propoxyphene has also been demonstrated through its long history of successful use by medical practitioners in the relief of pain.

Some studies have failed to demonstrate the efficacy of propoxyphene. Others have failed to show that it is any more effective as a pain reliver than aspirin. The same may be said, however, of other well-established pain relief medications, including codeine. The simple fact is that it is often very difficult to demonstrate the efficacy of a pain reliever in a clinical study. This is so in part because the nature and causes of pain may vary, and in part because the perception of pain involves an important, yet variable, psychological component, the effects of which are difficult to measure or control in clinical studies.

It is important to recall that studies using laboratory animals are not complicated by these psychological factors and that, in such studies, the pain relieving properties of propoxyphene are consistently confirmed. In addition, many of the studies referred to earlier in these hearings compared propoxyphene with other pain relievers on the basis of a single dose. Our knowledge of the pharmacology of propoxyphene indicates that it achieves its greatest pain relieving effects after several doses have been administered. This is in fact the way the drug is used.

In the final analysis, the true measure of the therapeutic usefulness of a drug is determined in the field of clinical practice. Here propoxyphene products have become well established. In practice, the physician's choice of an analgesic for mild-to-moderate pain is limited to: (1) the familiar nonprescription drugs like aspirin and acetaminophen, which in many cases of chronic or recurring pain have already been tried by the patient and found wanting; (2) to meperidine or opium derivatives like codeine (which carry a risk of dependence); and (3) to other analgesics, such as propoxyphene or pentazocine (Talwin). There are always people who will respond better to one drug than another. Propoxyphene alone will work remarkably well in some patients whose pain is not well controlled by analgesics that some might regard as superior on the average. In short propoxyphene is a useful and well-established part of the physician's armamentarium for the control of pain.

Over the past 20 years, Lilly has promoted its Darvon products ethically and responsibly. The Company has provided the medical profession with the most current information concerning propoxyphene through advertising, labeling, and the efforts of its pharmaceutical representatives. These persons are well-trained. All of them are college graduates. More are pharmacists.

Studies conducted before the drug was introduced into the market—including an evaluation carried out at the U.S. Public Health Service, Addiction Research Center in Lexington, Kentucky—showed, contrary to Dr. Wolfe's allegation, that its potential for abuse was limited and that its dependence (or addiction) liability was less than that of codeine. Experience has confirmed these findings.

You have heard testimony in these hearings about the pharmacology and toxicology of propoxyphene. Much of that information was developed in studies that were sponsored by Lilly, shared with FDA and DEA, and disseminated widely to the medical profession.

In 1975, the North Carolina state toxicologist (Dr. McBay) reported that deaths associated with the use of propoxyphene were increasing in that state. Lilly promptly investigated the report and subsequently sponsored a nationwide study by a respected toxicologist, Dr. Bryan Finkle of the University of Utah. Dr. Finkle reviewed medical examiner reports and files in 18 geographic areas in the United States and Canada which represented a total population of over 50 million persons. He concluded that most of the deaths associated with propoxyphene involved use of the drug at doses far in excess of therapeutic amounts and in combination with alcohol and other drugs, especially tranquilizers and other central nervous system depressants. A majority of the persons had a history of suicidal tendencies, emotional instability, or drug or alcohol abuse.

In April 1976 Lilly published the results of Dr. Finkle's study in a letter to the editor of the *Journal of the American Medical Association*. In cooperation with the Food and Drug Administration, the Company revised the labeling for its propoxyphene products to reflect the new findings. A brochure containing the new labeling and Lilly's letter to the editor of *JAMA* was personally delivered to 114,000 physicians by Lilly pharmaceutical representatives, and copies were mailed to other physicians.

In February 1977, acting on the recommendation of the Department of Health, Education, and Welfare, the Drug Enforcement Administration issued an order