Statement of
Sidney M. Wolfe, M.D.
Director, Public Citizen's Health Research Group
and member of OTA Advisory Panel and Expert Working Group
on the study, *Drug Labeling in Developing Countries*
May 20, 1993

Introduction

In addition to thousands of hours of staff time spent by OTA, especially Hellen Gelband and Bob McDonough, those of us on the advisory panel and also on the working group spent hundreds of hours studying the labels, assessing the importance of differences between U.S. and developing country labels, discussing our concerns and formulating conclusions. Of all the governmental and other advisory groups I have participated in, rarely have I worked with a group of medical scientists who were more unanimous in almost all of our conclusions about the drugs with the most seriously deficient labeling.

There is little question that there have been many thousands of preventable deaths and injuries caused by the reckless and dangerous labeling of these drugs in developing countries by U.S.-based drug companies. This conclusion is consistent with our definition of the most serious type of labeling deficiency, a score of 2 for a section of the labeling in which there was:

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

Four Examples from the 59 Drugs with the Most Seriously Deficient Labeling (in each of these examples two or more parts of the label were very deficient).

1. Choledyl Pediatrico (the asthma drug, oxtriphylline, **WARNER-LAMBERT**). The most serious deficiencies on the label of this pediatric dose form are:

a. Warning section does not include manifestations of toxicity such as convulsions, rapid heart rate, heart arrhythmias or that children can have unusual sensitivity to the central nervous system stimulant effects of this drug;
b. the adverse reaction section omits problems such as life-threatening heart arrhythmias, circulatory failure, low blood pressure and other serious problems;
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a. the indications section promotes the product for a dangerously wider spectrum of purposes than the two for which it is approved in this country, rheumatoid arthritis and osteoarthritis. Instead, the drug is indicated broadly for conditions "requir[ing] analgesic or anti-inflammatory activity;"

b. the warning section fails to mention that there is a markedly increased risk of ulcers with doses higher than 20 milligrams and fails to mention some of the serious adverse reactions such as liver damage.

3. Norinyl 1-50 (the birth control pill containing norethindrone and mestranol, **SYNTEX).** The most serious deficiencies in the labeling of this drug are:

a. label has no information on indications and usage;

b. label does not list contraindications such as coronary artery disease, cancer of the breast or uterus, or phlebitis;

c. label does not warn about adverse effects such as strokes, blood clots to the lung, heart attacks and blood clots in the legs and other oral contraceptive risks.

4. Norisodrine (the asthma drug, isoproterenol, **Abbott).** There were serious deficiencies in (5) different parts of the label of this drug including:

a. no information on usage and indications;

b. no information on contraindications such as in people who have heart arrhythmias;

c. no information on warnings and precautions such as the fact that deaths with cardiac arrest have occurred after excessive usage;

d. no information about adverse reactions such as palpitations, anginal-type pain and flushing of the skin.

These and the other seriously and dangerously deficient labels overstate the benefits and/or understate or fail to tell about the risks. These labels and the predictable false and misleading advertising and promotion which follows from them will clearly sell more drugs to doctors and patients because their assessment of the benefit/risk ratio for the drug will be distorted.

By thus misleading doctors and patients into the belief that drugs are more effective and safer than they actually are, the drug industry is turning drugs with a favorable benefit/risk ratio--had they been accurately labeled--into dangerous or lethal weapons which will inevitably cause preventable injury or death to the patients in the developing countries who use them.

Since our study found that none of the 19 companies whose drugs were analyzed was significantly worse or better than any other, the results are an indictment of the entire US-based drug industry. There is little doubt that the foreign-based multinational drug companies are no better but they were not the subject of this study. Since the countries chosen for the study are from Africa, Asia, and South and Central America there is reason to be quite concerned that what we found in those countries may well be true in most of the rest of the developing countries of the world.

The findings of this study are disgraceful to the American-based drug industry in a country which is looked to for leadership in drug regulation by most of the rest of the world. Whereas the Food and Drug Administration usually does a creditable job in approving drugs and assuring that thĕ U.S.labels on those drugs are consistent with the scientific evidence about their safety and effectiveness, people in third world countries who need, if anything, more protection because of their weaker drug regulatory authorities and the over-the-counter availability of many prescription drugs, are less protected because of the double standard of these labels.

In conclusion, the use of these dangerous labels in developing countries is immoral and unethical but since neither of these considerations have put an end to these practices, it is time to make them illegal. Option 1, to require that the U.S.-approved labeling be placed on all products sold in developing countries would be the option I would prefer.

