
				Insert does not note that use in "anxiety states" is limited to generalized anxiety disorder and does not note lack of evidence of efficacy in other anxiety states (e.g., due to physical disease, agitated depression mimicking anxiety, character pathologies).	2
			a	Insert contradicts U.S. labeling in recommending use in behavioral disorders associated with mental retardation.	2
			wp	Insert does not note that this phenothiazine antipsychotic may have additive effects with anticholinergics (such as atropine) and interaction with organophosphate insecticides.	1
				Insert does not warn about risk of exfoliative dermatitis, lupus-like syndrome, and cardiac arrest.	2
			ar	Insert does not mention among adverse reactions risk of sudden death secondary to asphyxia due to inhibition of cough reflex.	1
3	Piperazine-derivative antihistamine/vasodilator	pi	ind	Manufacturer provided inadequate evidence, or poorly designed studies to support indications for cerebral trauma sequelae, postapoplectic sequelae, and symptoms of cerebral arteriosclerosis,	2
			wp	Insert does not note that extrapyramidal symptoms have been associated with this drug.	2
				Insert asserts that product "hardly affects blood pressure."	2
				Insert does not provide recommendations about pediatric use.	1
			da	The pediatric dose on the current labeling is too high; adult dosages may also be too high.	2
			od	Insert provides no information about overdose.	2
3	Piperazine-derivative antihistaminehasodilator	pi	dcp	Insert omits information about clinical pharmacology.	1
			ind	Company provided inadequate evidence of efficacy of drug in treatment of cerebral arteriosclerosis, cerebral or cranial trauma, and postapopiectic disorders.	2
			wp	Insert omits general antihistamine precautions.	2
			ar	Insert omits general antihistamine adverse effects.	2
			od	Insert omits information about signs and treatment of overdose.	2

3	Synthetic androgen	pi	ind	Product is indicated for the treatment of virginal breast hyperplasia; company did not provide adequate evidence of efficacy for this indication.	1
				Product is indicated for the treatment of precocious puberty.	1
			ci	Insert omits contraindications regarding use in patients with undiagnosed genital bleeding.	2
			wp	Insert omits warning that patients should be monitored during treatment for signs of hepatic dysfunction.	2
3	Systemic antifungal agent	pg	ind	Entry does not state that this product is not indicated for trivial infections.	2
			wp	Entry omits warnings regarding prophylactic use, tumorigeniaty, use in pregnancy, teratogenicity, and suppression of spermatogenesis.	2
3	Systemic corticosteroid	pi	ing	Insert does not list inactive ingredients.	R
			ind	A number of overly broad and unsupported indications are listed: indication for "arthritis in general," "dermatitis in general," allergic rhinitis (without qualification that systemic corticosteroids should only be used in severe cases), osteoarthritis, corneal marginal ulcers, "purpura vascular alergica," "pseudohemophilia" cirrhosis of the liver, hepatic coma, hepatitis A virus, acute pancreatitis, orchitis, toxoplasmosis (without qualification regarding the limited situations where its use as adjunctive therapy maybe indicated), "certain types of tuberculosis" (without qualification about the limited situations where it may be indicated).	2
			wp	Insert does not warn about the following: increased potassium and calcium excretion, development of cataracts, increased risk of ocular infections, risk of reactivation of tuberculosis in those with a positive tuberculosis test (the insert lists tuberculosis as a relative contraindication to glucocorticoid therapy).	2
				Insert does not caution about the following: increased effect of steroids in hypothyroidism and cirrhosis; risk of hemorrhage with concurrent administration of steroids and aspirin in hypoprothrombinemia; risk of using systemic steroids in diseases where intestinal perforation may occur, including recent intestinal anastomosis and diverticulitis; caution about use in renal insufficiency; and caution about use in patients with myasthenia gratis.	2
3	Systemic corticosteroid	pi	ing	Insert does not list inactive ingredients or preservatives.	R
			ind	Product is indicated for torticollis and is indicated for hay fever without qualification that the use of systemic corticosteroids is only justified in severe cases of hay fever that are intractable to adequate trials of conventional treatment.	2
			wp	Insert does not provide the following precautions: warning against vacdnating patients who are receiving this corticosteroid; precautions regarding the enhanced effects of systemic steroids in hypothyroidism and cirrhosis; caution about use in patients with ocular herpes simplex, psychic derangements, and ulcerative colitis.	2
				Insert has no information about use in pregnancy.	1
			ar	Insert omits significant adverse reactions, including fluid retention and electrolyte disturbances, muscle weakness, peptic ulcers, and impaired wound healing.	2

Continued on next page

Addendum 3-4-Products With a Primary Overall Score of 3-Continued

overall score	Type of drug	Source	Category	Nature of problem	Query score
3	Systemic corticosteroid	pi	dcp	Insert does not have information about actions or pharmacokinetics.	1
			ind	Insert includes indications for hemodynamic shock and endotoxic shock.	2
			wp	Insert does not warn about increased calcium excretion with corticosteroid administration.	1
				Insert does not have a warning about the possible need for salt or mineralocorticoid replacement if mineralocorticoid secretion is impaired; insert does not note that the rate of absorption with intramuscular administration is slower than with intravenous administration.	2
			ar	Insert does not list the following adverse reactions: congestive heart failure in susceptible patients, hypokaiemic alkalosis, musculoskeletal side effects (e.g., muscle weakness, steroid myopathy, decreased muscle mass, osteoporosis, vertebral compression fractures), pancreatitis, ulcerative esophagitis, thin fragile skin, petechiae and ecchymoses, facial erythema, increased sweating, suppression of reactions to skin tests, convulsions, pseudotumor cerebri, headache, menstrual irregularities, suppression of growth in children, secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, ophthalmic disorders (cataracts, exacerbation of glaucoma etc.), blindness with intralesional therapy around the face and head, negative nitrogen balance, hyperpigmentation, hypopigmentation, subcutaneous atrophy, sterile abscess, Charcot-like arthropathy.	2
3	Systemic corticosteroid	pg	ing	Entry does not list inactive ingredients.	R
			wp	Entry does not warn about patients' decreased resistance to infections while on steroids.	2
			ar	Entry does not describe with specificity the adverse reactions associated with corticosteroids.	2
				Entry has no warning about blood pressure elevation.	1
3	Thiuram-derivative drug used in alcoholism treatment	pi, pg	dcp	Insert does not have section on clinical pharmacology.	1
			ing	Insert does not list chemical or structural formula or inactive ingredients.	R
			wp	Insert does not warn against possible severe reactions to this product.	2
				Insert does not warn about carcinogenicity.	1
				Insert does not contain a suggestion that patient carry an ID card indicating that he or she is taking this drug.	1
				Insert does not have warning about possible reaction with alcohol that may occur in hepatic insufficiency and in patients with cerebral damage.	2
				Insert states that "precautions should be taken" when using this product in concomitant conditions (such as diabetes and hypothyroidism) but does not state specifically that these conditions may elicit an accidental reaction.	2
				insert does not alert physicians to the possibility y that patients who are dependent on alcohol may also be dependent on narcotics and sedatives.	1
				insert does not list all of the characteristics of the reaction of this drug with alcohol.	1
			ar	insert states that this drug "does not produce any side effect unless an alcoholic drink is ingested."	2

3	Topical corticosteroid oral paste	pi	dcp	Inadequate evidence to justify statement in insert that [w]hen, used topically in 0.1 % concentration [this product] produces results clinically superior to 1% concentrations of other corticosteroids."	1
			ci	Insert does not contraindicate product in patients with hypersensitivity to its ingredients, and in patients with viral, fungal, or bacterial infections of the mouth or throat.	2
			wp	Insert does not warn about use in pregnancy.	1
				Insert does not warn about masking signs and symptoms of infection.	2
				Insert does not recommend further evaluation if substantial repair of oral tissues has not occurred in 7 days.	2
			ar	Insert does not warn about adverse reactions that may occur from systemic absorption of steroid preparations.	1
3	Topical nitrofuran antibiotic	pi	dcp	Insert does not describe the antimicrobial spectrum of this antibiotic.	2
			ing	Insert does not list inactive ingredients.	R
			wp	Insert does not caution about overgrowth of nonsusceptible organisms.	2
				Insert does not warn that various skin reactions may occur.	1
				Insert has no information about use in pregnancy.	1
3	Tricyclic antidepressant	pg	dcp	Entry has no clinical pharmacology section.	1
			ing	Entry does not list inactive ingredients.	R
			wp	Entry has no warning about risk of developing extrapyramidal symptoms, tardive dyskinesia or neuroleptic malignant syndrome.	2
				There is no warning about the following: that this tricyclic antidepressant may cause an exacerbation of paranoid symptoms in paranoiacs, the drug may cause manic depressive patients to shift into mania the drug may cause schizophrenic patients to develop increased symptoms of psychosis.	2
				Entry does not include list of drug interactions other than with monoamine oxidase inhibitors (e.g., alcohol, barbiturates, other CNS depressants, anticholinergics, and interactions with electroconvulsive therapy).	2
				Entry does not include admonition to prescribe this antidepressant in the smallest suitable amount in view of the risks of suicidal overdose.	2
			ar	Entry lacks warnings about the following adverse reactions: skin rash, drug fever, drowsiness.	1
			da	There is no mention that dosage should not exceed 300 mg per day until this dosage is tried for two weeks.	2
			od	Entry does not have information about overdose.	2

Continued on next page

Addendum 3-4-Products With a Primary Overall Score of 3-Continued

overall score	Type of drug	Source	Category	Nature of problem	Query score
3	Xanthine-derivative bronchodilator	pg	dcp	Entry does not include information on bioavailability (including differences in half-life for newborns, renal deficient patients, alcoholics, and smokers).	1
			wp	Entry does not warn about manifestations of toxidty from conventional doses and excessive doses, including convulsions, tachycardia ventricular arrhythmias; or that children may have a marked sensitivity to the CNS stimulant action of this drug.	2
				Entry does not include caution about use in patients with liver impairment or severe hypoxia.	1
				Entry does not list drug interactions, such as with erythromycin, troleandomycin, and lincomycin.	1
			ar	Entry omits adverse reactions associated with this xanthinederivative bronchodilator, including tachycardia extrasystoles, flushing, hypotension, circulatory failure, life-threatening ventricular arrhythmias, tachypnea albuminuria increased excretion of renal tubular cells and red blood cells, diuresis, hyperglycemia, syndrome of inappropriate antidiuretic hormone.	2
			od	Entry does not include information on treatment of overdose.	2

SOURCE KEY: pi - package insert; pg. prescribing guide entry; pipa. package insert pending approval; pl -. package label; pds - product document.

CATEGORY KEY: dcp= description/clinical pharmacology; ing - ingredients; ind = indications; ci - contraindications; wp - warnings and precautions; ar - adverse reactions; da - dosage and administration; od - ovedose information.

Addendum 3-5-Products With Labeling That Was Adequate Except for Failure To List Inactive Ingredients

Type of drug	Source
Aminoglycoside antibiotic for ophthalmic and otic administration	pi
Antacid	pl
Anthelmintic drug	pg
Antihistamine	pi
B complex vitamin	pi
Combination aminoglycoside and polymyxin antibiotic for ophthalmic use	pi
Combination synthetic opioid and aspirin	pi
Corticosteroid for ophthalmic administration	pi
Dietary fiber supplement	pg
Long-acting nitrate vasodilator	pi
Multivitamin and multimineral preparation	pi
Multivitamin and multimineral preparation	pi
Quinoline-derivative antiprotozoal agent	pi
Selective alpha-blocking agent	pi
Synthetic androgen	pi
Topical analgesic combination	pi

SOURCE KEY: pi - package insert; pg - prescribing guide entry; pl - package label.

Addendum 3-6-Products With Labeling That Was Not Evaluated Fully (Score = NA)

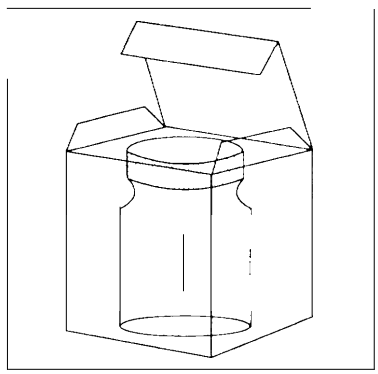
Type of drug	Source
Aminoglycoside antibiotic	pi
Aminoglycoside antibiotic for ophthalmic and otic administration	pi
Anabolic steroid	pi
Anesthetic for ophthalmic administration	pi
Anticholinergic antispasmodic	pi
Arterial vasodilator antihypertensive	pi
Artificial sweetener	pi
Combination corticosteroid and antibiotic for ophthalmic administration	pi
Combination topical antifungal	pl
Corticosteroid and anesthetic combination for topical administration	pg
Direct-acting arterial vasodilator	pi
Methylxanthine bronchodilator	pl
Multivitamin and multimineral preparation	pg
Multivitamin and multimineral preparation	pi
Multivitamin with iron and calcium	pi
Nitrate vasodilator	pi
Nitrate vasodilator	pi
Opioid analgesic	pi
Oral contraceptive	pg
Penicillin-derivative antibiotic	pi
Phosphoric acid-derivative antibiotic with anesthetic	pi
Polyene antifungal agent	pi
Polyene antifungal and antiprotozoal agent	pi
Quinolone antibiotic	pg
Quinoline antiprotozoal drug	pi
Systemic corticosteroid	pi
Tetracycline analogue antibiotic	pi
Thiazide diuretic	pi
Topical anthelmintic	pi
Vinca alkaloid antineoplastic agent	pi
Vitamin and vasodilator combination	pi

SOURCE KEY: pi= package insert; pg - prescribing guide entry; pl - package label.

Drug Prescribing Information in the United States and Other Countries

4

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.

Multinational Pharmaceutical Corporations and U.S. Extraterritorial Jurisdiction | 5

The largest pharmaceutical companies in the world have sales of over one billion dollars annually and operate across the globe. While every company has headquarters in a particular country, they all have manufacturing and other facilities in other countries. Foreign operations may be managed or controlled by the headquarters, but they are subject most directly to the laws of the countries in which they are located. For U.S.-based multinational corporations (MNCs), U.S. law applies fully to a company's domestic operations, but only certain aspects of foreign operations that affect U.S. commerce directly are governed by U.S. law. The extent to which drug labeling in developing countries can be influenced by U.S. law is, therefore, limited, The discussion of U.S. extraterritorial jurisdiction in this chapter is key to understanding the potential for the United States to extend its control over labeling beyond U.S. borders. This chapter also describes MNCs generally, including their basic structure and operations, and more specifically, characteristic features of typical U.S. pharmaceutical MNCs.

"A strange justice that is bounded by a river"

Pascal

THE MULTINATIONAL CORPORATION

The distinguishing characteristic of an MNC is that it has direct investments in several countries. The MNC does not merely market its product in other countries, but owns or controls production or service facilities in foreign countries. This is often referred to as direct foreign investment, which under U.S. law means ownership of at least 10 percent of voting securities of a corporation or an equivalent interest in an unincorporated firm (236). (Others define it as investment accompanied by significant ownership of at least 10 to 25 percent of stock in the foreign company or significant management control (256)). The MNC's

foreign investments are directed and managed according to a business strategy that links the entire enterprise (80). Some scholars further distinguish MNCs as those enterprises that transact a substantial amount of business abroad so that their financial status is dependent on operations in several countries and their management decisions take into account multinational alternatives (80).

PHOTO CREDIT: P. MERCHEZ, WHO



Suburban pharmacy in Latin America displaying products from around the world.

It may be somewhat misleading to refer to an MNC as a single entity when it actually consists of a number of separate corporations linked economically, operating in different countries (80). Some experts use the term MNC to describe the headquarters of the enterprise, and describe the entire operation as a "multinational enterprise." In this report, the term MNC is used to refer to the entire enterprise.

The Rise of the U.S. Multinational Corporation

U.S. MNCs have existed since the early 1900s, but have attained their great prominence since the 1950s (253). In the early expansionary years, there was considerable concern that direct investment by multinationals could pose a threat to national sovereignty and hinder rather than promote economic development of host countries. This was of particular concern to developing countries. These concerns led to the negotiation of codes of conduct that set standards of behavior for MNCs (255). The codes, voluntary agreements between countries, were negotiated between industrial countries and within the United Nations to address the concerns of investment in developing countries (125,255).

The concern over foreign direct investment has largely dissipated, and it is, on the whole, seen as a positive force, especially for developing countries. One reason may be that developing countries have become more comfortable and sophisticated in controlling foreign investment and in insuring that it meets their countries' economic needs (255).

Expansion of U.S. MNCs has continued in the 1980s as Eastern Europe, the former Soviet Union, and China began to allow direct foreign investment, mainly through joint ventures with domestic partners. The dominance of U.S. MNCs has eroded, however, as non-U.S. multinationals, primarily from Western Europe and Japan, have taken a larger role in the world economy (92). In 1960, U.S. direct investment abroad accounted for one-half of all foreign investment in the world; by 1987, it accounted for one-third (238). The number of MNCs based in developing countries has also increased, but they are still few and small relative to the multinational giants of the industrial countries (225).

The rapid growth of MNCs has transformed the world economy in just 30 years. According to one U.S. business magazine, "competition for goods, services, and ideas pays no respect to national borders or the old geopolitical divides that supposedly separate North from South, East from West" (124). However, while the MNC has changed the nature of global markets, the international legal system has continued to treat the separate corporate entities of an MNC as separate corporations, subject to the laws of their host countries. One commentator has noted that,

"while the home country regulates the head and shoulders of the MNC, various other countries regulate its limbs and extremities" (172). Although the MNC is a single corporate enterprise and major strategic business decisions are made at corporate headquarters for all operations, individual subsidiaries are usually managed by nationals of the country in which they are located, and national legal systems address the individual parts.

The Structure of U.S. Multinational Pharmaceutical Corporations

A U.S. MNC is a company with headquarters in the United States and with subsidiaries in other countries. The foreign subsidiaries often are incorporated under the laws of the "host" countries in which they are located. The country in which corporate headquarters is located is referred to as the "home" country. A large U.S. pharmaceutical MNC may have up to 50 or more foreign subsidiaries, of which perhaps a third are major operations. For example, the 1989 Bristol-Myers Squibb Company's annual report filed with the U.S. Securities and Exchange Commission (29) (the "1989 10-K") states that the company owns 22 major manufacturing facilities in Australia, Brazil, Canada, Denmark, England, France, Italy, Japan, the Netherlands, the Philippines, and Venezuela, and has well over 100 foreign subsidiaries. Pfizer Inc.'s 1989 10-K (176) states that its major manufacturing facilities are located in Great Britain, Ireland, France, West Germany, Japan, Brazil, India, Mexico, Argentina, Spain, and South Korea, with an additional 40 plants around the world, and a total of more than 150 foreign subsidiaries.

