alence, is a consideration that relates to the desirability of such a program. If our report was a useful one, it should throw some light on the question now before you, so I am happy to have this opportunity to give you some of my interpretations of our findings and conclusions.

I should say that our considerations were limited to solid dosage forms, that is capsules and tablets taken by mouth to produce an effect after absorption into the body so that everything I will say should be interpreted in that context.

The important question to be asked is: To what extent can the chemically equivalent drug products of different manufacturers be interchanged without a change in the therapeutic effect that will be produced? Drug products are said to be chemically equivalent when they contain the same amount of the same *active* ingredient in the same dosage form. Drug products are said to be bioequivalent when their active ingredients are absorbed from the gastrointestinal tract at substantially the same rate and to the same extent as indicated by the time-course of their concentration in the blood. They are said to be therapeutic equivalents when they produce the same therapeutic effect with no difference in toxicity or side-effects.

Now it is a well-known and well-publicized fact that a number of studies, involving the products of a score or so of drugs, have shown that there were differences in the concentration of the active ingredient in the blood following the administration of chemically equivalent products from different sources. Clearly, this means that the standards for such products, or the enforcement of the standards, or both, were inadequate to assure the bioequivalence of those products.

It is very important to point out, however, that two drugs may differ in bioavailability, that is be bioinequivalent, but may still be therapeutically equivalent. It is entirely possible, and, in fact, frequently true, that the concentration in the blood produced by two products may differ substantially, yet, for both, that concentration may fall well within the range between that required for the desired therapeutic effect and that at which unacceptable toxic effects are produced.

On the other hand, it is also true that in a very few instances, differences in bioavailability have led to well-documented therapeutic failures. The rarity with which such failures have been documeted should not mislead one into believing that they are rare occurrences. There are so many other variables that affect the response observed when a drug is administered that it may be difficult to distinguish bioavailability as the source of the problem unless a careful study is undertaken to find out. For drugs with a narrow margin of safety, which must be administered in doses that do not much exceed that required for the therapeutic effect, significant variation in bioavailability is practically a guarantee of a significant incidence of therapeutic failure or toxic effect.

We therefore concluded that there are least *some* categories of drug products for which it will be necessary to establish adequate and standard bioavailability before interchangeability could even be considered.

The classes of drugs for which direct demonstration of bioavailability would be necessary constitute a small minority of all drugs. They are those with narrow margins of safety between the therapeu-