OFFICE OF TECHNOLOGY ASSESSMENT ■ U.S. CONGRESS

REPORT *brief*

APRIL
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Labeling for half the products examined had serious problems

While appropriate drug-prescribing information—"labeling"—is the norm in the United States, it is not always so in developing countries. In **DRUG LABELING IN DEVELOPING COUNTRIES**, OTA examines labeling by U.S.-based multinational pharmaceutical companies for the drugs they sell in developing countries. Four countries—Brazil, Kenya, Panama, and Thailand—were chosen for the report.

Of the 241 drugs sampled, ***two-thirds failed to provide the labeling information a physician needs to use the drugs safely and effectively.*** On a scale from 0 (no problems) to 3 (most serious problems), half were rated 2 or 3. Reliance on this labeling information alone could lead to serious or life-threatening medical problems or, at best, ineffective treatment.

Here are some examples of what OTA found:

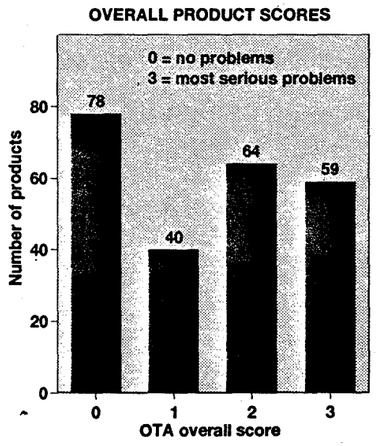
- A combination drug including a corticosteroid, an antihistamine, and an antipsychotic was recommended for relief of itching. It had no warnings about the serious side effects of steroids, including suppression of the adrenal gland, or about the side effects of antipsychotics, including the risk of tardive dyskinesia, a sometimes irreversible movement disorder, and the risk of neuroleptic malignant syndrome, a potentially fatal side effect.
- A synthetic version of the male hormone testosterone was recommended for treating women for frigidity and benign breast conditions, to suppress production of breast milk, and to relieve menopausal symptoms. The company provided inadequate evidence that the drug is effective for these indications, and the labeling failed to warn about serious side effects of this potentially dangerous drug.
- A drug for relief of pain and inflammation was recommended for a number of minor ailments, such as headache, without mentioning potent side effects of this drug, including the complete shut down of the body's production of white blood cells—a fatal complication and the reason the drug is no longer on the U.S. market.
- One indication for a magnesium-containing antacid was to add it regularly to infant formula to "prevent milk from souring and forming curds in the stomach," to aid digestion, and to prevent constipation in healthy babies. The company provided no evidence to support these uses, and the labeling did not warn of the danger of magnesium overdose in infants.

Latin American Pharmacy

OTA REPORT *brief*

CURRENT STATUS

Consumer activists first raised the issue of inadequate drug labeling in developing countries in the late 1970s, and they still play a key role in highlighting problems and pushing for improvements. Because the governments of developing countries lack the resources necessary to review and evaluate proposed drug labeling, solutions have been sought largely outside these governments.



Under the Federal Food, Drug, and Cosmetic Act (FDCA), the U.S. Food and Drug Administration (FDA) has no authority to require specific labeling for products sold in other countries. The reach of the U.S. Government is limited further because the bulk of products sold by U.S-based multinational corporations in developing countries is manufactured not in the United States, but in third countries. Although legislative remedies are possible, they would require a controversial exercise of extraterritorial power.

International mechanisms available to tackle the issue include codes of conduct, which are voluntary binding agreements among countries, or less authoritative agreements, such as guidelines. Multinational treaties also are possible, but politically difficult.

In the absence of stronger measures, The World Health Organization (WHO) has developed two programs—the Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce and the Ethical Criteria for Medicinal Drug Promotion—that encourage countries to require better prescribing information.

And the pharmaceutical industry has itself adopted the International Federation of Pharmaceutical Manufacturers Association's Code of Pharmaceutical Marketing Practices. *While these programs and others under the auspices of national governments (including the United States, through the Agency for International Development) are important, they do not constitute complete or substantial solutions.*

The Office of Technology Assessment (OTA) is an analytical arm of the U.S. Congress.

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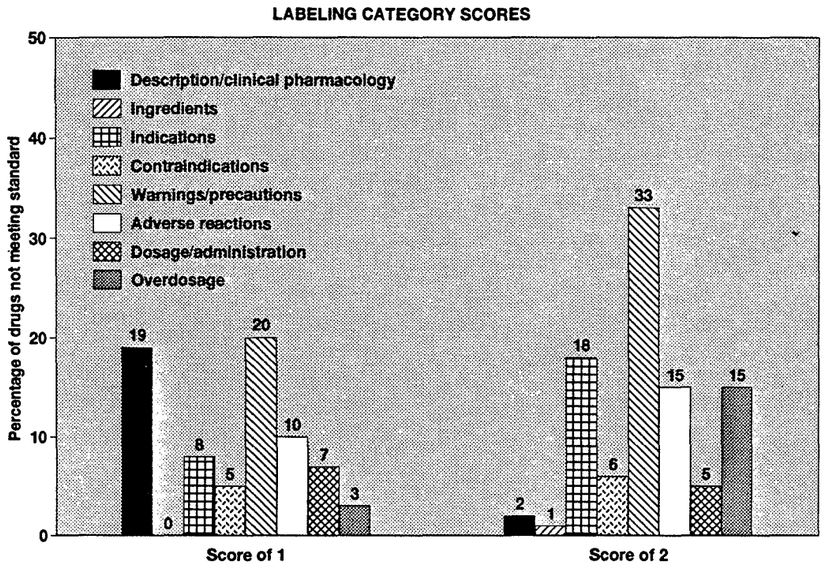