Subsidiaries of these companies that do not produce pharmaceuticals may be small marketing facilities, they may be "holding companies" whose sole function is to own stock in or supervise the management of other companies, or they may be engaged in other commercial activities. In addition to making pharmaceuticals for human use, Merck & Co., for example, is a diversified corporation that develops and markets animal health and agricultural products and specialty chemicals, e.g., for water treatment, oil field drilling, food processing, cleaning, and disinfecting (155).

In the pharmaceutical industry, foreign operations are usually carried out by subsidiaries owned entirely or in the majority by the parent corporation. Complete ownership is preferred because it allows the company to protect its technology and trademarks, maintain control over the quality of production, and ultimately, protect its reputation (65). But joint venture arrangements, in which a certain percentage of the subsidiary's stock is held by host country nationals, are common. A joint venture may be the only way a company is a!lowed by a foreign government to operate the subsidiary. This is particularly true in some developing countries whose governments



PHOTO CREDIT: P. MERCHEZ, WHO

Pharmaceutical paekaging in Latin America.

are attempting to promote national businesses (181). It is the smaller MNCs, however, that are more likely to be forced by host governments to enter into joint ventures, because they do not have the bargaining power to insist on complete ownership (65).

Developing countries account for less than 10 percent of worldwide pharmaceutical production (68), and in 1980 (the latest year for which data

are available) a handful of developing countries-Argentina, Brazil, Egypt, India, Mexico, and the Republic of Korea—accounted for **two-**thirds of it **(68).** Developing countries rely heavily on imports of finished products or bulk products which are then repackaged for sale by subsidiaries of MNCs (223). Certain developing countries, however, are beginning to require that MNCs establish more sophisticated manufacturing facilities in their countries.

Indonesia recently passed legislation requiring all foreign-controlled pharmaceutical companies to establish Indonesian production of at least one raw material used in pharmaceuticals sold there



PHOTO CREDIT: W. LINDWER, WHO

Drug packaging in Kenya.

(135). Similarly, in India, foreign companies must establish a certain percentage of bulk drug manufacturing capacity, rather than just formulation and packaging plants (140). Producing active ingredients involves more investment and transfer of technology than does formulation. Because the risk of disclosing trade secrets is also higher, companies generally prefer to avoid transferring technology (182).

By selling the rights to its patents, a manufacturing process, a trademark, marketing services, or other technical skills, MNCs also may license their proprietary products to a foreign company for production and sale. In return, the MNC receives royalties on the products. This arrangement allows the company to sell its product abroad without taking the risks of direct investment (18 1). Syntex Corporation, for example, told OTA that at least one of its products included in the OTA survey was produced and marketed in Panama under a licensing arrangement with another company, and another one was produced and marketed in Thailand by a subsidiary of another MNC (213). The degree of control exercised by the licenser over the way in which a product is marketed or labeled is determined by the licensing contract.

INTERNATIONAL LAW AND EXTRATERRITORIALITY

Most international law is "customary" law, embodying general principles recognized by most civilized nations (105). The goal of international law is to promote stability among nations. Long-range interests of individual nations and the need for reciprocity in international relations determine the legal domain which each nation will claim as its own (136). International law is made by countries entering into treaties in which they agree to take, or refrain from taking, certain actions. International agencies, such as the United Nations, can influence the development of international law by promulgating guidelines or codes of conduct, but such proclamations are effective only if adopted by individual states. The United Nations International Court of Justice (ICJ) was setup to resolve disputes among countries, but the system works only when countries submit to the Court's jurisdiction and adhere to its decisions. To date, the ICJ's docket has been very light (6).

A nation's decision to exercise extraterritorial jurisdiction is usually guided by the basic principles of international law: the territorial principle, the nationality principle, and the protective principle. The *territorial principle* remains the fundamental doctrine of international law. It provides that each nation has the exclusive right to regu-

late the conduct of all residents, individuals, and corporations within its borders (82). A corollary to the territorial principle is that foreign governments do not have the right to interfere in the internal affairs of another State. Therefore, under an absolutist interpretation of the territorial principle, the United States would never have the right to exercise jurisdiction over a foreign subsidiary of a U.S. company because such action would impinge on the sovereign interests of the country in which the subsidiary operates (73).

The territorial principle, however, is not absolute. The *protective principle* recognizes a country's right to extend its jurisdiction to conduct occurring outside its borders if the action threatens the national security or functioning of government activities. Examples of such conduct are counterfeiting currency or forging entry visas outside a country's boundaries (189). A broader exception is the *nationality principle*, which recognizes a country's interest in maintaining some degree of control over its citizens residing or traveling in other countries. Other examples are the U.S. policy of requiring its citizens to pay certain income taxes when residing abroad (237), and the selective service law, which requires all male U.S. citizens, regardless of foreign residence, to register for U.S. military service (50 U.S.C. App. § 453).

The nationality principle may also be applied to corporations, which, in legal terms, are "persons." However, there is international disagreement on how the nationality of a corporation is determined. Most nations assert that a corporation is a citizen of the country in which it is incorporated, or the country housing the center of the corporation's activities. A subsidiary, although part of a larger corporation with headquarters in another country, is usually considered a national of the country in which it operates. The United States, however, has exercised jurisdiction over foreign corporate subsidiaries based on ownership or control by a U.S. corporation, primarily to enforce trade embargoes and boycotts, a practice that is a source of international controversy (2,218).

The United States is also a proponent of extraterritorial jurisdiction based on the effects *principle*, which holds that a nation may exercise jurisdiction over certain conduct occurring outside its territory if it has a "substantial," "direct," or "adverse" effect within the country. It is usually limited to acts "generally recognized as constituent elements of a crime or tort under the laws of the States that have reasonably developed legal systems" (73). The effects principle can be viewed as a modification of the territorial principle in that jurisdiction is based on addressing an adverse effect within the territory. The effects principle, however, is not universally accepted as a legitimate basis for extraterritorial jurisdiction under international law (218).

The United States has used the effects principle primarily to enforce economic laws, antitrust laws in particular. The effects principle was first pronounced in a 1945 case in which a U.S. court was asked to decide whether U.S. antitrust laws could be applied to an anticompetitive agreement between several European companies and a Canadian corporation. The Canadian corporation had corporate links to the United States. The court decided that "a state may impose liabilities, even upon persons not within its allegiance, for conduct outside its borders that has consequences within its borders which the state reprehends" (228). The controversial U.S. position on antitrust law is discussed later in this chapter.

Principles of international law can only provide general guidance, especially when debating extraterritorial jurisdiction. Application of one principle may lead to results that are contradictory to another principle. Which principle should be given greater weight in a particular situation can be determined only by examining the competing interests of the countries and other parties involved. In many situations, one country may believe a particular extraterritorial act is in accordance with international law, and another will see it as contrary. As one U.S. court stated, "[f]rom

the body of international law, Congress may pick and choose whatever recognized principle of international jurisdiction is necessary to accomplish the purpose sought by the regulation" (229). To understand the U.S. position on extraterritorial jurisdiction, it is helpful to examine U.S. statutes, court cases, and other actions concerning extraterritorial jurisdiction in the field of foreign relations law.

U.S. Foreign Relations Law

The American Law Institute's recent *Restatement (Third) of the Law: The Foreign Relations Law of the United States (6) (the* "Restatement"), developed by prominent U.S. judges, legal academicians, and lawyers, is the most thorough analysis of U.S. foreign relations law. The Restatement brings together all relevant precedents in an attempt to develop a coherent doctrine that addresses the question of extraterritorial jurisdiction "as it would be pronounced by a disinterested tribunal, whether United States or some other national or an international tribunal."

In international law, where no single body provides a definitive legal opinion (as the Supreme Court does for U.S. constitutional law), the Restatement is very influential. A criticism of the Restatement is that it reflects the U.S. view of international law and, especially with respect to extraterritorial jurisdiction over U.S. foreign subsidiaries, the U.S. interpretation of international law is at odds with most other countries (186, 220). The Restatement should be cited with caution because it not only summarizes the law as reflected in judicial cases and legislative and executive actions, it expands on the precedents and prescribes what direction the law should take, so it does not necessarily reflect current law.

The Restatement recognizes that the territorial, nationality, and effects principles provide a basis for exercising jurisdiction over an activity, person, or corporation. With respect to MNCs, the general rule is that *country A* may not exercise jurisdiction over a subsidiary incorporated under the laws of *country B* merely because it is owned or controlled by citizens of *country A.* There are, however, limited exceptions to this rule, including regulations directed at the parent corporation (located and incorporated in *country A),* requiring that *uniform* accounting standards be used for all MNC operations; regulations requiring that certain information about foreign operations be disclosed to investors; and regulations requiring that tax returns of the entire MNC be consolidated. These laws may be important to the regulating country and should not interfere in the internal affairs of the host country.

The Restatement also recognizes that, in certain circumstances, regulation of foreign subsidiaries is necessary to further important national interests. The United States has regulated foreign subsidiaries to enforce trade sanctions in time of war or when it has felt the actions of another country threatened U.S. interests. The Restatement cautions that these actions should not be taken unless it is important for carrying out an essential national program, and the regulation will not conflict with the laws or policies of the host country. The Restatement specifically rejects asserting extraterritorial jurisdiction over "predominately local issues, such as industrial and labor relations, health and safety practices."

The framework provided by the Restatement invariably leads to conflicts with the foreign country sovereign right to regulate activities within its territory. The United States has been more willing than most countries to regulate extraterritorially (186) and not surprisingly, the Restatement attempts to present concrete guidelines for resolving the types of conflict that have arisen when the United States has enforced its extraterritorial laws and regulations.

The Restatement's approach to resolving disputes over extraterritorial jurisdiction is based on the longstanding international doctrine of comity. Comity captures in a single word a complex and ill-defined concept used by courts in setting limits on their extraterritorial powers. It has been defined by the U.S. Supreme Court as (94):

> ...neither a matter of absolute obligation on the one hand, nor one of mere courtesy and good will upon the other. . .it is the recognition which one nation gives to the legislative, executive, or judicial acts of another nation, having due regard both to international duty and convenience, and to the rights of its own citizens or of other persons under the protection of its laws.

U.S. courts have relied on the comity doctrine to decline jurisdiction to show respect for foreign sovereignty, protect parties' expectations in international commerce, and to avoid interference in foreign relations (175).

Elements of the principle of comity have been integrated into the Restatement's "rule of reasonableness," which can be used to decide whether an extraterritorial action is in accordance with international law. According to the rule, a nation should exercise extraterritorial jurisdiction only if: 1) it has a legal basis for exercising jurisdiction under the nationality or effects principle, and 2) it determines that it is reasonable to exercise jurisdiction in the particular situation. For example, if the United States wanted to regulate foreign subsidiaries operating in Latin America, it should consider the links between the business carried out by the foreign subsidiaries and the United States. The United States is less justified in regulating a foreign subsidiary engaged in purely local business transactions, or one that is owned partially by foreign nationals than it is in regulating one with significant business transactions with the United States and owned entirely by the parent company.[1]

The character of the activity to be regulated may also be relevant. For example, if the foreign subsidiary's main activity is building roads or hospitals under contract to the foreign government, U.S. legislation affecting this contract will interfere with the foreign government's sovereignty. Consideration should also be given to the expected impact of the regulation on current business practices and on whether reasonable commercial expectations will be disrupted.

Finally, the Restatement instructs the United States to evaluate the impact that the proposed legislation would have on the current international political, legal, and economic system and on the likelihood of direct conflicts with the other country's laws (6). These considerations involve balancing the competing interests of the countries involved directly in the situation, and the impact the decision will have on international economic and social discourse (136). Depending on the weight given to various factors, analyses using the rule of reasonableness could support two contradictory positions, providing for little predictability **(73).**

The Restatement claims that the rule of reasonableness is emerging as a principle of international law (6), but there is debate over this point in international legal circles (175). Even the U.S. Government has not endorsed the approach unconditionally, and might choose to exercise extraterritorial jurisdiction when the factors enumerated above appear to weigh against the decision (25). The rule of reasonableness is relevant to the debate because it reflects, to some degree, U.S. interpretation of extraterritorial jurisdiction and sets forth some of the factors that lead to disagreement in related disputes. It should be noted, however, that many other countries believe that U.S. extraterritorial jurisdiction does not extend as far as provided for in the Restatement 186).

A final issue not considered by the Restatement, but important in international economic and business policy, is national treatment. The U.S. Government often protests the actions of foreign governments when they give preferential treatment to their own national companies, placing U.S. foreign subsidiaries at a disadvantage.

[1] Other countries would object to the United States exercising jurisdiction on the basis of U.S. ownership of a corporation that is located and incorporated abroad (2),

By passing U.S. legislation intended to control the operations of foreign subsidiaries of U.S. MNCs, and also expecting the host government to extend preferential treatment to those subsidiaries as if they were national companies, the U.S. Government may itself be perceived as a source of unfairness (25).

Extraterritorial Jurisdiction in the US. Courts

U.S. courts are concerned primarily with illegal conduct within the United States, but sometimes the courts apply U.S. law to acts occurring outside the country.[2] One area in which U.S. courts have been particularly active with respect to foreign corporations, including subsidiaries of U.S. companies, is in antitrust law. There are other areas of law in which U.S. courts struggle with the proper limits of extraterritorial jurisdiction over foreign subsidiaries; however, antitrust law has been particularly fertile and the doctrines developed by the courts are generalizable to other areas of judicial action.

The primary antitrust statute is the Sherman Act (15 U.S.C. § 1-7), which makes it illegal for an individual or corporation to enter into any agreement, conspiracy, or combination that restrains trade among the States or among foreign nations, or to take any action to monopolize trade (i.e., to control prices or preclude competition). The Federal Trade Commission Act (15 U.S.C. § 45 et. seq.) and the Clayton Act address other aspects of anticompetitive behavior. These three statutes have been called by the Supreme Court the "Magna Carta of Free Enterprise" (230).

The application of U.S. antitrust laws extraterritorially has not been without controversy, and has been opposed by a number of foreign governments (73,218). Opposition stems from the fact that antitrust law was originally unique to the American legal system. The United States was, therefore, prosecuting companies for actions that were legal in the countries in which they took place. Although a number of European countries have recently passed antitrust laws, few impose penalties as severe as those in the United States (104). Most controversial have been private antitrust suits brought by U.S. citizens. Because they are private, the U.S. Government cannot readily use diplomatic channels to ease the conflicts they engender (185).

In 1982, Congress amended the Sherman Act with the effect of constraining the extraterritorial reach of antitrust law. The changes were made in response to concern that U.S. businesses were being hindered from entering into international transactions because of uncertainty about the applicability of U.S. antitrust laws (234). Congress noted that there was a lack of consistency both among judicial interpretations and between the judiciary and the executive branch over the "quantum and nature of the effects required to create jurisdiction" (234). For example, while one court required conduct that "directly affect[s] the flow of foreign commerce into or out of this country" (221), another court reasoned that "it is probably not necessary for the effect on foreign commerce to be both substantial and direct as long as it is not *de minimus" (50).*

To remedy this situation, the amendments provided that a transaction between two foreign firms, even if U.S.-owned, would not be subject to U.S. antitrust laws unless there was a direct, substantial, or reasonably foreseeable effect on domestic commerce (15 U.S.C. § 6a, 15) (58). Absent a significant adverse effect, a foreign transaction that violates U.S. antitrust laws and involves U.S. companies or their subsidiaries is subject only to the laws of the country in which the business is conducted (234). In addition, Congress stated in the legislative history that the amendments were not designed to alter the right

[2] The court must decide that a case: 1) concerns conduct that is under the jurisdiction of U.S. law and 2) that it has jurisdiction over the defendants. This section addresses only issues of the former type ("subject jurisdiction") and not of the latter type ("personal jurisdiction").

of U.S. courts to "recognize the special international character of transactions" and to employ notions of comity to decline to exercise jurisdiction over a case, even when the antitrust act specifically gave the court the authority to prosecute the case (234).

The instruction on employing notions of comity gave U.S. courts the right to take into account diplomatic and political considerations in deciding whether to exercise jurisdiction, even when there is an effect on U.S. commerce. The factors that courts consider are (27,141 ,219):

1. the degree of conflict with foreign law or policy,
2. the nationality and allegiance of the parties and the principal places of the business of any corporations,
3. the extent to which enforcement in either country can be expected to achieve compliance,
4. the relative effect of the conduct on the United States as compared to other nations,
5. whether there was intent to harm the United States, and
6. the relative importance of the violations under U.S. law versus the law of the foreign country in which the conduct occurred.

Trade Embargoes and Economic Sanctions

Trade embargoes and other economic sanctions have been used by the United States in times of war to conserve U.S. resources, to cut off critical supplies to enemies, and to preserve neutrality (161). More recently, trade sanctions have been used to express opposition to domestic and foreign policies of other countries, e.g., violating human rights laws, supporting terrorism, or using military force within another country's borders (218).

A trade embargo or economic sanction is usually implemented after the President issues an Executive order, pursuant to congressional authority, announcing the sanctions and the reasons for them. The Executive order will often instruct an executive agency, e.g., the U.S. Department of Commerce or Treasury, to promulgate regulations to implement the sanctions. A trade embargo may prohibit all U.S. export trade with a certain country, or may be limited to certain goods, such as military equipment. Alternatively, the United States may halt all financial transactions with a country and may freeze its financial assets held within the United States. To make the embargo more effective, the United States sometimes orders U.S.-owned or -controlled foreign subsidiaries to cease trading with a targeted country (76). Several statutes authorize the President to take such action during peacetime.[3]

The Export Administration Act (EAA) (50 U.S.C. App. § 2401 et. seq.) permits extraterritorial export controls. The EAA authorizes the President to restrict the export of goods and technology that would "make a significant contribution to the military potential of another country" or prove detrimental to the national security of the United States, or to impose such restrictions as necessary to further "significant foreign policy goals" of the United States. (50 U.S.C. § 2402, 2404, 2405).

