

Our National Center for Drug Analysis, and our Washington laboratories, led the investigation of this problem. It became evident that manufacturing problems resulted from the mixing of the ingredients, which contained only about one active part to 400 inactive parts. All the firms involved cooperated by voluntarily withholding distribution, and discontinuing the manufacture of digoxin tablets, until the problem could be solved.

FDA met with industry representatives to discuss both manufacturing and analytical techniques. Our people recommended a modification of the mixing techniques in the early stages of manufacture which provided the solution. In order to check the process, FDA, with the concurrence of industry, has certified each batch since then before shipment.

Both the U.S. Pharmacopeia and the National Formulary are seeking clinical tests such as excretion and absorption profiles on human beings to evaluate clinical effect. In addition, they are attempting to develop *in vitro* tests which approximate the *in vivo* situation.

Senator NELSON. You mean the USP and NF are seeking these tests on all drugs?

Dr. EDWARDS. I think eventually that would be their ultimate goal. They are doing this by drug categories at this point in time but they are attempting to increase the scope of what are the various factors that go into developing uniformity for these drugs.

Senator NELSON. Well, then, will these become additional factors in meeting USP and NF standards?

Dr. EDWARDS. That is right; yes.

We have made our own efforts to assure that chemical drug equivalents, when administered in the same amounts, will provide essentially the same availability as measured by blood levels, excretion, and absorption profiles, et cetera. We have developed certain in-house biological availability requirements for abbreviated new drug applications but information and techniques thus far in this whole area have been slow in coming and must be considered preliminary. On the basis of currently available evidence, the quality of marketed drugs in regard to their purity and the uniformity of content of active ingredients is not suspect. This includes all marketed drugs, generic as well as brand name. Even though there have been indications that different brands of a few drugs in chemically equivalent formulations have given significantly different biological responses, we have reason to believe this is not a frequent phenomenon.

The next subject I would like to briefly address ourselves to, Mr. Chairman, is this problem of communications with the profession and other Federal purchasers.

All of the Food and Drug Administration's scientific work in new drug approval and surveillance, and all of the NAS-NRC evaluations, are in fact to no avail unless the results are communicated to the prescribing physicians.

Drug information is communicated in a variety of ways—in full disclosure package inserts, in advertising messages, and, of course, by detail men.

The package insert is the key to what can and what must be communicated to assure safe and effective drug therapy. As I indicated,