BATCHES REJECTED FOR CERTIFICATION

Five (5) batches from three (3) manufacturers have been denied certification for failure to meet USP and/or F.R. requirements.

Senator NELSON. So there were 44 digoxin products in the marektplace by 44 different companies?

Dr. CROUT. They were all making an identical product. They were making 0.25 milligram tablets, and there were, as I recall, 44 manufacturers.

Senator NELSON. How many of those had brand names and how many of those were generic?

Dr. CROUT. Well, the most prominent brand name is Lanoxin made by Burroughs-Wellcome. I am not aware of any other brand name for digoxin. I think the other 43 were sold under the generic name of digoxin.

Senator NELSON. Do you have the names of the companies that were manufacturing this drug?

Dr. CROUT. We can submit that.

Senator NELSON. Would you submit names of those companies for the record?

Dr. CROUT. Yes, sir.

Senator NELSON. And there was only one that met the standards?

Dr. CROUT. No, by no means. Well, beginning back in 1969, the firms that had tablets out of compliance, from the standpoint, remember, of content uniformity, they had mixing problems—some tablets had more digoxin than was supposed to be in the tablets, some had less—entered into a voluntary certification program.

Several firms dropped out of the business at that time, and we ended up with something on the order of 30 to 35 firms making digoxin between 1970 and now. The tablets entering the market from 1969 through now have met the USP standards for content uniformity.

In 1970, I believe, 1970 or 1971, a new problem appeared with digoxin. The discovery was made that certain of the tablets lacked bioavailability; that is, that the blood levels in patients receiving those products were not up to standard, even though the tablets themselves were meeting USP specifications at that time.

So between 1971 and late 1973 a number of things happened in the research scene. The Food and Drug Administration, and the USP, went to work to develop a dissolution rate test for digoxin. When that became available in late 1973, we published our new regulations and said all manufacturers must meet the new USP dissolution rate specification.

Senator NELSON. Was there a direct correlation between the dissolution rate and the bioavailability?

Dr. CROUT. If you will allow the word "direct" to be interpreted a little broadly, yes; there is a pretty good correlation.

We then tested almost all the products that were on the market in late 1973 for the new dissolution rate standard. We tested about 30 manufacturers' products. There may be a few more, but we tested 30 manufacturers. Twenty of those passed, and the other ten were recalled.