The EAA's extraterritorial provisions were first applied to limit the compliance of U.S.-controlled foreign subsidiaries with an Arab trade boycott of Israel, The antiboycott provision, however, applied only to transactions relating directly to "U.S. commerce," which occur when the foreign subsidiary acquires goods and services from a person in the United States to fill a *specific order* for a person outside the United States

[3]The Trading with the Enemy Act of 1917 (50 U.S.C.§ 5(b)) authorizes the imposition of embargoes during times of congressionally declared war.

(15 C.F.R. § 769.1 (1991)). Foreign subsidiaries were also exempted if the national laws of their host country required compliance with the boycott, recognizing the host country's sovereign right to regulate commerce within its borders (218).

The second statute commonly used to impose economic sanctions is the International Emergency Economic Powers Act (IEEPA)(50 U.S.C. § 1701-1706).

Enacted in 1977, the IEEPA authorizes the President to act when faced with:

> . . . any unusual and extraordinary threat, which has its source in whole or substantial part outside the United States, to national security, foreign policy or the economy of the United States, if the President declares a national emergency with respect to such threat (50 U.S.C. § 1701).

The President is authorized to investigate, regulate, or prohibit certain financial transactions, such as transactions in foreign exchange, banking transactions, and property transfers. (50 U.S.C. § 1702). The IEEPA was used by President Carter in 1981 to freeze Iranian assets held by U.S. corporations or their foreign subsidiaries. In addition, President Carter prohibited all U.S. banks and their wholly owned foreign banking subsidiaries from engaging in financial transactions with Iran (218). In 1990, President Bush invoked the IEEPA, as well as the EAA, to impose comprehensive economic sanctions against Iraq.[4]

Under each of these statutes, the President may assume jurisdiction over a foreign subsidiary based on its ownership or control by a U.S. corporation or U.S. citizen (133).[5] However, this extraordinary power is available only during a national emergency or when foreign policy considerations make such action imperative (218).

Before issuing regulations under these statutes, the President must make a case that important U.S. interests are being threatened and no amount of compromise or negotiation can address the problem. Sanctions cannot be implemented under the EAA or the IEEPA until the President has consulted with Congress and, in the case of the EAA, with the affected industries. The EAA requires the President to conclude that (162):

1. export controls are likely to achieve the intended foreign policy purpose;
2. the United States can effectively enforce the sanctions;
3. the sanctions are consistent with U.S. foreign policy objectives;
4. the benefit to U.S. foreign policy objectives exceeds any adverse effects the sanctions will have on U.S. exports and international competitiveness, including the impact on the reputation of U.S. companies as reliable suppliers of goods; and
5. reasonable effort has been made to achieve the desired aim through negotiation or other means (50 App. U.S.C. § 2405).

There are comparable procedural requirements under the IEEPA (50 U.S.C. § 1703). Despite the limits on using these sanctions, a number of foreign countries contend that the United States does not have the legal right to exercise jurisdiction over foreign incorporated subsidiaries under any circumstances (59).

In response to these objections, the United States has, at times, controlled the actions of U.S. -owned foreign subsidiaries by **regulating the** behavior of the U.S. citizens or domestic corporations responsible for the operations and corporate policies of the subsidiaries. This approach is less controversial because the right to exercise some control over private citizens, whether they

[4] See also 55 FR 31803, 55 FR 31805, 55 FR 33089, and 55 FR 33091.

[5] The use of control as a test for exercising jurisdiction over separate corporate entities is also found in domestic law. See e.g., 47 U.S.C. § 2 19(a), 49 U.S.C. § 310, and 26 U.S.C. § 825c. See also reference number 19.

reside at home or abroad, is recognized under international law, as is the right to regulate domestic corporations.

The effectiveness of indirect controls depends on the situation. For example, the 1970 regulations that implemented trade sanctions against Rhodesia in support of a United Nations effort to promote self-determination for the black majority population (The United Nations Participation Act, 22 U.S.C. §287 (1979)) were worded very broadly to capture almost all possible transactions. The regulations prohibited U.S. citizens and residents who were officers, directors, and principal managerial personnel of foreign subsidiaries from *authorizing* or *permitting the* foreign subsidiary to engage in a prohibited transaction with Rhodesia. A U.S. citizen could be in violation of the regulations even if he did not actively engage in the transaction (218).

The Rhodesian regulations contrast with similar regulations implemented during the 1980 boycott of the Moscow Olympics, under which U.S. citizens and domestic corporations were prohibited from "actually" authorizing, arranging, directing, or participating in a prohibited transaction (15 C.F.R. § 385.2 (d)(3) (1982)) (218). These terms imply that direct involvement was a necessary element for attributing liability to a U.S. citizen or corporation. This left open the possibility of U.S.-owned foreign subsidiaries engaging in business transactions related to the Moscow Olympics.

The indirect approach to regulating foreign operations of U.S. MNCs does not interfere directly with another country's sovereign right to control the actions of corporations operating within its borders. Wholly owned subsidiaries that are managed almost exclusively by foreign nationals may escape regulation. However, even indirect regulations may cause international tension because U.S.-owned foreign subsidiaries may feel pressure to support U.S. policy or may be directed to do so by the corporate parent, even if technically exempted from the regulations.

The Foreign Corrupt Practices Act

In the examples discussed above, foreign subsidiaries were caught in disputes between the United States and foreign governments. In some cases, the actions of U.S.-owned foreign subsidiaries themselves may prompt regulation. The prime example is the Foreign Corrupt Practices Act (FCPA) of 1978, which addresses the bribery of foreign officials by U.S. MNCs. The FCPA is one of the few pieces of legislation that requires foreign operations of a U.S. MNC to comply with the same standards for corporate behavior that govern domestic companies. However, the FCPA does not regulate the foreign subsidiary directly, but instead imposes liability on a U.S. domestic corporation or it officers, directors, stockholders, agents, or employees if they knowingly bribe a foreign official or authorize a payment that they know will be used as a bribe (15 U.S.C. § 78dd-1, 78dd-2).

In 1977, the U.S. Securities and Exchange Commission (SEC) revealed that approximately 400 U.S. companies, including 117 large and prominent corporations, had used secret "slush funds" to bribe or make questionable payments totaling over $300 million to foreign officials (26,231). Twenty-two pharmaceutical and health care companies admitted to making total payments of more than $31.4 million (210).[6] Most of these transactions occurred in other countries, and according to some corporations, were necessary to compete there.

Congress, however, concluded that such bribery could lead to public scandals with serious foreign policy implications. According to a House of Representatives report, the 1976 revelation that Lockheed Corp. had made significant payments to certain government officials in

[6] See generally reference numbers 233 and 240.

Japan "shook the Government of Japan to its political foundations and gave opponents of close ties between the United States and Japan an effective weapon to drive a wedge between the two nations" (233). Alleged payments by U.S. corporations to certain officials in the Italian Government were judged to have "jeopardized U.S. foreign policy. . with respect to the entire NATO alliance" (233).

Foreign policy implications were not, however, the only concern. Congress believed that corporate bribery offended the moral expectations and values of the American public and distorted the competitive market because firms that were too inefficient to compete on price, quality, and service were able to compete with bribes. In addition, exposure of these illegal payments could lead to costly lawsuits, cancellation of contracts, and even appropriation of assets, thereby adversely affecting U.S. investors and destroying investor confidence in U.S. corporations (122, 233).

The FCPA was passed despite testimony by the U.S. Department of State that it would be "presumptuous" and "counterproductive" to impose U.S. standards in countries with differing histories and cultures, and despite opposition from business leaders who claimed they would no longer be able to compete in certain countries (26). The legislation attacked the problem of corruption on two fronts: 1) accounting practices for public corporations were changed to prevent companies from hiding such payments and 2) bribery of foreign officials by any U.S. citizen, resident, or U.S. domestic corporation was made a criminal act.

Under the latter provision, U.S. citizens and U.S. corporations, their directors, officers, employees, agents, or stockholders are prohibited from offering or promising money or anything of value to any other person, knowing that all or part of the gift would be offered, given, or promised to any foreign official to influence an official act or decision (15 U.S.C, § 78dd-2(2),(4)). A payment is illegal if it "induce[s] the recipient to misuse his official position" (66). The FCPA permits payments designed to facilitate routine governmental actions (so-called "grease payments") as may be necessary to obtain permits, licenses, visas, work orders, phone service, power, and water supply. (15 U.S.C. § 78dd-l(b),(f)(3)(A), 78dd-2(b),(h)(4)). In addition, a U.S. citizen or corporation is not guilty if he or she makes a payment without knowing that it will be used improperly. However, this knowledge will be imputed if the circumstances warrant (66):

> . . .a knowledge of the facts will be inferred where the defendant had notice of the high probability of the existence of the fact and failed to establish an honest, contrary belief.

Violations of the FCPA are punishable by substantial monetary penalties and in certain cases, imprisonment (15 U.S.C. § 78dd-l(a), 78dd-2(b), 78dd-l(g)) (66).

The original bill introduced into the House of Representatives applied the bribery provisions to U.S.-owned foreign subsidiaries directly, because Members believed that failure to include them would create a "massive loophole" through which questionable payments could be made (233). Congress eventually rejected direct regulation of corporate subsidiaries operating abroad because of the "inherent jurisdictional, enforcement, and diplomatic difficulties raised by inclusion of foreign subsidiaries of U.S. companies in the direct prohibitions of the bill" (232). However, by allowing courts to impute knowledge to a company or individual if the circumstances warrant, the FCPA is designed to apply to most transactions.

Despite the fact that the FCPA has such broad extraterritorial reach, it has engendered little international opposition. One reason might be that it applies only to U.S. nationals and domestic corporations, over which the United States clearly has jurisdiction. In addition, almost every country has national laws prohibiting bribery, extortion, kickbacks, and other such payments (204). At the time the FCPA was passed, the

Organization for Economic Cooperation and Development, which consists of the United States, Japan, and most Western European countries, issued voluntary guidelines for MNCs including a statement that MNCs should not bribe or make any other improper payments or illegal political contributions to public officials (49). The United Nations was also considering a resolution condemning corrupt practices in international commerce and calling for unilateral and multilateral action to end such practices (204). Therefore, despite the fact that many countries were not prepared to take unilateral action against their MNCs, there was international consensus that bribery of foreign officials by multinational enterprises should be controlled.

Extraterritorial Regulations Relating to the Health and Safety of Foreign Nationals

The Restatement leaves activities that primarily affect the health, safety, and welfare of the national population in the exclusive domain of 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 to comply with domestic health, safety, and labor standards when operating abroad and those that do exist are mostly designed to protect U.S. citizens. For example, the United States recently extended the protections afforded by age-discrimination laws to American citizens working for U, S.-owned or -controlled foreign subsidiaries (29 U.S. C, § 623(h)) (43,293),

Although it may be risky to draw conclusions about the limits of U.S. extraterritorial jurisdiction relating to health and safety from the lack of such regulations, this lack and some related history cannot be ignored. In the late 1970s, for example, strong evidence linked the aggressive marketing of infant formula by subsidiaries of U.S. companies in developing countries to an increase in infant mortality. (See ch. 6.) Legislation was introduced in the House of Representatives to regulate these marketing practices. The legislation did not pass and instead, Members of Congress asked the World Health Organization to convene an international meeting *on* the issue (250). The injuries caused by the marketing practices primarily affected foreign nationals, many in developing countries. Congress deferred to an international forum rather than trying to change the situation through U.S. law.

Deference to an international forum is consistent with the principles of international law. 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 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 U.S. interest in promoting the health and safety of foreign nationals is not analogous to preventing bribery, and it is difficult to find support under international law for exercising extraterritorial jurisdiction over foreign drug labeling. The United States has limited authority, if any, to regulate the subsidiaries under the effects principle. This study assumes that U.S. corporations are in compliance with national laws and are, on the whole, providing information that is at least as good as, or better than, information provided by 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. This leaves the nationality principle; however, the United States is virtually alone in its position that

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 in providing comprehensive and informative labeling, as defined by U.S. standards. This probably 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 many developing countries have laws regulating pharmaceutical labeling, and 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.

SUMMARY

From a business perspective, MNCs operate as unified corporations, but their actions in each country are governed almost entirely by host country laws, and to only a limited extent by the laws of the home country. This is consistent with the main principle of international law, which recognizes the sovereign right of each country to regulate activities within its borders. This right is not absolute, however, and the United States has assumed extraterritorial jurisdiction over activities in foreign countries in a number of cases, more than the rest of the world has generally approved of.

Many examples of U.S. extraterritorial jurisdiction over foreign subsidiaries concern trade and economic sanctions implemented during times of war or international tensions. Under these laws and regulations, the United States is controlling foreign subsidiaries of U.S. companies because their actions may undermine important foreign policy goals. In a sense, the subsidiaries become pawns in an international dispute rather than being the focus of the action.

The debate over extraterritorial jurisdiction revolves around determining to what extent a U.S. foreign policy interest or a domestic interest is significant enough to support extraterritorial action. The only obvious precedent for regulating drug labeling by foreign subsidiaries is the Foreign Corrupt Practices Act. In the FCPA, the behavior of foreign subsidiaries was the focus of the legislation because bribery had adverse impacts on U.S. foreign relations, as well as domestic interests. The FCPA does encroach on the sovereignty of foreign nations because it addresses bribery of foreign officials. It does not, however, directly regulate the actions of the foreign subsidiaries, and limits the criminal penalties to U.S. corporations or U.S. citizens. Moreover, it does not conflict with other nations' laws because most counties forbid bribery. There are significant problems applying this precedent to the issue of drug labeling, however.

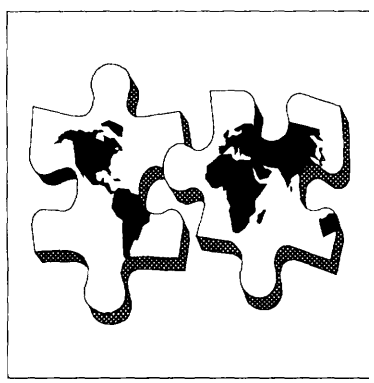
Direct regulation of the drug labeling practices of U.S.-controlled foreign subsidiaries would be a bold step beyond current U.S. interpretations of international law. Although many developing countries appear committed to improving the labeling of pharmaceuticals, it is not known whether the governments of such countries would welcome *unilateral* action by the United States. Even indirect regulation of U.S. subsidiaries would be an extraordinary approach to the problem of inadequate labeling. Although the United States has amoral interest in ensuring that its corporations do not cause injury to any consumer, regardless of citizenship, the United States cannot ignore the sovereign right of the foreign country to set its own consumer safety standards. Problems related to extraterritorial jurisdiction could be avoided through a collaborative effort with developing countries, or by including in any legislation a provision for national regulatory authorities to reject U.S. attempts to control foreign labeling, in whole or in part.

Codes of Conduct and Voluntary Guidelines for Pharmaceutical Information

6

This chapter examines the potential for improving the quality of drug labeling in developing countries through means other than strengthening national drug regulation directly. Every country has laws governing at least some aspects of pharmaceutical registration and labeling, and a designated individual or agency to carry out those laws, In the United States and other industrialized countries, substantial resources are devoted to making sure the laws and regulations are upheld, even then with imperfect results. There is convincing evidence that in many, if not most, developing countries either the laws are too weak to ensure a safe and effective drug supply, or more commonly, the governments are unable to allocate sufficient resources to implement the laws fully.

Legitimate differences of opinion may exist about the extent of this problem, but both the OTA survey and a recent survey by Silverman, Lydecker, and Lee (212) confirm that pharmaceutical manufacturers are providing inadequate prescribing information for at least some of their products sold in developing countries. SiIverman, Lydecker, and Lee make the important point that, overall, labeling by *domestic* companies in developing countries is worse than that of multinational corporations (MNCs), but both studies found significant problems with multinational labeling as well.



Alternatives to national regulation include codes of conduct and voluntary guidelines drawn up by international bodies (e.g., agencies of the United Nations). The main targets of codes and guidelines have been multinational corporations, which still leaves the problem of domestic companies to be solved. This study has focused only on U.S.-based multinationals; the mechanisms discussed in this chapter would apply to all multination-

als and in some cases, to domestic companies (e.g., when a code of conduct is adopted as law in a country).

There is no current international code of conduct for pharmaceutical labeling. The draft United Nations Code of Conduct for Transnational Corporations, which generally addresses labeling of all consumer goods by multinational corporations, comes closest, but it may never be ratified. A possible model for a pharmaceutical code is the World Health Organization (WHO) Code of Marketing of Breast-Milk Substitutes, which addresses the promotional practices of multinational corporations in developing countries. WHO has developed *guidelines*, which are of lesser standing than codes of conduct, for pharmaceutical promotion ("Ethical Criteria for Medicinal Drug Promotion") (264).

Codes of conduct usually refer to voluntary actions of governments, but in the case of pharmaceuticals, the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) has adopted its own code of conduct for marketing and labeling. A discussion of the provisions of this code and its impacts are included in this chapter.

CODES OF CONDUCT AND GUIDELINES UNDER INTERNATIONAL LAW

Since the 1970s, countries have become increasingly interested in the role MNCs play in national and global economics. A result of the increased attention has been the development of codes of conduct providing standards for national laws to regulate MNCs, and business Widelines that MNCs may adopt as corporate policy. Codes of conduct have been formulated by both governmental and nongovernmental organizations, including the United Nations (U. N.) and its agencies, the International Labor 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 principle which multinationals should follow, such as the OECD Guidelines for Multinational Corporations, to codes aimed at corporate operations, such as the U.N. Conference on Trade and Development Code of Conduct on Restrictive Business Practices (98).

Codes of conduct function as formal pronouncements by nations on policy matters (48). They are not legally binding instruments unless adopted into the national law of a country or ratified as a treaty. Nonetheless, when a number of countries endorse a code of conduct, through a U.N. resolution or other legal instrument, it is likely to have an impact. Codes are "politically-agreed behavior which cannot be legally enforced directly, but cannot either be legitimately infringed" (125). Even the process of developing a code, through the pooling of information, opinions, and experiences, may facilitate regulation and increase cooperation.

Rather than becoming parties to a code of conduct, countries may instead endorse a resolution, stating general agreement with a set of principles, but assuming no obligation to take further action. Such instruments are usually called guidelines, and as the name implies, are meant to provide a framework for further action. Though not as strong a force as a code of conduct, guidelines may become the basis of national laws or be used to develop codes of conduct.

