drug efficacy. These variations indicate that therapeutic equivalence, or equal biological activity, cannot necessarily be inferred from equivalence in the chemical institution of different formulations of the same drug. In the Drug Efficacy Study, it has been found that, in many cases, no data bearing on biological activity of chemically equivalent drugs are available other than those submitted by the manufacturer who originally filed a New Drug Application for his product. For this reason, the following qualifying addendum was approved by the Policy Advisory Committee of the Drug Efficacy Study and was forwarded to the Food and Drug Administration with each of the 26 groups:

"Drugs of identical chemical composition (so-called generic drugs) formulated and marketed by numerous individual firms under generic or trademarked names have been evaluated for efficacy as a group without consideration of 'therapeutic equivalence.' In the event that no evidence for pharmacological availability or therapeutic efficacy in man can be presented for any of the drugs in the attached listing, their classifications of effectiveness may need to be modified if future regulations of the FDA require such proof."

This statement defines the problem but offers no solution. Theoretically, biological tests in man of every formulation of a drug would be needed in order to establish proof of therapeutic equivalency. In many but not all instances, blood levels might be a satisfactory index of therapeutic activity as well as of the absorption of oral preparations. Furthermore, if appropriate chemical or physical tests should be found to correlate consistently with serum concentrations, these in vitro tests might be substituted for the more burdensome tests in animals or man. Indeed, blood levels in animals can be acceptable tests only if they correlate with comparable observations in man. The more potent the pharmacodynamic action of the drug, the more imperative would be the need for proof of the equivalence of biological and physical or chemical tests.

The Policy Advisory Committee of the Drug Efficacy Study is aware that consistent evidence of therapeutic equivalence of oral preparations, even when based upon simple study of blood concentrations in man, might require the testing of each lot of each formulation and so become a large-scale clinical operation requiring consent of large numbers of patients and volunteers. A strict interpretation of therapeutic equivalence might even require biological tests of individual capsules or successive batches of the drug selected at random.

Moreover, variation in biological response of individual subjects would seem likely to be greater than compositional differences among enteric-coated tablets or time-release capsules. Let us not deceive ourselves: if tests in human subjects constitute the only reliable method of demonstrating therapeutic equivalence, an unacceptably large burden will be imposed on drug manufacturers. Such biological tests may represent the most valid measure of comparative therapeutic activities, but the measure is one that is impossible of technical achievement by the pharmaceutical and medical professions.

What, in this less than perfect world, can be done? All producers of drugs should be required, as they are now, not only to provide evidence of composition, purity, and quality but also evidence of physical availability as judged by tests of disintegration, dispersion, and dissolution rates in appropriate solvents. In the majority of cases, this should suffice, but in every case in which there may be doubt of biological equivalence (eg, calcium added to tetracycline), biological tests should be required.

The exploration of possible chemical, physical, and animal tests that might satisfactorily be substituted for biological tests in man has already begun, and this should most certainly be encouraged. Particular attention is being paid to relatively insoluble drugs dispensed in solid forms as tablets or capsules. A Joint Panel of the United States Pharmacopeia and the National Formulary has been at work for some months on the development of standards and test procedures in vitro that will permit better definition of physiological availability. Biological data on the lack of therapeutic equivalence of various preparations of chloramphenicol recently dramatized this problem. Critical investigation of the chemical and physical properties of these preparations is currently in progress, and such investigations should certainly be encouraged.

The whole subject will require extensive scrutiny as well as close attention to process control of the uniformity of the chemical and physical properties of both generic and trademarked preparations. Appraisal of problems concerned with particular drugs will represent various degrees of medical, as well as technical difficulty. For example, are high blood concentrations of short dura-