tic and toxic levels. Most commonly used drugs do not fall in that category.

Most drugs are administered in fairly standard doses without regard to the size of the patient and without regard for the fact that people vary widely in the rate at which drugs are broken down in the body and excreted. This reflects the fact that many drugs have such wide margins of safety that the dosage can be one aimed at producing, in the vast majority of patients, a concentration well above the minimum needed for the desired effect. Moderate variations within that range, whether owing to differences in bioavailability or in any other factor such as the size of the patient, are without therapeutic significance.

It was the opinion of our panel that appropriate groups of experts would not find it difficult to deal with the problem of distinguishing between those drugs for which proof of bioequivalence should be required and those for which such proof should not be considered necessary.

As I noted earlier, there have been a number of studies that showed significant differences in the bioavailability of marketed drug products and these differences reflected what we interpreted as inadequacies in the standards established by the compendia, that is, the U.S. Pharmacopeia and the National Formulary, and/or the way in which those standards are applied. I will not go into the specifics of our criticisms. However, it was our view that considerable tightening of those standards should be effected and that it would be desirable for the improvement of those compendial standards to precede the development of a list of interchangeable products even though the development of such a list was considered the ultimate goal of a rational drug program.

When we presented our conclusions to Senator Kennedy's Subcommittee on Health, he pressed us for an answer to the question of whether one might not proceed with the list of interchangeable products without waiting for a general overhaul of the compendial standards. I believe all those members of the panel who were present conceded that for some of the drugs with wide margins of safety, one could draw up such a list without need for concern about therapeutic inequivalence. We all felt that without improved standards that list would be far more limited than it would be if standards were first drawn up that would give better assurance of bioequivalence. One would have to be more conservative under present circumstances than would be the case if improved standards had been established. I believe there was also some concern that once the list of interchangeable products had been established, some of the impetus for improved standards would have been lost and they might never be established.

I guess the question that Senator Kennedy asked us is essentially the same as that being discussed today since the MAC list is essentially a list of interchangeable drug products. And I would have to reach the same conclusion today that I did then—namely, that I see no danger of therapeutic inequivalence if the list of drug entities to be included is based on careful selection by appropriate experts. However, I believe that the list will necessarily be more circumscribed than would be possible if the compendial standards were improved to give better assurance of bioequivalence.