One might question the purpose of codes of conduct, given what seems to be rather weak means of enforcing them. It is important to remember, however, that all international law is, to some extent, voluntary because it is based on the consent of individual nations. There is no supranational organization with the power to enforce international laws, nor is there a legislative body in which the majority of nations can bind the minority (25 1). The main difference between inter-

national law[1] and voluntary codes of conduct is the degree to which a country agrees to be bound and the corresponding action that the international community will take in response to a breach of a country's obligations. If an obligation is established under international law, it might be acceptable for another country to take retaliatory action to enforce that obligation; for example, through a trade embargo. A country would not be justified in taking such extreme retaliatory action in response to infractions of a code of conduct by another country, but might respond by not abiding by the code with respect to that country.

A related question is why codes of conduct are not adopted as multilateral treaties, which have the strongest standing under international law. Codes represent a compromise that allows countries to come to agreement on certain policies, and to relieve tensions within the international community without giving up their sovereign right to regulate within their borders. Many countries perceive treaties that address domestic issues (e.g., the treatment of corporations operating within a country's borders) as unacceptable threats to sovereignty (125).

Codes serve a number of purposes. The principles embodied in a code maybe used as a model for national regulation; its widespread endorsement provides assurance that such legislation is acceptable to the international community and its enforcement is unlikely to create international tensions. Courts and other governmental agencies may also look to codes of conduct when interpreting relevant national laws or interpreting the reasonableness of private contractual provisions, However, some countries, including the United States, might disagree that codes of conduct should be used by courts or government agencies. These "minimalist" countries emphasize the voluntary nature of codes of conduct and resist efforts to expand their significance beyond a statement of general principles if their provisions are not adopted in national legislation or other binding instruments (11).

A question with respect to MNCs is whether, and under what circumstances, they will comply with a code of conduct that has not been implemented in national laws. Even where codes have no formal legal standing, they create standards by which corporations' actions can be measured. Corporate behavior that is at variance with the code may result in adverse publicity or governmental action (125).

Although codes of conduct may be enforced only by the signatories, most codes establish an organization to monitor implementation and to provide interpretations of the code as needed. This organization is a locus for continued exchange of information and debate among signatories. It can also receive reports of violations and arbitrate complaints. Although these organizations usually have authority to clarify the meaning of provisions that apply in a particular dispute, in most cases they may not make a finding on the merits of the dispute, but they do provide a public forum for debate and may serve as triggers for further political intervention (125).

In sum, codes of conduct are political instruments that are likely to influence corporate and governmental behavior, but because they are voluntary, their influence may be limited. Industrialized countries have not been willing to agree to binding international agreements to govern the operations of MNCs, so codes of conduct provide an alternative means of affecting MNC behavior (125).

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[1]The Statute of the International Court of Justice identifies three sources of international law in order of importance: 1) international conventions or treaties, 2) customary international law, and 3) general principles of law recognized by civilized nations. Customary international law is derived from the practice of states. A practice rises to the level of customary international law when the practice is adopted by most states and the states conform with the practice out of a "recognition that a rule of law or legal obligation is involved" (105),

The United Nations Code of Conductor Translational Corporations

Work on the U.N. Code of Conduct for Transnational Corporations (the "Transnational Code") began in 1977 and a draft was completed in 1982. While agreement was reached quickly on roughly 80 percent of its provisions (225), the code has not been, and may never be, adopted in full. As drafted, however, the Translational Code is more comprehensive than any international voluntary code now in existence. It attempts to create a single framework for the rights and responsibilities of MNCs and governments with respect to foreign investment by providing guidelines on how MNCs, both privately and government owned,[2] should operate in host countries,[3] and how the host countries should treat MNCs operating within their borders (224). Most of the provisions on which there is agreement address the role of the MNC in the host country. These include requirements that MNCs observe national laws, respect fundamental human rights, adhere to socioculturral objectives, support consumer and environmental protection, comply with the fiscal policies of host countries, and observe fair labor standards (225).

The Code also contains general guidelines for consumer protection, although this is not its central focus. The current draft requires that all MNCs obey the consumer laws of the countries in which they market products (this includes all types of consumer products, not only pharmaceuticals) and provide consumers with "all appropriate information on the contents and, to the extent known, on possible hazardous effects of products, . .by means of proper labeling, informative and accurate advertising or other appropriate methods" (227). MNCs would also be called on to cooperate with international organizations in developing and promoting national and international health and safety standards (227). Both of these provisions *could* require an MNC to go beyond the requirements of national laws. However, no more specific guidance is given on what is meant by phrases like "appropriate information" or "possible hazardous effects," or on acceptable means of conveying the information. MNCs would retain a great deal of discretion in deciding the appropriate content of labeling if the Translational Code were ratified as it now stands.

The Code calls for national laws and bilateral, regional, and multinational agreements to implement it (227). The Commission on Translational Corporations, which drafted the Code, is the international body designated to assist with its implementation. The Commission is expected to:

1. facilitate dialogue among governments, trade unions, consumer groups, and other relevant groups;
2. develop procedures for providing clarification of the Code;
3. help negotiate Code-related agreements between governments or translational corporations; and
4. act as an information clearinghouse on issues related to the Code.

Some commentators question the need for the Code, believing that it reflects outdated political concerns about the nature of foreign direct investment and the role of MNCs in developing countries, based on the experiences of the 1960s and 1970s (22,226). The U.N. Centre on Translational Corporations concedes that developing countries have become more sophisticated in regulating MNCs and that tensions between industrialized and developing countries have eased

[2] There is no practical distinction between transnational colorations and MNCs, except that some commentators use MNC to refer to Privately owned companies, while the term translational corporation, as used in the U.N. Transnational Code, refers also to government owned companies.

[3] A host country is the country in which an MNC has a foreign subsidiary. The home country is the country in which the MNC has its headquarters.

since they began drafting the Code. However, supporters still believe that the Code can make a contribution, even in the changed investment environment (225). As of early 1993, negotiations are being conducted at a higher level, being chaired by the President of the U.N. General Assembly.

International Code of Marketing of Breast-Milk Substitutes

The WHO International Code of Marketing of Breast-Milk Substitutes (Breast-Milk Substitutes Code) is not directed at pharmaceuticals, but is of relevance because it was developed in response to specific marketing practices of MNCs and, at the time of drafting, was seen as a possible precedent for a pharmaceutical marketing code.

For a number of years, MNCs advertised aggressively, and successfully promoted the use of breast-milk substitutes (infant formula) in developing countries. The marketing programs included direct promotion to the public through radio, television, posters, handouts, and through the use of "milk nurses" —sales representatives dressed as nurses who marketed infant formula to new mothers in maternity wards (180). The companies marketed formula directly to health providers as well, giving free samples, calendars, booklets, and "lavish assistance" in the form of "social entertainment at conferences, travel and fellowships, and of funds for research" (120).

Consumer groups and physicians began to criticize these marketing practices because companies ignored the health implications of their successful marketing. Many mothers in developing countries did not understand the difficulty they would have using infant formula once they left the hospital. The lack of clean water and the high cost of the formula made it impossible for many of them to use formula correctly. Once they became aware of these problems, however, most mothers could no longer return to breast feeding because lactation had ceased after they began to use formula. The contaminated or diluted bottles of formula mothers were forced to use led to an increase in malnutrition and diarrhea, and in some cases, the infant's death.

A public campaign was instituted against these marketing practices, including the initiation in 1977 of an international boycott against Nestle Corp., one of the leading manufacturers of breast-milk substitutes. The boycott was organized by a U.S. group called the Interfaith Center on Corporate Responsibility, but was soon taken over by the International Baby Food Action Network (IBFAN), an organization devoted solely to carrying out this campaign (180). In 1981, after considerable international debate (including congressional hearings in the United States), WHO member countries adopted a voluntary International Code of Marketing of Breast-Milk Substitutes (268,269). The Code was adopted by 118 countries; the United States was the only WHO member country to vote against it.



PHOTO CREDIT: J. LITTLEWOOD, WHO

The WHO Code of Marketing of Breast-Milk Substitutes encourages breast feeding infants.

The Code instructs manufacturers to refrain from certain promotional practices, including direct advertising to the public and distribution of free samples. Samples may be distributed to health professionals only if necessary for professional evaluation or research at an institutional

level. In addition, financial or material inducements are not to be used to promote products, and bonuses based on volume of sales are prohibited (269).

The Code also contains detailed instructions for proper labeling. Article IX requires that all containers of infant formula include a "clear, conspicuous, and easily readable and understandable message" informing the consumer that breast feeding is superior. The label should not contain pictures or text that idealize the use of infant formula, for example, by describing formula as being "humanized," or "maternalized," and should not include pictures of infants, except if necessary for graphic illustration of instructions. The label should also state that the product should be used only on the advice of a health worker and should provide instructions for use and carry warnings about the health risks associated with inappropriate preparation. Labels should also include a list of the ingredients, instructions on proper storage conditions, a batch number, and the expiration date.

IMPLEMENTATION OF THE CODE

The Resolution adopting the Breast-Milk Substitutes Code instructed the Director General of WHO to "give all possible support to Member States" for its implementation and in particular, in the preparation of national legislation and other measures related to the promotion of breast feeding (268). To assist in this effort, each country is required to make an annual report to WHO on the actions it has taken toward implementation, information that is compiled in a biannual report. According to the 1990 report, over the previous 9 years, more than 150 countries and territories had taken some action to implement the Code, but as of 1988, only 6 developing countries had adopted the Code in its entirety (21). Other steps taken by developing countries include (281):

- education of health officials on the Breast-Milk Substitutes Code;
- adoption of country-specific codes of conduct based on the principles of the Breast-Milk Substitutes Code, often with a mechanism to monitor and enforce compliance;
- adoption of legislation implementing certain provisions of the Code, or revisions of existing legislation to implement the Code;
- government control of all imports and distribution of infant formula; and
- public education on the benefits of breast feeding.

Consumer organizations have played an active role in promoting the Code. IBFAN, which has more than 100 affiliates working in over 60 countries, supports research, education, and other efforts to implement the Code (281). The International Organization of Consumers Unions (IOCU) has published a guide for health care workers that explains the Code. The guide is available in eight languages and more than 25,000 copies are in circulation. Consumer groups also have helped educate and train health workers in countries with limited resources (28 1).

Industry has also responded to the Code. The International Association of Infant Food Manufacturers, an industry group with 35 member companies in 15 countries, has instituted a complaint mechanism and is developing an arbitration mechanism to address violations of the Code that cannot be dealt with by direct negotiations between the company and the complainant (281). Nestle Corp. created the Nestle Infant Formula Audit Commission (NIFAC), an independent nine-person commission that reviews allegations that Nestle's advertisements, promotional activities, or corporate policies violate the Code.[4] As of 1984, NIFAC had reviewed 80 complaints, with the number of complaints declining over the years (180).

[4] NIFAC was headed originally by former U.S. Senator and Secretary of State (during the Carter Administration) Edmund Muskie (180).

Despite widespread support for the Code, several countries report that manufacturers continue to distribute free samples of infant formula in hospitals and clinics (188,28 1). However, the more aggressive marketing practices, such as the use of milk nurses, have stopped (180). The requirement that countries report their progress under the Code, as well as the actions of public interest groups and industry with respect to violations, has kept the issue of breast-milk substitutes on the international agenda.

A Code of Marketing of Pharmaceuticals

At the same time the Breast-Milk Substitutes Code was being drafted, WHO also debated developing a code of conduct for the marketing of pharmaceuticals (270). The pharmaceutical industry opposed the idea and in 1981, when the move for a pharmaceutical code was strongest, the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) developed its own industry code for marketing practices (see below) (145,251). WHO reportedly decided to refrain from promoting its code until it could evaluate the impact of the IFPMA Code (223). The debate remained alive, however. Heated discussions took place at the Sixth Session of the U.N. Council for Trade and Development in 1983 (174), as public interest groups continued to press for a WHO code. WHO's rejection of the idea was made clear in 1986 when the Director General stated that there is no place for "supranational regulation by WHO of drug promotion" (103,263).

In addition to industry opposition to a WHO pharmaceutical code, the U.S. executive branch has, in the past, expressed opposition to WHO formulating codes directed at specific industries. The United States, under the Reagan Administration, voted against the Code on Breast-Milk Substitutes for this reason (48, 183). The response to a pharmaceutical code, however, could be different depending on the political climate.

U.S. governmental support for a code of conduct could be spurred by public support. A major impetus behind the Breast-Milk Substitutes Code was public outcry against the marketing practices of infant formula companies, generated by intense publicity by consumer advocates. There is currently no strong, vocal public support for a pharmaceutical code, and it may be difficult to generate interest for one. Unlike the Breast-Milk Substitutes Code, which addressed easily understood marketing practices, a pharmaceutical code must address a range of pharmaceutical products and complex national standards for safety, efficacy, and labeling. Given the statements of WHO, the strong industry opposition, and the lack of clear public support, a WHO code on pharmaceutical marketing is unlikely to materialize in the foreseeable future.

The Ethical Criteria for Medicinal Drug Promotion

In 1968, WHO adopted *Ethical and Scientific Criteria for Pharmaceutical Advertising (267).* This document was revised and expanded in 1988 to cover a broad range of "informational and persuasive activities by manufacturers and distributors" (273). The revisions were based on results of a 1986 survey of governments and private parties that posed questions about the role of scientific data sheets, symposia, free samples, medical representatives, package inserts for patients, packaging and labeling, advertising, and promotion of pharmaceuticals to health professionals and the general public. The survey also asked about what information was included with pharmaceutical products exported from the responding countries.[5]

The revised document, now called the *Ethical Criteria for Medicinal Drug Promotion,* (Ethical

[5]Respondents included 17 (of 24) governments (11 industrialized, 6 developing) and 14 (of 18) associations, representing the drug industry, pharmacists, consumers, and medical specialties (273).

Criteria) focuses on various aspects of pharmaceutical promotion, including the content of drug advertising to medical professionals and the public, the use of medical representatives, the provision of free samples to the public, post-marketing surveillance, dissemination of information, drug packaging and labeling, patient information, and package inserts and booklets. The Ethical Criteria do not specify criteria for labeling and packaging. They instruct companies to comply with national laws, and if there are no national laws or if the laws are rudimentary, the company is expected to provide information consistent with that required by another reliable drug authority. In addition, 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 give more specific standards for advertisements than for labeling. They state that advertisements should usually contain:

1. the names of active ingredients, using either the international non-proprietary names (INN)[6] or generic names;
2. the brand name;
3. the content of active ingredients per dosage form or regimen;
4. the name of other ingredients known to cause problems;
5. approved therapeutic use;
6. dosage form or regimen;
7. side-effects and major adverse drug reactions;
8. precautions, contraindications, warnings;
9. major interactions;
10. name and address of manufacturer or distributor; and
11. references to scientific literature as appropriate.

These categories of information are derived from WHO's drug information sheet, which is suggested as a guideline for labeling (271).

The Ethical Criteria are not as strong a pronouncement of public policy as a code of conduct would be. The preface to the Ethical Criteria "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 regulations.

The Ethical Criteria do not constitute legal obligations, and do not necessarily represent the consensus of all WHO member countries (264).

The Executive Director of the IFPMA, to which the U.S. Pharmaceutical Manufacturers Association belongs, has stated that its members have not adopted the Ethical Criteria because their Code of Conduct (discussed in detail below) is binding on its membership and with respect to prescription drugs, is fully congruent with the Ethical Criteria, even though the two documents differ in the amount of detail each contains (285). Consumer groups, however, are very concerned with many of the details. For example, whereas both the Ethical Criteria and the IFPMA code permit abbreviated information with reminder advertising, the Ethical Criteria limit the defini-

[6] Since 1950, WHO has coordinated the development of International Non-Proprietary Names (INNs) for pharmaceuticals, and as of 1989, WHO had selected over 5,000 INNs for pharmaceutical substances (257). WHO recently published its 60th list of proposed international non-proprietary names (194).

tion of reminder advertisements to printed advertisements that do not make claims for the drugs (i.e., promote them for a specific indication) while the IFPMA Code has no such restriction and leaves the definition of a reminder advertisement to the companies (196).

WHO's recent evaluation of the Ethical Criteria notes that "effective oversight and control of promotion is possible only when a comprehensive drug licensing [registration] system is in effect" (285). Control of promotional material requires specific standards for individual drugs, which means the country must have reviewed the scientific evidence for the individual drug and determined the proper labeling. Even countries with strong registration systems may not regulate advertisements effectively (285). Few countries screen advertisements before they appear. This is the case in the United States, where a recent study found that a large percentage of pharmaceuticals ads did not meet FDA regulatory standards (262).

The World Health Assembly, the legislative body of WHO, recently asked member states to intensify efforts to implement the Ethical Criteria by involving government authorities, pharmaceutical manufacturers, firms engaged in promotion of pharmaceuticals, health personnel responsible for prescribing, dispensing, supply and distribution of drugs, universities and other teaching institutions, professional organizations, professional and general media (e.g., medical and other journals), and consumer groups. The Director General of WHO was directed to convene a meeting of the Council for International Organizations of Medical Sciences (CIOMS)[7] and other interested parties to discuss new approaches to implementing the Ethical Criteria (265).

IFPMA CODE OF PHARMACEUTICAL MARKETING PRACTICES

The International Federation of Pharmaceutical Manufacturers Associations (IFPMA), formed in 1968, is an association of associations. It comprises about 50 associations of pharmaceutical manufacturers (e. g., the U.S. Pharmaceutical Manufacturers' Association) from 51 countries (108). The member companies of the IFPMA manufacture close to 80 percent of the world's prescription pharmaceuticals (excluding those manufactured in China and the former Warsaw Pact countries) (91). IFPMA registered as a nongovernmental organization with WHO in 1971, stating its intent to collaborate in the following areas: technical and scientific assistance, economic assistance, and medical assistance.

In 1981, after widely publicized criticism of some pharmaceutical companies practices in developing countries, IFPMA adopted "A Code of Pharmaceutical Marketing Practices" (IFPMA Code) as industry's statement on what constitutes proper promotional practice for prescription drugs.[8] The IFPMA Code is a model that can be used by companies belonging to IFPMA's member associations in setting corporate policies for promotion and advertising. The IFPMA Code applies primarily to advertising, not labeling, but it reflects industry's philosophy on the type of information that should be provided with its products.

[7] In order to facilitate international adverse drug reaction reporting, representatives from regulatory authorities and manufacturers formed CIOMS with the objective of developing an appropriate, internationally acceptable form for reporting adverse drug reactions. CIOMS is also involved in a collaborative project between pharmaceutical manufacturers, representative bodies of medical specialties, and national drug regulatory authorities, that will involve updating the classification and definition of adverse drug effects, an essential requirement for post-marketing surveillance (285).

