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 at 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 therapeutic 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.