An additional responsibility is an administrative chore, for it involves the constant attention to the details of drug supply and preparation of progress reports to the FDA showing the continuing toxicological, teratological and carcinogenic investigations are being correlated and integrated with the studies in man. Indeed it is a complex exercise not to be undertaken by the inexperienced or uninformed.

The ethical manufacturer 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 three 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 socio-economic 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 four 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 three months for the first year of distribution, every six months during the second year, and once a year thereafter. Any contraindication to use or toxic effect not already detailed in the labeling must be investigated and reported within fifteen days after such knowledge is available to the producers.

No one has a greater interest or responsibility in the safety and effectiveness of a drug product than the manufacturer, who can ill afford to market a drug that will demonstrate a toxic response not commensurate with its effectiveness. To insure the continuing flow of all essential information in respect to an FDA approved drug product the pharmaceutical manufacturers support the Armed Forces Institute of Pathology in its investigation of tissue reaction to possible toxic drug effects and the American Medical Association's Council on Drugs and its Panel on Hematology of the Registry on Adverse Reactions.

More than seven hundred doctors of medicine are engaged full time by PMA member firms. There is a grave responsibility in the overall development of a new prescription drug product. Less than an honest appraisal of the product and constant surveillance of the claims made for it by its marketers could destroy a scientific reputation that was not obtained without great effort.