[8] The IFPMA Code is directed at promotion and advertising of pharmaceutical products directed to the health care professions, but advertising of self-medication products to the general public is excluded from the scope of the Code, as is advertising to pharmacists where this is intended to support advertising to the public of such products (1 11).

Section I of the Code outlines general principles that should govern all printed advertising. It states that industry has an obligation to provide "scientific information with objectivity and good taste, with scrupulous regard for truth and with clear statements with respect to indications, contraindications, tolerance and toxicity" (1 11). In addition, a product should be promoted only for those indications supported by current scientific evidence, and no product should be promoted as being safe and effective for an indication until it is approved for that use. Pharmaceutical companies are also expected to provide essential information on the safety, contraindications, side-effects, and toxic hazards of their products, subject to the legal, regulatory, and medical practices of the country.

Section IV of the Code expands on these requirements with respect to printed promotional material and recommends that all advertisements include: the name of the drug (usually the brand name); a list of active ingredients, using the International Non-proprietary Name (INN), if possible; at least one approved indication for use, with dosage and method of use; and a succinct statement of side-effects, precautions, and contraindications. Exceptions are made for short advertisements, known as "reminders," provided the reminder states that further information is available on request. Finally, the word "safe" is not to be used without qualification in any advertisement (11 1).

The remaining sections of the Code cover other promotional practices, such as the use of medical representatives, symposia, medical congresses, and other means of verbal communication. The Code confirms the importance of these promotional practices for the dissemination of information, but stresses that scientific objectives should be their main focus. The Code requires that medical representatives be "adequately trained and possess sufficient medical and technical knowledge to present information on their company product in an accurate and responsible manner" (1 11). This stops short of WHO's Ethical Criteria, which require that medical representatives refrain from providing inducements to prescribers and dispensers and that the main part of medical representatives' remuneration should not be directly related to their sales volume (264). The IFPMA Code also stipulates that supplies of samples should be limited to the amounts necessary for a health professional to become familiar with the drug. The Ethical Criteria state that free samples of prescription drugs should be provided only in modest quantities and generally only on request (264). The IFPMA Code also responds to criticisms that pharmaceutical companies sometimes make medical promotional material look scientific. The Code states that promotional material, such as a mailing or medical journal advertisement, must "not be designed to disguise its real nature" (111).

Implementation Mechanisms

The original Code did not contain provisions for monitoring or enforcement. In 1982, apparently in response to criticism from consumer groups, the IFPMA established a complaint procedure for reporting alleged violations (90). Not all complaints go directly to the IFPMA because all member associations have adopted the Code, or more detailed codes, and some national organizations have their own adjudicating committees to address complaints (285). If the complaint is made directly to the IFPMA, the IFPMA contacts the appropriate member association in the country of the company's headquarters and, if applicable, the member association in the country in which the violation occurred. (In cases involving nonmember companies, IFPMA makes informal contact, whenever possible, encouraging them to follow the IFPMA Code.) (109) The member association refers the matter to the company concerned, and the company's response is sent back to IFPMA through the member association.

The response is reviewed by the IFPMA "President's Committee," consisting of the presi-

dent, two vice-presidents, and an executive vice-president. The Code also notes that the committee is counseled by three independent reviewers (1 11); however, the *Ten Year Report on the IFPMA Code* (1 10) makes no mention of the independent reviewers and the executive director of the IFPMA has stated it is not feasible to have outsiders review the complaints (187). When the President Committee has reviewed a case, a formal reply is sent to the complainant. The IFPMA states that no member company or member association has failed to take corrective action when found to be in violation of the Code (1 10).

Because the Code is voluntary, IFPMA relies on adverse publicity as a "stick" to keep members in compliance. Status reports on the Code (the list of all complaints made, the companies involved, and the actions taken) are public and can be obtained from IFPMA, though they are not distributed widely. Code-related activities are also summarized (by number and type of complaint, and by action taken) in the IFPMA newsletter, *Health Horizons,* and certain international pharmaceutical publications also report on complaints brought under the IFPMA Code (e.g., *SCRIP World Pharmaceutical News).*

Reporting and Resolution of IFPMA Code Violations

The IFPMA complaint procedure has been used by consumer groups, WHO, and by individuals. Between 1982 and 1991, the IFPMA received 72 complaints, comprising 926 separate cases. Forty percent of the complaints (accounting for 86 percent of the cases) were brought by consumer groups, with WHO accounting for another 35 complaints (involving 100 cases) (1 10). In 1987, 13 complaints involving 509 separate instances were filed. The majority of these complaints were filed by the Medical Lobby for Appropriate Marketing (MaLAM), an international doctors lobbying network (See ch, 7.) (130). Most of their complaints referred to advertisements in prescribing guides (1 10).

Approximately 56 percent of complaints (535 citations) concern Section IV of the IFPMA Code. In particular, these complaints have focused on the lack of full disclosure of active ingredients, the nature of indications and the disclosure of side effects, precautions, and contraindications. Many of the complaints have focused on reminder advertisements, which need not carry complete information unless the pharmaceutical's use entails specific precautionary measures (1 10). MaLAM, one of the groups whose complaints have focused on reminder advertisements, claims that the IRMA has refused to clarify the exact definition of a reminder or the phrase "specific precautionary measures." According to MaLAM, IFPMA has permitted relatively long advertisements (more than 200 words) to be classified as reminders, exempting them from the more inclusive requirements for full advertisements. MaLAM also cited examples of reminders that, as required, state "further information is available on request," but either fail to provide an address, or refer readers to information available only if the drug is purchased (130,196).

From August 1989 through August 1990, over half of the 34 breaches of the Code (out of 74 cases resolved) were for failure to adequately support claims for a product with scientific evidence, or for making claims not in accordance with "needs of public health." Six advertisements were cited for using the word "safe" without proper qualification. Twelve other advertisements failed to include all the information required by the Code (109). U.S. pharmaceutical companies were responsible for six of the 34 breaches: one for failing to use the non-proprietary name, three for failing to include complete information in advertisements, one for including advertising claims that were stronger than justified, and one for using the word "safe" in an unqualified manner (109).

Not all complaints are found by the President's Committee to violate the Code. Of the 926 cases resolved between 1982 and 1991, approximately

56 percent were declared by the IFPMA to be breaches; 21 percent were not breaches; 10 percent were declared invalid because the complaint was based on false or out-of-date information, or was a repeat complaint about the same advertisement; and 13 percent did not involve member association companies.[9]

Criticisms of the Code

The IFPMA Code has been criticized by both pharmaceutical associations and health activists because its requirements lack specificity and are prone to subjective interpretation (103,196,223). The Code requires, for instance, that information on products conform to "ethical standards and standards of good taste" (111), without further explanation. On another point, the Code states that a product should not be promoted as safe and effective for a particular indication before it has been approved officially for that indication, but also states that the scientific community and the public have a right to be "fully informed" of the results of investigational studies (111). So while the Code does not permit a company to market a drug for indications not approved by a regulatory authority, the company may disseminate the results of studies that support unapproved indications.

With respect to pharmaceutical sales representatives, the Code does not define what constitutes "sufficient training" or the type of information sales representatives must provide, and it does not provide guidance on what might be a reasonable amount of free samples. According to one activist, the only provision that is not ambiguous is the requirement that the word "safe" be qualified (103).

IFPMA has also been criticized for the amount of time it takes to make a determination on alleged infractions; MaLAM has claimed that the delays permit companies to continue running advertisements that violate the Code (130). MaLAM filed 208 complaints in January 1987, and the IFPMA responded with an interim report on 165 of them 7 months later. This interim report listed 89 infringements, and 28 "invalid complaints." The remaining 43 complaints were not acted on because the companies involved were not members of IFPMA associations.

In April 1987, MaLAM filed another 254 complaints, and the IFPMA responded to 111 of them almost a year later, in March 1988, leaving 143 complaints unresolved. This response included findings of 44 new breaches and 42 repeat advertisements from the first submission by MaLAM (130). IFPMA classified these 42 repeat submissions as invalid complaints, rather than continued infractions, as MaLAM contended they were (130). One activist, who filed 259 complaints between November 1985 and April 1988, reported that the average time taken to resolve 222 of his complaints was about 7 months (195).

IFPMA explains that the large number of complaints received in 1987 could be interpreted as an attempt to "break the system," as many of them did not include documentation, making resolution of those cases more difficult (1 10). IFPMA also points out that a delay in issuing a decision does not necessarily delay remedy of a breach. IFPMA claims that companies often take remedial action soon after being informed of a complaint, before the IFPMA decision is made.

Perhaps the most controversial aspect of the Code is IFPMA's interpretation of provisions requiring deference to national laws. IFPMA acknowledges that it would be desirable for labeling, packaging, leaflets, and data sheets used in developing countries to be consistent with the ones used in industrialized countries. However, it recognizes that a company ultimately must follow the regulations of the country in which the drug is marketed. According to IFPMA, regulato-

9 Although the IFPMA may contact the member association in the country where the company is located, the complaint is not a breach unless the company is part of a member association of the IFPMA (1 10).

ry requirements differ among countries for good reasons (11 1):

> . . . [t]he decision of a national authority with regard to the permitted indications and precautionary information to be provided about the product must take precedence.

Furthermore, when a product has been evaluated and registered by an established regulatory authority, the approval by itself is accepted as adequate evidence of the product's efficacy. IFPMA does not challenge the decisions or judgments of national regulatory agencies in any country (9).

MaLAM asserts that the IFPMA position is flawed, noting that the Code recognizes that "Third World countries are not aware of the indications, contra-indications, side-effects, etc. of individual drugs that have been adopted in developed countries" (11 1), yet IFPMA advocates deferring to regulatory bodies of developing countries on those issues. MaLAM contends that the point of self-regulation is to develop a voluntary standard that is compatible with, but different from, the government standard. According to MaLAM, industry standards should meet or exceed those of the government, especially when the government agency has limited resources for drug regulation (139).

Despite the criticisms of the Code, it remains one of the few formal mechanisms for challenging specific advertisements. The complaint procedure has been responsible for at least some improvements in pharmaceutical promotion. In the past 2 years, IFPMA has received only 17 complaints involving 34 different instances (1 10). Consumer groups, however, still report violations of the Code and continue to push for stronger mechanisms for controlling promotion of pharmaceutical products (39).

SUMMARY

Codes of conduct offer a possible means of setting international standards for drug labeling without compromising the sovereignty of individual countries. However, even though the codes are voluntary, they are not necessarily easy to develop, as the Translational Code demonstrates. While not binding legally, they are formal pronouncements and will not be endorsed by governments that do not agree with their provisions. The most relevant precedent for a pharmaceutical labeling code is the Breast-Milk Substitutes Code. That Code was devised at a time of public outrage at the behavior of certain MNCs, however, and addressed a less complex issue than that of drug labeling.

Codes of conduct provide general guidance and principles for behavior. A code of conduct for pharmaceutical labeling might define the categories of information that should be on a label and create some uniformity in labeling format. It could also address the type of information that should be presented to a developing country regulatory body with an application for registration. A code would not, however, define the content or wording of the label for each individual product. The overall impact of such a code would depend to a great extent on how it was implemented and monitored over the long term.

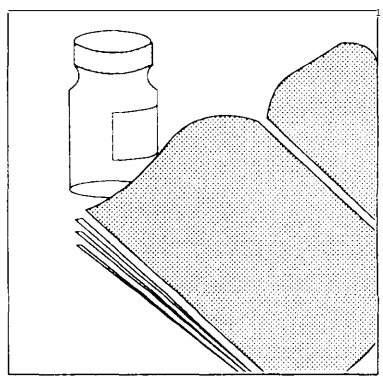
Efforts to Improve Drug Information In Developing Countries

7

Drug labeling is not the only, or necessarily the most important, pharmaceutical issue facing developing countries, but it is recognized as an essential component of effective drug regulation. The World Health Organization (WHO), national governments, and private organizations have made efforts to promote the rational use of drugs, and within that broad objective, to improve the prescribing information available in developing countries. The activities of WHO, the U.S. Food and Drug Administration (FDA), and private groups related to drug labeling are discussed in this chapter.

THE WORLD HEALTH ORGANIZATION

In the past decade, pharmaceutical programs of the World Health Organization (WHO), in conjunction with other donors, have assisted developing countries in formulating comprehensive national drug policies (135). The focus of many national programs is pharmaceutical supply and consumption in the public sector, but strengthening regulation has been another priority. The following discussion covers briefly the main WHO activities directed specifically at improving drug regulation and prescribing information for physicians.



Action Program on Essential Drugs

WHO direct country support for pharmaceutical issues is provided primarily through the Action Program on Essential Drugs (APED). APED promotes the rational use of drugs all over the world, especially in developing countries. [1]The core of the

[1] For an overview of the history of the APED and the political constraints on WHO's efforts in this area, see reference number 183.

Action Program is WHO's "Model Essential Drug List," which can be adopted by countries, modified to fit their health needs, and used to promote the rational use of a limited number of pharmaceuticals. APED also promotes improved registration systems to better ensure that only safe, effective, and properly labeled products enter the market.

WHO provides training materials and seminars to achieve its goals. Among the publications relevant to drug labeling are: the *Model Guide to Good Prescribing (286),* developed in conjunction with the Groningen University in the Netherlands, and designed to be used in undergraduate medical education; the *Manual for Rural Health Workers: Diagnosis and Treatment with Essential Drugs (47);* and *The Essential Drugs Monitor,* a quarterly newspaper that discusses all aspects of essential drug programs, focusing on existing programs in developing countries. The *Essential Drugs Monitor is* distributed to 28,000 subscribers and is read by 180,000 people worldwide (286). APED also has a Documentation Center that distributes more than 20,000 publications a year and issues a periodically updated bibliography of available materials (on diskette and in printed form) (286).

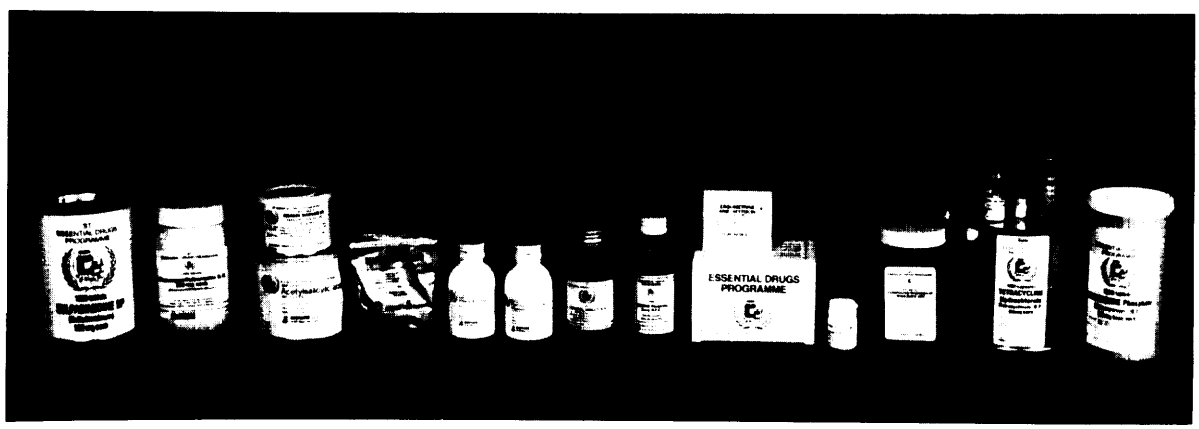
Drug Management and Policies

WHO's Division of Drug Management and Policies (DMP), which is independent of the Action Programme on Essential Drugs, is responsible for a number of functions involving pharmaceutical issues. The DMP's units include Biological Standardization, Drug Regulatory Support, Drug Safety and Efficacy, and Quality Assurance. The DMP develops the *Model Prescribing Information* used by APED and coordinates the exchange of information on safety and efficacy of pharmaceuticals. In addition, the DMP is responsible for monitoring and further developing WHO's Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce, which is discussed below.

WHO Certification Scheme

In **1969,** WHO endorsed requirements for "Good Practices in the Manufacture and Quality Control of Drugs" (Guidelines on Good Manufacturing Standards) (285). These guidelines were the starting point for the "Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce," which was adopted in 1975 (275). The Certification Scheme was designed to assist countries lacking a comprehensive or effective drug control or registration system to ensure the safety and quality of imported drugs. Under the Certification Scheme, an importing country may request that the regulatory authority of the country in which the drug is manufactured provide a cer-

PHOTO CREDIT: T. FARKAS, WHO



Sample of WHO essential drugs.

tificate assuring that it was manufactured in accordance with good manufacturing practices. As originally designed, the certificate included the name and dosage form of the drug, the active ingredients, and either certified that the product was approved for marketing in the country of origin, or explained why it was not. In addition, the

PHOTO CREDIT: OXFAM PHOTO, WHO



Drug prescribing by village health worker in Bangladesh.

regulatory authority certified that the factory producing the drug was inspected regularly and complied with WHO guidelines on good manufacturing practices,

In 1984, the Third International Conference of Drug Regulatory Authorities (cosponsored by WHO and the U.S. FDA) recommended that the product labeling information approved in the country of origin be submitted with the certificate. They also recommended that the Certification Scheme be broadened to include imports of raw materials and unfinished products (275). These recommendations were adopted in 1988 (277). The new certificates require copies of all labeling supplied with the product in the country of origin, including approved packaging materials and package inserts (277).

WHO recently issued proposed new guidelines for the Certification Scheme, which were endorsed by the World Health Assembly (266). The new guidelines call for the issuance of one of three different certificates: certificate of a pharmaceutical product (see figure 7-1), statement of licensing status of a pharmaceutical product, and batch certificate of a pharmaceutical product (285). The certificate of a pharmaceutical product is used by an importing country when: 1) the country is evaluating whether to approve a product for import and sale and 2) when administrative action is required to renew, extend, vary, or review an existing license for import and sale (285). The company exporting the product is responsible for requesting that a certificate be issued. So, if OTA, Inc. wished to export a drug to Thailand, and the Thai regulatory authority wanted a WHO certificate of a pharmaceutical product, OTA, Inc. would ask the FDA to issue a certificate to Thailand. Under WHO's Guidelines, the certificate is considered a confidential document.