Each section of the labeling was evaluated using specific criteria. Minor problems score 1 and serious problems score 2. Overall scores were derived from an algorithm combining category scores.

OPTIONS TO CONSIDER

OTA identified the following options to improve drug labeling in developing countries:

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 or a translation in the appropriate language.

Limiting this requirement to developing countries whose governments have agreed to it would mitigate objections by the international legal community over possibly unwarranted extraterritorial reach of U.S. law.

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 Transnational Corporations.

A WHO code of conduct for pharmaceutical labeling was debated by the World Health Assembly through the early 1980s. By 1983, it was off WHO's agenda, in part

because the United States opposed codes of conduct to control specific industries. Given the findings of this OTA study and other recent work, it might be time to reconsider this position. An international code of conduct would apply to all pharmaceutical manufacturers, multinationals as well as domestic companies.

The United States could press for adoption of the U.N. Code of Conduct for Transnational Corporations, a code that would apply to the whole range of consumer products, and which has existed in draft for many years.

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

The Ethical Criteria are considered "guidelines," a nonbinding, weaker form of policy than a code of conduct. These could be strengthened with U.S. support. The United States also could help developing countries to incorporate the Ethical Criteria into their national laws, which would make them enforceable.

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.

U.S. assistance to improve the legal and technical drug regulatory infrastructure in developing countries, currently at a minimal level, could be expanded by the FDA and USAID, and through support of WHO programs.

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

Progress in improving labeling in developing countries could be monitored by periodic surveys. No provision for criminal or civil penalties would be attached to this option, avoiding possible objections of the international community to extraterritorial application of U.S. laws.

Copies of the report for congressional use are available by calling 4-9241.

Copies of the report for noncongressional use can be ordered from the Superintendent of Documents, U.S. Government Printing Office, S/N 052-003-01314-2, $11 each, P.O. Box 371954, Pittsburg, PA 15250-7954, (202) 783-3238.

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P. MERCHEZ, WHO

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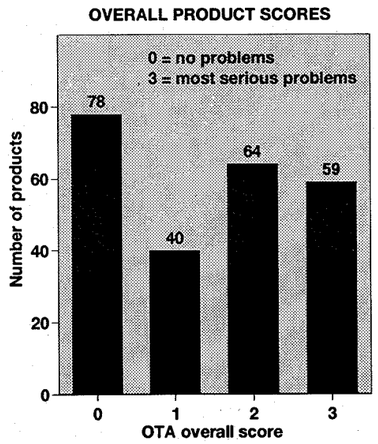

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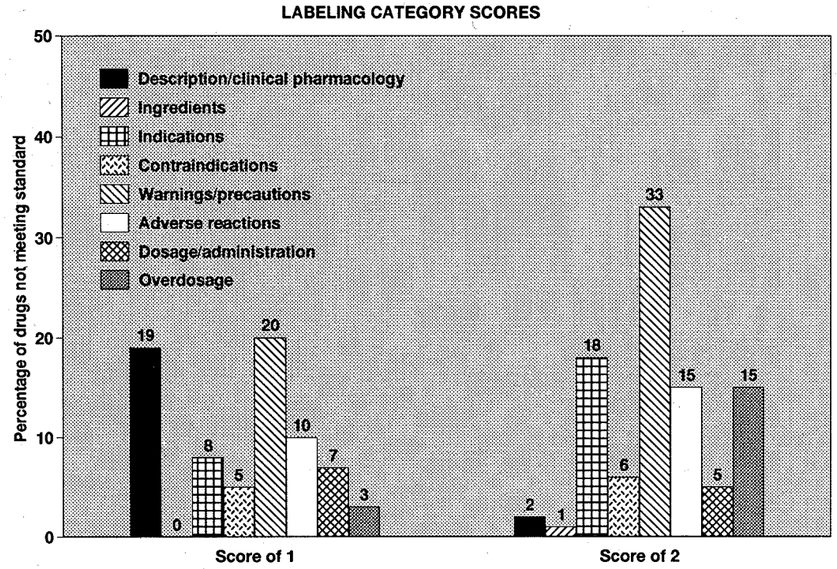

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