The ethical manfacturer of drug products, having established the safety and therapeutic action of the product under investigation, must make the final decision. Does this product represent a significant advance in therapeutics? What makes this drug product a useful therapeutic agent for the physician in his practice? What is the ratio of clinical effectiveness to the toxic potential?

At this stage of development the producer of a new drug product has a very substantial financial investment that has resulted in only a minimum of information on which to predict the commercial value. Also, this one drug product containing an active ingredient which has shown promise among the thousands that have been synthesized, has alone progressed to this stage of development.

Approximately 3 years after the decision to investigate a new drug product, plans are made for carrying out a phase III, broadly based, clinical trial. Prior to the initiation of this phase of the study, detailed analyses and review of the data derived from the phase II studies are completed. Any further modifications of the clinical data sheet, which are a consequence of new observations during the phase II period, are incorporated in a further revision of the clinical data sheet. At this point, a copy of FDA Form 1573 is sent to selected clinical investigators throughout the country. (A sample copy of this form is attached for your information.) This study provides a wide experience of use in all ethnic and socioeconomic groups in the total population. This is a broad test of the efficacy of the product in the specific clinical situations for which it is intended to be used. The sample of patients must be large enough to yield data upon which judgment can be made concerning the safety and efficacy of the product. As many as 150 (or more) clinicians may participate and the total number of patients under their observation will frequently exceed 1,500 and often 3,000. Although it is estimated that an additional 18 to 24 months will be required for the completion of the phase III trial, it is likely that more than 4 years will pass between the initiation of clinical research on a product and the completion and filing of its NDA. During this period the monitor maintains close contact with each investigator so that he is informed of developments throughout the clinical trial and obtains periodic reports of the progress of the trials.

A sample copy of the New Drug Application Form FD 356 H is included as an attachment. The detailed information required to complete this application can be appreciated in part by review of the form. FDA approval of an NDA does not terminate the monitoring of the drug product by the medical department of the sponsoring firm. Once the drug product is available on prescription, there is no way of preventing its being used in dosages and for indications not included in the approved labeling. A drug product may be used improperly resulting in failure in therapeutic response or causing drug reactions. Both drug failures and adverse effects must be carefully investigated and reported to the FDA. These reports must be submitted every 3 months for the first year of distribution, every 6 months during the second year, and once a year thereafter. Any contraindication to use or toxic effect not already detailed in the