PHOTO CREDIT: M. SENTIS, WHO

Man purchasing low-priced essential drugs in Nepal,

Figure 7-I—Facsimile of WHO Certification Program Certificate

Exporting (certifying) country
Importing (requesting) country:

Certificate of a Pharmaceutical Product

Proprietary name (if applicable) and dosage form:

Active ingredient(s) and amount(s) per unit dose:

1. Is this product licensed to be placed on the market for use in the exporting country? If yes, complete box A; if no, complete box B

A	B
Product licence holder:	Applicant for certificate:
Status of licence holder:* a☐ b☐ c☐ d☐	
Number of product licence and date of issue:	status of applicant:" a☐ b☐ c☐ d ❑
is an approved technical summary appended? yes ❑ no	Why is authorization lacking?:
Is the attached product information complete and consonant with the licence? yes non not provided	not ❑ required; not required; under ☐ consideration; refused
Applicant for certificate if different from the licence holder.	Remarks:

2. Does the certifying authority arrange for periodic inspection of the manufacturing plant in which the dosage form is produced? yes / no ❑ — If No, proceed to question 3

Periodicity of routine inspections (years):
Has the manufacture of this type of dosage form been inspected? yes ❑ no ☐
Do the facilities and operations conform to GMP as recommended by the World Health Organization? yes no ☐

3. Does the information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product undertaken by another party?
yes ☐ no ☐ If no, explain:

Address of certifying authority:

Name of authorized person:
Signature:
Stamp and date:

Telephone/fax numbers:

This certificate conforms to the format recommended by the World Health Organization.

● Specify whether the person responsible for placing the product on the market;
(a) manufactures the active ingredients and the finished dosage form;
(b) manufactures the finished dosage form;
(c) packages and/or labels a finished dosage form manufactured by an independent company;
(d) is involved in none of the above.

SOURCE: World Health Organization, *Implementation of WHO's Revised Drug Strategy-Safety and Efficacy of Pharmaceutical Products, Progress Report of the Director General, A45/13* (Geneva, Switzerland: WHO, 1992).

The statement of licensing status of a product attests that the product has been licensed for sale in the country of export. The statement is intended to be used by importers considering bids made in response to an international tender for drugs (285). The batch certificate of a pharmaceutical product provides information on the quality and expiration date of a specific batch of the product, including results of any analyses undertaken on the batch. For most products, the batch certificate is issued by the manufacturer. For vaccines, sera, and other biological products, the certificate is issued by the regulatory authority (285).

By 1990, 129 countries had notified WHO that they intended to use the Certification Scheme; however, most of the countries opted to use it as a means of controlling imports, not as a means to support exports (52), Countries were regularly requesting certificates for imports, but did not have a policy of providing certificates with exports. This is not surprising because in order to issue a certificate a country must ensure that:

- the authorization for sale or distribution is subject to appropriate testing,
- its pharmaceutical industry conforms with recommended standards for the manufacture and quality control of pharmaceuticals,
- the competent authority is given the authority to carry out complete inspections of the pharmaceutical manufacturing facilities, and
- the country's inspectors are qualified and experienced.

It is likely that only those countries with developed drug regulatory bodies could provide certificates that meet these criteria (285). In addition, evidence suggests that the Scheme is not used optimally by developing countries, particularly in Africa, which relies heavily on imported pharmaceuticals (275,200).

The Certification Scheme has limitations. Certificates may be difficult to obtain for drugs manufactured in more than one country or manufactured in one country and packaged in another. Donated drugs or drugs procured from wholesalers and brokers with a wide variety of sources may not be easily certified. Products manufactured specifically for a foreign agency or government may differ from the manufacturer's standard products and labeling from the standard product may not be appropriate for the special product (275). If a country requests a certificate only at the time of frost import or when a drug is reregistered, the country may not obtain updated information about the drug (164). Countries with inadequate administrative or legal infrastructure for drug regulation may be unable to use the Certification Scheme effectively (164).



PHOTO CREDIT: P. MERCHEZ, WHO

Transport of essential drugs in Latin America

APED and DMP have initiated activities to improve the Certification Scheme and expand its adoption. The United States Agency for International Development (USAID) is supporting a WHO evaluation of the Certification Scheme in

developing countries and the DMP is carrying out field trials in a number of countries (259, 286).

Distribution of Prescribing Information

In addition to labeling provided with a drug, compendia of pharmaceutical information from industrialized countries are useful sources of prescribing information for officials and physicians. WHO is working to provide national drug regulatory authorities in developing countries with three of these compendia, which contain information approved by the regulatory authorities in those countries: the *Dictionnaire Vidal (249) (in*formation approved by the French Ministry of Health); Association of the British Pharmaceutical Industry *Data Sheet Compendium* (10) (information in compliance with the regulations of the United Kingdom), and the *Physicians' Desk Reference* (information in compliance with regulations of the U.S. FDA) (258).

DMP has also begun work on a series of publications entitled *WHO Model Prescribing Information* for those drugs on the essential drugs list that are of particular interest to developing countries. The first one, *Drugs Used in Anesthesia (280), was* published in 1989; *Drugs Used in Parasitic Diseases (282)* was released during 1990; and *Drugs Used in Mycobacterial Diseases (284) in 1991,* with more in preparation.[2]

Access to New Information on Safety and Efficacy of Pharmaceuticals

Most industrialized countries have formal programs for monitoring adverse reactions associated with pharmaceuticals. Developing countries typically do not have the resources to do this in their own countries, and as a result, may not be able to respond to the need to revise labeling, or even withdraw a drug from the market. One WHO priority is to secure the regular exchange of information on the safety and efficacy of pharmaceuticals and to promptly transmit new information on serious side effects to national health authorities (258). The DMP receives information regularly on decisions of regulatory authorities and voluntary decisions of manufacturers related to the safety of pharmaceuticals. During 1986, for example, WHO received information on decisions about 360 pharmaceutical products from 35 countries (258). This information is disseminated monthly to the drug regulatory authorities of member countries through the *WHO Pharmaceutical Newsletter (285).* DMP also produces *WHO Drug Information,* a quarterly journal that provides discursive commentaries on the more important actions of national drug regulatory bodies (258,285).

WHO has established collaborating centers in each of its five regions for the purpose of information dissemination, training, and operational research. The most recent collaborating center was established in India in 1988 to serve 11 countries in Southeast Asia (131,274).

These collaborating centers are distinct from the WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden, which is an international center for monitoring adverse drug reactions. Thirty-three countries, including the United States, provide case reports on adverse drug reactions to the Uppsala Centre where the data are combined and analyzed to detect relationships between drugs and rare adverse reactions (290). The information in the database at Uppsala, which as of 1991 contained 950,000 individual case reports (290), is available only to the countries that participate in reporting. Nonparticipating countries may learn about the adverse reactions through medical journals or through the regulatory actions of participating

2 WHO is currently working on prescribing guides for drugs used in treating sexually transmitted diseases, including AIDS, and other bacterial diseases, and in neurology and dermatology (285).

countries, but there is no guarantee that they, in fact, will (290).

THE U.S. FOOD AND DRUG ADMINISTRATION

The FDA is primarily a domestic agency, but being the regulatory agency for one of the largest pharmaceutical markets in the world, it is also involved in international pharmaceutical issues. The FDA is not a development agency and it does not generally help other countries with projects specifically designed to improve the marketing and labeling of drugs, but it does assist developing countries by sharing its expertise with their drug regulatory personnel.

Most of FDA's international activities are coordinated by its International Affairs Staff (IAS) under the Associate Commissioner for Health Affairs. The IAS is principal FDA contact point and liaison with foreign counterpart agencies, foreign embassies, international regional organizations, U.S. Government agencies (e. g., the Office of International Affairs, U.S. Public Health Service; USAID, the U.S. Trade Representative), and U.S. embassies. IAS arranges the participation of FDA officials in U.S. delegations to international meetings, such as those held by WHO. Four IAS officials are responsible for bilateral liaison within broad geographic regions.

One of FDA's most visible international activities is the dissemination of information about regulatory actions. FDA sends monthly updates to WHO and representatives of the European Community on important regulatory developments, including proposed regulations and policies; reports of serious adverse reactions from pharmaceuticals; the monthly list of approvals for new drugs, medical devices, and biologics; and other public information. WHO may incorporate this information in its newsletters, which are distributed internationally.

The FDA also sends its *Medical Bulletin (see, e.g.,* ref. 150) to more than 800 government and academic organizations around the world. Many of these institutions are in industrialized countries (e.g., more than 129 Canadian institutions are on FDA's mailing list), but a number are in developing countries. The *Medical Bulletin* focuses on new FDA policies and findings on particular drugs and devices, For example, a recent issue discussed the dangers of angiotensin converting enzyme (ACE) inhibitors during the second and third trimesters of pregnancy, allergic reactions with dialysis and ACE inhibitors, new Halcion labeling, warnings about sporicidin products, FDA proposed food labeling reforms, recommendations on silicone breast implants, and foodborne diseases in nursing homes (150).

Until the end of 1991, the FDA sent quarterly information packets to WHO, the Pan American Health Organization (PAHO), and approximately 70 drug regulatory authorities throughout the world (95). This policy has now modified to sending important policy papers to WHO and to 62 foreign embassies located in Washington, DC. The material sent by FDA does not necessarily focus on labeling for specific drugs but instead highlights regulatory decisions that U.S. regulators believe are important (32).

The FDA also has a special procedure for notifying foreign purchasers that a drug or medical device has been withdrawn from the U.S. market for safety reasons. FDA contacts the U.S. company for a list of foreign individuals, institutions, and government agencies that have imported the product. The IAS works with the U.S. Department of State to provide the U.S. embassies in the countries in which the product is sold with a list of the purchasers so that the purchasers can be notified (168). FDA provides a summary of the reasons for withdrawal, and encourages the U.S. company to provide foreign purchasers with complete information. FDA may evaluate the effectiveness of the company's notice by requesting that the U.S. embassies follow up with foreign purchasers to see whether information was provided. If the company has not provided adequate information, FDA may ask them to send it but does so without legal authority. There have

been few drug withdrawals in which FDA has used this special notification procedure (31).

FDA also responds to requests for information from other countries. FDA is currently setting up an electronic bulletin board that will contain all public information issued by the FDA including: *Enforcement Report (weekly* recall list), a drug and device product approval list, *Medical Devices and Radiological Health* news, *FDA Medical Bulletin, FDA Consumer Information,* FDA's *Federal Register summaries,* speeches by FDA officials, FDA congressional testimony, special AIDS information, *Veterinary Medicine* news, and notice of upcoming FDA public meetings. The electronic information will be available through INTERNET, a worldwide research computer network of government, military, academic, and other organizations (32).

The IAS administers the FDA International Visitors Program. In the year ending September 1991, FDA was visited by 603 representatives from 61 countries. In 1990, the IAS arranged visits to the FDA by 789 foreign officials representing 65 countries and multinational organizations (168).

FDA cooperates with WHO in various activities. In 1980, the FDA and WHO cosponsored the first International Conference of Drug Regulatory Authorities, held biannually since then, bringing together regulatory authorities from all over the world. FDA representatives have provided advice and other assistance to various WHO programs including the Action Program on Essential Drugs, WHO's Management Advisory Committee, the Certification Scheme, the Ethical Criteria for Medicinal Drug Promotion, the preparation of Model Drug Prescribing Information, the Model Lists of Essential Drugs, and the Global Program on AIDS (166). FDA is also a WHO Collaborating Center for Monitoring of Adverse Drug Reactions, providing WHO with a monthly accounting of all serious adverse reaction reports (168).

FDA staff have also assisted WHO with drug regulation projects in developing countries (17). In 1988, for example, the FDA provided a drug specialist for 2 years to PAHO, a regional office of WHO, to assist with formal training programs designed to strengthen national drug agencies and improve pharmaceutical manufacturing (57). Most recently, the FDA agreed to assist USAID in its support of a WHO evaluation of the Certification Scheme (see above) (24,259), and USAID and the FDA will assist in a WHO evaluation of its "Guiding Principles for Small National Authorities" (24, 278).

THE U.S. AGENCY FOR INTERNATIONAL DEVELOPMENT

Until recently, USAID was not involved directly with WHO's pharmaceutical work, but has just begun funding a WHO evaluation of both the Certification Scheme and the "Guiding Principles for Small National Authorities." USAID is also supporting a WHO project to develop country-specific research on current pharmaceutical use in developing countries. The research will be carried out by the International Network for the Rational Use of Drugs (INRUD) (see below for description of INRUD), which will develop a *Drug Use Indicators Manual. The* manual will include background, definitions, methodologies for collecting drug use indicators,[3] and extensive appendices containing data collection methods, drug and problem lists, and data collection forms (24,113). A report on these activities should be available by the end of 1992.

USAID is also engaged in a 5-year cooperative agreement with the U.S. Pharmacopoeia to assess and facilitate the distribution of pharmaceutical

[3] Drug use indicators include: average number of drugs used per facility; percent of antibiotics or injections; percent of patients not provided drugs; number of essential drugs in stock, patients reporting correct dosing, etc. (1 13).

information in developing countries, including both information provided to the drug regulatory authorities and to health workers (24). Finally, US AID has requested proposals for a 5-year contract addressing three areas of pharmaceutical distribution in developing countries: drug regulation and registration; rationalization of procurement strategies; and the development of pharmaceutical information for prescribers, consumers, and drug regulatory authorities (24).

CONSUMER HEALTH ADVOCATES

A variety of organizations and individuals address themselves to pharmaceutical issues in developing countries. This section concentrates on groups that act as advocates for political change or focus on the role of multinational pharmaceutical companies in the area of drug information. The many organizations that provide health care or focus on health issues other than pharmaceuticals are not discussed here.

Public health advocacy may take several forms. The most common form is the dissemination of information to the public and the press about actions of industry, international organizations, or governments, that are inconsistent with consumer interests. Consumer boycotts, while difficult to organize, can also be powerful. In addition, public interest organizations may operate as information clearinghouses and many provide educational programs in developing countries.

Numerous public interest groups operate in individual countries. Many of the individual health and consumer groups in both developing and industrialized countries are part of a larger international network, Health Action International (HAI), which itself works closely with the International Organization of Consumers Unions, an umbrella group that helps promote consumer issues and consumer advocacy in many countries, These two groups and selected smaller consumer groups are discussed below.

The International Organization of Consumers Unions

The International Organization of Consumers Unions (IOCU) was formed in 1960 as a multipurpose resource for its membership of 130 consumer groups in 51 countries. IOCU's central office is in the Hague, and its two regional offices are in Penang, Malaysia, and Santiago, Chile. IOCU acts as an information network, coordinates consumer activities, holds a triannual world congress, and organizes international seminars and workshops. In 1973, IOCU published one of the frost studies on drug labeling in developing countries (see app. A) (61,116) and it continues to be active in drug information as well as other issues of pharmaceutical distribution. In August 1990, IOCU sponsored an International Workshop on Consumer Health and Drug Information and Education in Penang, Malaysia. The major objective of the workshop was to determine how media could be used effectively to communicate information to parents about children's health and the rational use of drugs (54),

IOCU drug labeling activities include collecting relevant information (e.g., general prescribing information, lists of banned or restricted pharmaceuticals, reports of adverse effects) and passing this information on to developing countries. IOCU also publishes reports related to the pharmaceutical industry and rational drug use. In 1981, IOCU published a *Consumer Action and Resource Kit on Pharmaceuticals,* which focused on 44 "problem" drugs, that could be used by groups in developing countries to lobby against the sale of dangerous drugs (154).

IOCU also maintains a network called Consumer Interpol, consisting of approximately 260 correspondents in 79 developing and developed *countries* (117). The correspondents monitor information on newly discovered or newly regulated hazardous consumer products, including pharmaceuticals, such as notifications of banning, restriction, withdrawal, or nonapproval of products. This information is received by the Con-

sumer Interpol office in Penang and may become the basis for *Consumer Alerts* sent to all members of the network. As of March 1991, 85 *Consumer Alerts* had been sent out, covering hazardous toys, cosmetics, pharmaceuticals, electrical goods, food products, pesticides, and other items (4). Consumer Interpol also distributes a *Consumer Interpol Memo,* relating selected articles and news briefs on consumer issues, and a quarterly *Consumer Interpol Focus,* with feature stories on specific safety problems or major international initiatives to restrict global trade in hazardous products (3).

IOCU has published many books and pamphlets on technical aspects of pharmaceutical use. In 1988 it published several short pamphlets written by it pharmaceutical adviser, K. Balasubramaniam, including: *Policy Options in Pharmaceutical Patents for Developing Asian Countries (14); The Rational Use of Drugs: A Universal Concept (15); Global Marketing of Pharmaceuticals: Prescription for Disaster (12);* and *Policies and Strategies On Drug Pricing Regulations: International Experiences (13).* IOCU also supports publications by other consumer organizations.

With respect to pharmaceutical issues, IOCU plays a major role in one of the primary international consumer health organizations, Health Action International.

Health Action International

In 1981, 50 consumer organizations and individuals founded Health Action International (HAI) as an "international antibody" to the adverse effects of pharmaceutical marketing. HAI has coordinating offices in Europe, Asia, and Latin America. HAI's original agenda included (102):

1. developing an information clearinghouse;
2. responding to the IFPMA Code of Pharmaceutical Marketing Practices;
3. coordinating activist campaigns regarding specific drugs and companies;
4. promoting full implementation of WHO's Action program on Essential Drugs;
5. pressuring industry to market drugs that meet "real medical needs," have "significant medical value," and are acceptably safe and efficacious; and
6. supporting nondrug solutions to health problems.

HAI has coordinated international advocacy for essential drug policies in lobbying WHO, UNICEF, the European Parliament, and other international and regional bodies (16,97).

For a number of years, HAI lobbied WHO to pass a code of pharmaceutical marketing. In 1982, HAI published its own code of conduct that it hoped would be the basis for a U.N. or WHO international code. The HAI code demonstrates the degree of specificity that consumer groups seek. With respect to labeling, HAI's code calls for package labels with:

1. specific information on whether the product is for prescription or OTC use;
2. the non-proprietary name for all active ingredients printed in equal or greater size than the print used for the manufacturer's name;
3. information on the class and category of therapeutic use;
4. an explanation of all contraindications that may endanger life or severely endanger health; and
5. a list of all active ingredients.

HAI also would limit claims about efficacy, safety, or potency of the product unless they were qualified. In addition, the HAI Code would require that package inserts include: 1) only those indications approved by public health authorities or generally endorsed by reputable and independent scientific publications, 2) all contraindications that are not included on package label, and 3) a list of active and inactive ingredients (84). Finally, HAI would require graphic warning symbols on all promotional material indicating

products that should be avoided during pregnancy or lactation, on all prescription-only products to indicate changes in product information, and on new products for which reports of any adverse reactions or events are required (86).

