would it be fair to say that if not the intent, at least the effect, is to eliminate competition?

Dr. BANES. Well, the effect is to limit the number of laboratories that are capable of doing that kind of an analysis. And if the specifications say that this chloride determination shall be done in the following manner, then that effectively limits the number of laboratories that can do that test.

Mr. GORDON. Now, how important and widespread is the problem of lack of bioavailability?

How many drugs do you know of that have this problem?

Is this problem manageable by the FDA?

Would you comment on that, please?

Dr. BANES. Well, there have been many, many references to problems in bioavailability. In my opinion, the number of authenticated episodes of lack of bioequivalence among chemically equivalent products for which there are compendial standards are a handful. The numbers have a habit of varying. I would say somewhere between half a dozen and a dozen authenticated cases of lack of bioavailability when the products actually meet the standards that are set up for them. And where we have recognized these problems, investigation has shown the reason for them, and we have taken regulatory measures to eliminate these problems.

Digoxin tablets have been mentioned here and it seems to be a very popular example of this kind of problem. And I think it should be, because it is the most significant one that we have encountered because of the high toxicity of digoxin. It is a very important drug. It is very important for heart patients. It is very widely used, and if the tablets do not deliver the active ingredient to the bloodstream in a predictable manner, then difficulties will result.

Dr. Feldmann spoke about the timeframe, that methods of analysis for digoxin in blood were developed only within the last 5 or 10 years, that in 1971 the paper by Lindenbaum of Columbia University and his associates first pinpointed the problem. Following his discovery there were many other studies that confirmed his results.

Some of these studies showed a very good correlation between bioavailability and rate of dissolution of the tablets. That is, if the digoxin tablets dissolved very quickly, then there was good, uniform bioavailability. If the tablets dissolved very slowly, then you can expect that the tablets will not deliver the active ingredient. As a consequence, USP was the first in the world to adopt a dissolution standard for digoxin tablets. Although the problem was widely recognized, USP was the first to set up a standard. FDA followed it up with a certification program, so-called, for digoxin tablets. And in my opinion, given these two quick reactions, with a strict dissolution standard and FDA's program, there should be no problem in the future with digoxin.

I should say that digitoxin tablets will, in my opinion, present a similar problem. But we are moving there to preclude it without waiting for further evidence from scientists throughout the world.