HAI has published a detailed critique of the IFPMA Code and WHO's Ethical Criteria for Medicinal Drug Promotion (see ch. 6) (86). Another report by HAI presents evidence that the IFPMA Code is not effective in controlling advertising (39). In 1992, HAI carried out the first phase of an international survey of pharmaceutical marketing standards that will evaluate the implementation of WHO's Ethical Criteria for Medicinal Drug Promotion (97). Initial results indicate that the Ethical Criteria have not been effective because they have not been implemented at the national level (89).

HAI member groups also focus on problems with specific products or categories of product, trying either to have the products removed from the market or to change their labeling or promotion. Their campaigns usually consist of documenting problems with drug products, challenging the companies involved to respond to their criticisms and, if the company responses are not satisfactory, using public education campaigns "built on solid information and powerful emotional pleas" (102). The organization communicates through an international newsletter, *HAI News.*

One HAI international campaign was directed at removing inappropriate antidiarrheals from the market. Following a WHO paper on the limited efficacy of antidiarrhea drugs, HAI members in Latin America published a survey of antidiarrhea drugs marketed in Bolivia, Brazil, Chile, Colombia, Costa Rica, Ecuador, Guatemala, Mexico, Peru, Uruguay, and Venezuela. A number of products that WHO said were not efficacious, and potentially harmful, were widely available in those countries (87).

HAI has published various resource books on pharmaceuticals. *Problem Drugs (38),* a HAI "information and campaign pack" on various categories of "problem" pharmaceuticals, was first published in 1986. It has since been translated into 8 languages and a new edition is scheduled for release in 1993 (97). Other publications include: *Peddling Placebos: An Analysis of Cough and Cold Remedies (36), Antibiotics: The Wrong Drugs for Diarrhoea (35), Cleared for Export (33), The Provision and Use of Drugs in Developing Countries (71), Drugs and Primary Health Care (63), Promoting Health or Pushing Drugs? A Critical Examination of Marketing of Pharmaceuticals (39), A Question of Control (261),* and *Bitter Facts About Drugs (5). Andrew* Chetley, a prominent consumer advocate who has worked with a number of consumer groups, is the author of several of these publications and has recently written a book analyzing the role the pharmaceutical industry has played in health care in the developing world (37).

In addition to its publications and lobbying, HAI groups help promote and develop national drug policies and sponsor a wide variety of training and education programs. HAI seeks to promote the WHO Ethical Criteria for Medicinal Drug Promotion, and continues to expand and strengthen its ties to local consumer organizations in developing countries (88).

SOCIAL AUDIT

Social Audit, based in the United Kingdom, is an active HAI member. It has concentrated on the marketing practices of British multinational pharmaceutical corporations in developing countries, but it also has examined their activities in industrialized countries. In 1979, Social Audit published *Insult or Injury? An Enquiry into the Marketing and Advertising of British Food and Drug Products in the Third World (142),* a work funded largely by IOCU. In 1982, the group published *Drug Diplomacy: Decoding the Conduct of a Multinational Pharmaceutical Company (148). This* book chronicles Social Audit's campaign against the marketing claims made by Searle Pharmaceuticals for its antidiarrhea drug

Lomotil, a campaign that Social Audit maintains resulted in changes in the labeling (154).

In 1980, Social Audit published *Drug Disinformation: What British and Multinational Drug Companies Tell Doctors About Their Products, At Home and Abroad (143). This* book compared the information for about 900 drugs listed in MIMS prescribing guides in England and Ireland. Although over half of the entries were identical, the study found what they believed to be significant discrepancies for the prescribing entries for over 200 products.

The main force behind Social Audit is its Director, Charles Medawar. He continues to publish books and articles that keep the work of Social Audit visible. In addition to the titles listed above, he has written: *The Wrong Kind of Medicine? (144), Drugs and World Health (146),* "International Regulation of the Supply and Use of Pharmaceuticals" (145), and with the support of IOCU, *One Drug at A Time: A Report on the Limitation of Fixed Ratio Combination Drugs (149). In 1991,* Social Audit published *Power and Dependence (147), an* examination of the history of benzodiazepine (a class of sedatives that includes diazepam) marketing, focusing on the problems of dependence.

BUKO

BUKO (the Federal Congress of Development Action Groups), one of the founding members of HAI, is a West German network of approximately 200 consumer groups that focuses on "global malpractice in drug marketing by the multinational pharmaceutical companies" (62), in particular Swiss and German companies. In 1987, it published a short report on Hoechst, a German pharmaceutical company, with evidence that Hoechst was marketing drugs in developing countries that had potentially severe side effects, or which had been banned in developed countries, often without complete warnings (62). The study also attacked Hoechst's practices in Germany, such as the delay of a warning letter to German doctors about several reported adverse reactions (including six deaths) caused by one of its antidepressant products (62).

In 1990, BUKO, together with HAI, helped disseminate a study by two German physicians that examined more than 2,000 German and Swiss pharmaceutical products marketed in 26 developing countries. The majority of these products were marketed by large multinational corporations. The authors determined whether these drugs met the health needs of the countries in which they were marketed by comparing the sample drugs to those on WHO's Essential Drug List. The authors also evaluated the efficacy and safety of the drugs using authoritative pharmaceutical reference books from several countries (7,28,30,75). They reported significant problems in all areas. (See app. A, "The Hartog and Schulte-Sasse Study.")

In addition to its publications, BUKO produces a monthly newsletter *Pharma-Brief. The* newsletter contains summaries of research on pharmaceutical issues in developing countries and reports on consumer activities (64). BUKO also helps facilitate dialogue on pharmaceutical policies in developing countries. In 1987, for example, BUKO held a conference in Germany that brought together representatives of nongovernmental organizations from various developing countries, academia, and industry. The conference focused on the relationship among the number of pharmaceuticals on the market in a country, the quality of those products, and the need for essential drug policies in countries with limited budgets for health care (85).

Medical Lobby for Appropriate Marketing (MaLAM)

MaLAM is an international network of physicians that acts as a watchdog for advertising by pharmaceutical companies (199). MaLAM works to encourage companies to provide what they consider "sufficient, consistent, and accurate information" about their products, and primarily

targets marketing claims made in developing countries (254).

Each month, MaLAM's approximately 700 subscribers in more than 40 countries receive a draft letter addressed to a senior executive in a pharmaceutical company questioning a particular marketing practice. MaLAM subscribers are asked to sign the letter and return it to MaLAM. A final letter is sent after review by an international editorial board (153,254), The letters ask the company to provide evidence supporting the contested advertising claim. MaLAM publishes the responses it receives from industry in its newsletter. (Results of some of MaLAM's work are discussed in ch. 4 and 6.)

International Network for the Rational Use of Drugs (INRUD)

Developing countries typically lack the resources needed to evaluate national programs, including drug policies, An organization that provides support for evaluative research is the International Network for the Rational Use of Drugs (INRUD), a nonprofit group based in Boston, INRUD is a cooperative organization of health professionals, administrators, and researchers from developing countries who are interested in implementing new, innovative programs to improve the use of pharmaceuticals, and is supported by the development agencies of a number of countries (including USAID) and private foundations (127).

INRUD's strategy is to first engage in research designed to clarify the "dynamics of drug use and, . the underlying motivations, expectations. and incentives of providers and consumers" (128). According to INRUD, although a number of countries have tried to improve drug use by developing standard treatment protocols, providing drug information, drug bulletins, implementing changes in health training curricula, restricting drug advertising, and using public education, there has been little evaluation of these strategies; they are assumed to have a positive impact. However, studies in industrialized countries have revealed that some of these same interventions have not been very effective (127).

The initial INRUD network is limited to seven countries that have demonstrated a commitment to the rational use of essential drugs: Bangladesh, Ghana, Nigeria, the Sudan, Tanzania, Indonesia, and Nepal. Each country has a "Country Core Group" of four to eight people representing various professional disciplines and organizations, A "Central Support Group" is staffed by Management Sciences for Health and the Harvard Medical School in Boston. INRUD anticipates that other individuals and organizations interested in the program will become affiliate members and share in information gathering, training, and other activities (128).

INRUD also is developing a number of indicators of drug use to facilitate comparisons of drug use among countries and identify drug use problems, The study involves field work in Indonesia, Bangladesh, Nepal, Nigeria, and Tanzania. WHO plans to publish a manual on standard drug use indicators based on the results of this study (1 15), INRUD recently received a grant from US AID to conduct country-specific research with WHO on current pharmaceutical use in developing countries (see section on USAID, above).

INRUD publishes a newsletter, *INRUD NEWS,* reporting on its own activities and on other recent drug utilization studies, and has developed a computerized bibliography of published and unpublished literature relating to drug use in developing countries (114), In addition, NRUD has developed training materials to promote rational drug use, which it has used in Nepal and will use in Zimbabwe in 1993. INRUD's future plans include studies of the factors that influence drug prescribing behavior (129).

SUMMARY

Developing countries face many obstacles to maintaining effective pharmaceutical programs,

including lack of political commitment, poor planning capabilities, lack of trained personnel, inadequate financial resources, irrational prescribing and dispensing practices, and lack of public awareness of the problems (286). WHO programs and private groups have attempted to help countries by providing information and other services to improve drug regulation, including the regulation of drug labeling.

Appendix A: Major Studies of Pharmaceutical Labeling in Developing Countries

The 1970s marked the rise of the consumer movement and a time of increased attention to the operations of multinational corporations (MNCs) in developing countries. Concern was growing that many .MNCs operated in a virtually unregulated environment in developing countries, in some cases to the detriment of consumers. A number of consumer groups, health care workers, and representatives from international organizations raised concerns about certain corporate practices in developing countries. One issue raised with respect to pharmaceutical companies was the quality of their prescribing information, Small studies began to disclose that a number of pharmaceutical MNCs had labeling standards for developing countries that differed from those for industrialized nations. These studies are discussed below.

IOCU: The Chloramphenicol Study

The first comprehensive study of pharmaceutical labeling in the developing world was carried out by member groups of the International Organization of Consumers Unions (IOCU) in 1972 (1 16). IOCU examined 55 packs of chloramphenicol marketed by MNCs in 21 countries. Chloramphenicol is an antibiotic that can cause aplastic anemia, a serious blood condition. Although aplastic anemia is rare, when it does occur it has a fatality rate of 40 percent or more (210). Since the discovery of this connection in the 1950s, use of chloramphenicol has been limited in the United States and other industrialized countries to treating serious infections when alternative treatments failed. IOCU did not find a single label that included all the necessary contraindications, and they found wide variation in the warnings given with identical brands sold in different countries (34,61).

IOCU: The Clioquinol Study

A larger study was done during 1974 and 1975 on clioquinol, a drug originally introduced for treatment of amoebic dysentery, but often used for treatment of traveler's diarrhea (53). By the early 1970s, clioquinol was implicated in an epidemic of subacute myelo-optic neuropathy (SMON), an often fatal condition that causes blindness and paralysis. The epidemic claimed the lives of about 10,000 people in Japan. As a result, where it was still available, clioquinol was recommended only for treating acrodermatitis enteropathica, a serious chronic condition affecting the skin and bowels of young people.

At the time of the study, clioquinol had been banned in the United States and Japan, and was available only from a pharmacy in Norway, Sweden, Austria, Finland, France, Iceland, Italy, the Netherlands, Yugoslavia, New Zealand, some places in Australia, the Philippines, and Denmark. It was available without prescription, but in most cases only from a pharmacy, in the United Kingdom, Belgium, Ireland, Guatemala, Ghana, South Africa, Tanzania, Egypt, Lebanon, Zambia, Malaysia, Mexico, Sri Lanka, Israel, Greece, Tunisia, Thailand, Taiwan, Iraq, and Brazil,

The IOCU researchers obtained 107 drugs containing clioquinol from 39 countries, of which 83 samples from 34 countries included package inserts. Almost all of the package inserts recommended the drug for

the treatment of diarrhea and 50 of them recommended it as a prophylactic. The indications were often vague, e.g., "for specific medically indicated prophylactic use. " The dosage recommendations on 63 leaflets ranged from 400-1,500 mg per day for 3 to 28 days, despite the fact that the clinical literature recommended an adult dose of only 750 mg a day for 14 days (169). Twenty of the leaflets had no recommended dosage, Thirty-two leaflets mentioned the most important contraindications: hyperthyroidism, iodine allergy, and malfunctioning of the liver or kidneys; however, 37 leaflets listed no contraindications, including those from the United Kingdom, New Zealand, Belize, Brazil, Tanzania, Taiwan, Kenya, Spain, Malaysia, and Singapore. One explanation offered for the lack of contraindications on certain of these package inserts was that the insert recommended a maximum treatment of 3 days, after which it recommended consulting a doctor if the diarrhea was not cleared up. The risk of an adverse effect from clioquinol was relatively small if used in low dosage for a few days.

Information on side effects was also analyzed. Forty-five leaflets listed the major side effect, peripheral and optic neuropathy, but only 34 recommended stopping the drug at the first sign of peripheral neuritis or optic neuritis. The researchers concluded that warnings were deficient on inserts from the United Kingdom, Bahamas, Belize, New Zealand, Brazil, Indonesia, Thailand, Tanzania, Taiwan, Iraq, Kenya, Malaysia, and Singapore. However, the lack of complete warnings in the United Kingdom, Belize, Bahamas, and New Zealand was tempered by the fact that there were instructions that the drug be taken for no more than 3 days,

The study also looked at four other halogenated hydroxyquinoline drugs (the same chemical class as clioquinol) because there was some evidence that these drugs also could cause neurological illness. The researchers examined 44 leaflets from 24 countries. Again, there were many differences in indications, contraindications, and warnings on the package leaflets. There were differences among labels within the same country and among labels provided by the same manufacturer for a drug marketed in different countries. Some of the differences might have been attributable to different national regulations, but the differences within countries indicated that differing regulatory requirements were probably not the sole explanation. A number of lawsuits were brought against MNCs that marketed products containing clioquinol (primarily Ciba-Giegy, a Swiss company, and Takeda and Tanabe from Japan), Damage awards eventually reached almost $900 million.

Today, clioquinol is banned in the United States and United Kingdom, and in other industrialized and developing countries. However, a recent study found many products containing clioquinol in India, Indonesia, **Thailand, the Middle East, Egypt, Mexico,** Central America, Colombia, Venezuela, and Brazil, A number of these products are marketed by domestic companies and their labeling carries little or no warning of possible neurological damage. Despite clioquinol's history, it is considered safe and effective in a number of developing countries, and in India is considered an essential drug (212).

IOCU: The Anabolic Steroid Study

In 1983, IOCU released a study about the marketing of anabolic steroids in Germany, Australia, the United Kingdom, the United States, and a number of Asian countries (118),[1] According to the cited clinical literature, anabolic steroids were recommended only for treatment of certain serious anemias resulting from bone marrow failure, and for treating osteoporosis in the elderly. Anabolic steroids were also recommended for children with certain growth disorders, but because they can cause subsequent infertility, precocious or abnormal sexual development, and stunt growth, this indication was very limited. Other known side effects of anabolic steroids include irreversible symptoms of masculinization in women (deepening of voice, body hair growth, male-pattern baldness), and in men, atrophy of the testicles, inhibition of sperm development, and impotence, Anabolic steroids were also linked to liver tumors, jaundice, acne, and nausea.

IOCU examined 38 anabolic steroid products marketed in Indonesia, Bangladesh, the Philippines,

[1] ***This*** was not the first study to examine the labeling and marketing of anabolic steroids in developing counties. See also references 134,163,208,

Thailand, Mexico, Malaysia, the United States, and West Germany. Fifteen samples came from a single Dutch company, Organon, and the remaining drugs were marketed by Winthrop, a U.S. company, and Schering, a West German company, Package inserts, advertisements, and other promotional literature were examined.

The study found examples of these companies marketing the same product with complete warnings in developed countries and less-than-complete warnings in developing countries, Anabolic steroids were promoted in the developing countries for poor appetite in children, poor weight gain, listlessness, and lack of energy, sometimes using pictures of healthy, well-nourished children. In a number of countries, the drugs were available in easy-to-take drops and syrups, often flavored to make them more palatable to children. Package inserts in Bangladesh and the Philippines stated specifically that there were no contraindications in children. Another 16 package inserts failed to caution against use in children or to recommend that skeletal maturation be checked periodically by x-ray. A majority of the package inserts also failed to warn against use in patients with kidney or liver disease.

Side effects were also minimized. Nine package inserts *from* developing countries listed no side effects. The majority of products that did include warnings about side effects failed to warn against impotence, enlargement of breasts, liver damage, jaundice, or the more common side effects found in children,

The Yudkin Study

In the late 1970s, a British physician, J.S. Yudkin, compared the prescribing information in the African Monthly Index of Medical Specialties (MIMS)[2] with information on the same drugs in the British MIMS (292). He found significant discrepancies in indications and warnings. For example, tetracycline was marketed in Africa with no warning about the risk of tooth discoloration in children. In Britain, anabolic steroids, whose side effects include stunting of growth, virilization (appearance of secondary male sexual characteristics in women) and liver tumors, were recommended only to treat osteoporosis, renal failure, terminal malignancies, and aplastic anemia. In Africa they were also indicated for treatment of malnutrition, weight-loss, as appetite stimulants, and for excessive fatigue. In the African MIMS several different brands of liothyronine, a drug recommended for "severe thyroid deficiency" in Britain, were marketed for "lowered metabolic states. " Methadone, which was recommended in Britain for severe pain, was marketed in Africa as a cough suppressant.

The Social Audit Studies

A 1978 study by the British consumer group, Social Audit, funded principally by IOCU, focused on products of the major British pharmaceutical MNCs: Beecham, Boots, Fisons, Glaxo, ICI, Reckitt and Colman, and Wellcome (142). The study compared the information from British MIMS with MIMS guides from Africa, the Caribbean, and the Middle East. When available, the researchers also looked at detailed prescribing instructions in India and Malaysia. They found that dosage recommendations in developing countries tended to be greater, even double the dosages recommended in the United Kingdom. The study also found a marked lack of detail about contraindications. For example, the British official prescribing information for Ancoloxin (meclizine), an antiemetic, warned against use in pregnant women except in cases of severe vomiting. U.S. labeling also warned against use during pregnancy because animal studies had indicated the drug might cause birth defects. However, in Africa and some developing countries in other areas, it was indicated specifically for the treatment of nausea and vomiting in pregnancy, Even the detailed prescribing information in India did not contain warnings about potential birth defects. Another example was the painkiller, Paramol 118 (dihydrocodeine). In Britain this drug required warnings against use by children, people with impaired liver or kidney function, or during an asthma attack. This same drug was marketed in Africa without these warnings.

In contrast, indications were often more expansive in the developing country guides than in the U.K.

[2] MIMS are commercial prescribing guides distributed free to physicians. Their prescribing information is supplied by the pharmaceutical manufacturers and edited by the publishers. Production of the guides is paid for by advertisements.

MIMS. For example, a painkiller marketed in the United Kingdom for "persistent pain, particularly muscle pain, headache, neuralgia," was indicated in Africa and the Caribbean also for "fibrosis, lumbago, back pain, sprains, strains, dysmenorrhoea, dental pain, bursitis, trauma, and chronic rheumatic pain." While this detail was not necessarily misleading, the researchers concluded that the emphasis in indications coupled with deficient warnings demonstrated that the companies were more interested in drug promotion than in providing objective prescribing information. The researchers found that the quality of information did vary by prescribing guide and by company, but because no attempt had been made to obtain a representative sample from each company, no comparative analysis could be carried out.

Silverman, Lydecker, and Lee's Studies

Some of the most comprehensive and influential research on drug labeling in developing countries was carried out by U.S. researchers. In 1974, Silverman and Lee, of the University of California in San Francisco, published Pills, *Profits and Politics (209),* which focused on the policies of both U.S. and foreign pharmaceutical manufacturers and included evidence that these companies provided irrational prescribing information. Further work was published by Silverman in *The Drugging of the Americas (208),* which examined the prescribing information for 26 single-drug entities or fixed combinations, marketed by 23 MNCs as 147 different products in 12 countries in Central and South America (212).

The drugs in this study included antibiotics, oral contraceptives, nonsteroidal antiinflammatory drugs, steroid hormones, antipsychotic tranquilizers, antidepressants, and anticonvulsants. Each drug selected met the following criteria:

- it was a valuable and widely used drug;
- it had well-established clinical usefulness and known hazards;
- it was marketed in the United States and Latin America by the identical company, its foreign subsidiaries, or affiliates; and
- it was described in the U.S. *Physicians' Desk Reference* (PDR) and selected prescribing guides in Mexico, Central America, the Dominican Republic, Ecuador, Colombia, Brazil, and Argentina.

The PDR, which contains the labeling information approved by the U.S. FDA, was used as a standard. The researchers concluded that "with few exceptions, the indications included in the Latin American] reference books are far more extensive, but the listings of hazards are curtailed, glossed over, or totally omitted" (208). There also were examples of the same drug marketed by the same company with different information in different countries. One of these was chlorarnphenicol. The PDR recommended chloramphenicol for acute typhoid fever only, and to treat serious cases of salmonella, hemophilus influenza, some types of meningitis, and some forms of cystic fibrosis. In addition, the drug was not recommended for infants, pregnant women, or in patients in whom there was evidence of hypersensitivity, depression of bone marrow, signs of blood dyscrasia (abnormalities in the production of blood cells), or impaired liver or kidney function, Potential adverse reactions included aplastic anemia (which may be fatal), blood dyscrasias, nausea, vomiting, headache, mild depression, mental confusion, and other necrologic reactions. The PDR also recommended that periodic blood studies be done on patients taking the drug to avoid the most serious reactions.

The study examined five brands of chloramphenicol marketed by four companies in Latin America, including one brand that was removed from all markets in 1973, All the prescribing entries evaluated included broader indications than those in the PDR. The antibiotic was recommended for dysenteric infections, tonsillitis, colitis, whooping cough, and as a broad-spectrum antibiotic. The prescribing guides for Central America, Argentina, and Ecuador contained no contraindications or warnings. In other prescribing guides, the warnings and contraindications were limited. Listings for three of the brands, taken from four different prescribing guides, failed to warn against aplastic anemia or other blood dyscrasias.

Oral contraceptives were also examined. The PDR lists many contraindications, the most important being thrombophlebitis, impaired liver function, known or suspected estrogen-dependent malignancies, and unexplained abnormal genital bleeding. Many adverse reactions were also presented, including changes in li-

bide, nervousness, dizziness, loss of hair, and skin changes.

Again, Silverman found prescribing guide entries with far more indications than in the PDR. Entries for seven different oral contraceptives, marketed by five multinational corporations, recommended oral contraceptives for premenstrual tension, uterine bleeding, and various menstrual disorders. Thrombophlebitis was included as a contraindication in 14 out of 20 entries; suspected hormonal neoplasms in 4 out of 20; undiagnosed abnormal vaginal bleeding in 4 out of 20; emotional disease in 2 out of 20; and caution in cases of epilepsy, migraine, asthma, or cardiac or renal dysfunction was included in only one entry, Eleven entries listed no potential adverse reactions,

In *Prescriptions for Death: The Drugging of the Third World (210), Silverman, Lee,* and Lydecker returned to Latin America, but expanded Silverman's earlier work to include Central Africa (15 countries), Southeast Asia (4 countries), and the United Kingdom. The researchers examined 515 prescribing guide entries for 34 drug entities or fixed combinations marketed by more than 149 companies (46 were products of U.S. multinationals or their affiliates) (21 1). They examined many of the same drugs they had looked at in *The Drugging of the Americas.* This 1980 study again showed that certain prescription drugs were promoted in developing countries for more indications than had been approved in the United States and that mention of serious adverse reactions had been minimized or omitted from the labeling.

In Indonesia, Singapore, the Philippines, and Central America, chloramphenicol was still recommended for minor infections such as bronchitis, vaginal infections, and throat infections, and that almost all of the chloramphenicol products marketed in Indonesia had no warning about aplastic anemia. A number of products marketed in the Philippines, Malaysia, and Singapore also failed to mention aplastic anemia or had no warnings at all. In the African MINIS, however, which had been critiqued just a few years earlier by Yudkin, the authors found information almost identical to the PDR.

The authors looked again at tetracycline drugs, which are not recommended for most patients with impaired liver or kidney function. In infants and young children, tetracycline may discolor teeth and interfere with bone growth, so it is not usually recommended for women in the last half of pregnancy or for children under the age of 8 or 12. Of the 90 tetracycline products examined from developing countries, warnings about use in patients with kidney disease were given for 13; warnings about use with liver disease, for 9; and about use during pregnancy, for 9. Thirty-five products had no specific warnings, though some included vague warnings or referred the prescriber to the literature (210).

The study also analyzed prescribing information for certain combination antibiotics, clioquinol, dipyrone, and oral contraceptives. The investigators found that the dangers of serious or lethal side effects were frequently minimized or totally ignored, and claims of effectiveness often "wildly exaggerated" (210).

In 1984, Silverman, Lee, and Lydecker published the results of another survey. The 1984 study examined information from prescribing guides for 63 drug entities or fixed combinations, marketed as 1,069 different products by 303 drug companies in 15 countries (211). The study revealed that a number of pharmaceutical companies had made a "marked improvement" in their promotional and labeling practices in developing countries. The authors examined 103 chlorarnphenicol products and found that 93 carried warnings against use in trivial infections, for prophylaxis, or in prolonged therapy. They also examined the prescribing entries for 117 tetracycline products, and found that 109 carried suitable warnings, including contraindications for kidney and liver disease.

With respect to dipyrone, a pain reliever that was withdrawn from the U.S. and British markets because it could cause agranulocytosis, a fatal blood condition, the authors found that 119 out of 155 (76 percent) contained warnings of serious or possibly fatal agranulocytosis. In 1980, only half of the dipyrone products studied warned about agranulocytosis.

Clioquinol and the related halogenated hydroxyquinolines, which had previously been promoted as antidiarrhea agents, were also studied. Twenty-two out of 61 prescribing entries for products containing clioquinol failed to include warnings of severe and possibly fatal neurological damage. They concluded that most cases of irrational promotion (60 percent) involved domestic firms in developing countries. They cautioned that the "problem of irrational, inaccurate, or even dishonest promotion has not been solved" (21 1).

During 1987 and 1988, at approximately the same time OTA gathered its labeling material, Silverman, Lydecker, and Lee revisited the issue of drug labeling in developing countries, this time with partial financial support from 10 pharmaceutical companies. The researchers examined 40 single-drug entities or fixed combinations marketed as 1,500 products in the United States, the United Kingdom, and 74 developing countries-28 countries in Africa (both English and French speaking), 12 countries in Latin America, 11 countries in the Caribbean, and 6 countries in Southeast and southern Asia (212). The products were marketed by more than 400 companies, both MNCs based in industrialized countries and domestic companies in the developing countries.

The drugs chosen for the study were in the following categories, including many of the same drugs they had examined in previous studies: analgesics, antiarthritis drugs, antidiarrheals, antibacterial, appetite stimulants, cardiovascular drugs, cerebral vasodilators, psychoactive agents, major and minor tranquilizers, antidepressants, anabolic steroids, female sex hormones, and sex potions. As in their previous studies, prescribing guide entries were analyzed. Unlike the OTA study, Silverman and his colleagues focused on certain indications or warnings for each drug, rather than examining the entire label. The results of their study were published in the spring of 1992.

The authors concluded that most multinational corporations were willing to disclose major hazards and to limit their indications to those based on sound scientific evidence; there were, however, "glaring exceptions." They found that the total amount of misinformation presented to physicians had not changed because the improvements made by the multinational corporations appeared to be offset by the misleading labeling presented by the increasing number of local or domestic firms (212).

The UNCTC Study

In 1984, the U.N. Centre for Translational Corporations published a study that included a section on drug marketing by MNCs in developing countries, examining 12 products marketed in 12 countries. Each drug selected had some significant side effect or contraindication, The review found "significant discrepanc[ies]" between the information provided in the PDR and the information provided in the prescribing guides of Brazil, Colombia, Ecuador, Mexico, Venezuela and Central America. For example, clofibrate, a cholesterol-lowering drug, has some serious side effects, including gallstones, leukopenia (decreased production of white blood cells), and cardiac arrhythmias. In Brazil, Ecuador, and Mexico, the prescribing guide did not mention any of these effects. In Argentina, one MNC marketed 17 varieties of clofibrate with no mention of side effects, although the same firm sold the drug in the United States with complete side effect and warning information (223).

The study also looked at prescribing guide entries for five drugs containing dipyrone, a pain reliever that can cause a fatal blood disease. The United States had banned the drug, as had Australia, Sweden, and the United Kingdom, but it was still on the market in some European countries as an analgesic, antipyretic, and antispasmodic, The study found that dipyrone was widely used as a general painkiller in Brazil and Argentina, often without prescription or proper warning. In Thailand, the drug was dispensed over-the-counter more often than aspirin. In Costa Rica and Kenya, it was an ingredient in many popular medicines. A review of the prescribing guides found a number of entries promoting the drug for treatment of headaches, common cold, pneumonia, and rheumatoid arthritis, In some cases, the risk of the fatal blood disease was mentioned, but no mention was made of the need for hematologic tests to detect its onset early, Other entries mentioned no side effects. The U.N. study also cited a review by two researchers of 110 antibiotic preparations marketed in Central America. According to that study, prescribing guide entries for 40 of the preparations had no information on contraindications and 66 had no information on adverse reactions (79).

The U.N. study concluded that in most of the countries studied there were no limits on the amount of information that could have been provided. However, the study also noted that some companies had begun to respond to the criticisms with promises to dispense uniform labeling information and to support standard international drug prescribing information (223).

The Osifo Study

In the early 1980s, a small study was carried out in Benin City, Nigeria, to determine whether Nigeria's new labeling regulations altered the content of pack-

age inserts (171). Nosakhare Guy Osifo, a pharmacologist, examined package inserts for 28 prescription drugs marketed by 15 U.S. MNCs or their subsidiaries, Osifo found that the four package inserts supplied with products exported directly from the United States were identical or very close to the U.S. labeling. The remaining package inserts, included with 18 different products distributed by U.S.-controlled foreign subsidiaries, contained more indications and fewer warnings than appeared in U.S. labeling. Inserts for drugs specifically for use in critically ill patients, which were generally more dangerous products, tended to be more complete and accurate than those accompanying products for less serious conditions.

The Hartog and Schulte-Sasse Study

Hartog and Schulte-Sasse, two German physicians working with the support of BUKO-Pharmakampagne (a German public interest group that focuses on pharmaceutical issues) reported on more than 2,000 German and Swiss pharmaceutical products marketed in 26 developing countries (81).3 The study, published in 1990, evaluated whether these drugs, mostly products of MNCs, met the health needs of the countries where they were marketed by comparing them with WHO's Essential Drug List. They also evaluated the efficacy and safety of all the drugs and examined labeling and advertising.

Drugs were classified as inappropriate if:

1. there were no efficacy data to support the labeling or advertising claims;
2. the available data had been criticized as scientifically inadequate by a substantial number of experts; or
3. different researchers reported contradictory results.

Even if a drug was found efficacious, it was deemed inappropriate if there was a more effective or less dangerous alternative. Finally, a drug was considered inappropriate if the amount of active ingredients was too low at the recommended dose, or the drug would fail to be effective as administered (e.g., the oral form of an antispasmodic, butylscopolamine, which is effective only as an injection). Using these criteria, the researchers concluded that more than 60 percent of the drugs evaluated were inappropriate.

The WHO Essential Drug List includes only drugs that are of "utmost importance and are basic, indispensable and necessary for the health needs of the population." The drugs also are selected on the basis of cost and the practicality of prescribing a particular medicine under a variety of medical situations (e.g., in situations where there is little likelihood the patient would be monitored). Hartog and Schuhe-Sasse compared the products in their sample to therapeutic agents on the WHO list, looking specifically at ingredients, concentration, and dosage form. They concluded that less than 20 percent of their sample drugs would meet the criteria for inclusion in an essential drug list.

In the analysis of labeling, the study reported deficiencies in information in MIMS prescribing guides for English-speaking Africa and the Middle East, the Philippines, and India. They compared information in the Swiss pharmaceutical compendium with the developing country prescribing guides. They concluded that the prescribing guide entries typically included more indications and less information on adverse effects and contraindications than did the Swiss compendium.

The Industry Response

Industry responses to these studies have varied. The International Federation of Pharmaceutical Manufacturers Associations claims that companies quickly responded to *The Drugging of the Americas* by developing internal corporate policies to guarantee that claims about efficacy and disclosures about side effects were consistent worldwide (37). Some companies blamed MIMS editorial policies for discrepancies between the official drug datasheets and MIMS entries. Companies also noted that MIMS guides were not the sole source of information for physicians, and that their company representatives did provide complete information, or that information was available from the company on request (210).

[3]The study looked at 1,312 German products marketed in 1984/1985, 1,273 German products marketed in 1988, and 1,084 Swiss products marketed in 1988.

The primary explanation offered by companies for the differences between the information given in developing and developed countries was that developing countries had different laws and regulations. As a former President of the U.S. Pharmaceutical Manufacturers Association (PMA) explained shortly before the release of *Prescriptions for Death: The Drugging of the Third World*, "*our* foreign labels conform to the labeling regulations of the importing country which may forbid the sorts of disclosure required by the FDA" (148). Another PMA representative stated that it would be arrogant and paternalistic to insist that one nation's decision in the area of drug regulation was superior to another's (165),

Critics pointed out that regulatory policies were not responsible for the labeling differences between industrialized and developing countries. As evidence of this, they noted several examples where, in a single country, the same chemical entity was marketed by different companies with substantially different labeling. Also, since the information in most of the prescribing guides was not regulated by the host governments, the critics contended that regulatory policies were not responsible for the differences found in the guides.[4]

[4] See, e.g., references 62,134,142,148,154,260.

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

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



Brazil

DRUG REGISTRATION

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

All drugs not included in the Brazilian Pharmacopoeia are considered "new drugs"[1] and must be registered with the Ministry of Health (this excludes raw materials, which are regulated under other legislation) (106). To register a drug for marketing in Brazil, a company must submit an application that includes:

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

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

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

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

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

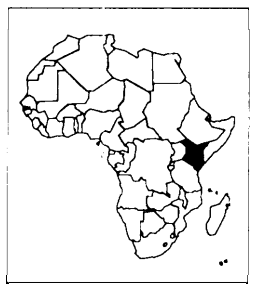
DRUG LABELING

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

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

1. name of product (trademark or generic);
2. pharmaceutical form;
3. number of units in package;
4. active ingredients;
5. complete formula of the product with quantitative composition;
6. name and address of manufacturer;
7. responsible pharmacist;
8. license number and date of issue;
9. batch number;
10. expiration date and date of manufacture;
11. storage instructions;
12. for prescription products, statement that it is supplied on prescription only;
13. indications;
14. side effects; and
15. precautions, if any.

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



Kenya

DRUG REGISTRATION AND LABELING

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

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

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

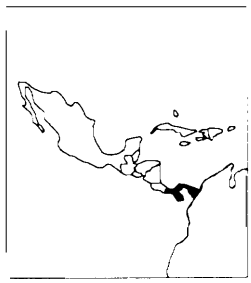
Initial applications for drug registration are assessed on grounds of safety, efficacy, and quality. Each registration application must include the following information (106):

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

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

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

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



Panama

DRUG REGISTRATION AND LABELING

According to Decree 93 of February 16, 1972, the Regulation on Registration of Pharmaceutical Specialties, almost all pharmaceuticals must be registered in Panama, The Ministry of Health controls the registration process and works in conjunction with the National University of Panama and specialized laboratories to review applications. In evaluating an application, the Ministry compares the safety and therapeutic advantages of the drug with similar products, and bases its decision on these comparisons.

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

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

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

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

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

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

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

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

Thailand



DRUG REGISTRATION AND LABELING

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

Regulation of the Private Market

As established by the Drug Act of 1967, the main legislation affecting the pharmaceutical industry in Thailand, every pharmaceutical product intended for sale must be granted a marketing approval by the Thai Food and Drug Administration (TFDA) of the Ministry of Public Health (MOPH) (193). The Drug Act applies to the private market, but since 1986 has not applied to the Governmental Pharmaceutical Organization (GPO), the government's own drug production company (272).

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

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

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

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

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

Regulation of the Public Market

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

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

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

Labeling and Promotional Regulation in Thailand

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

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

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

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

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

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