of a drug. There are many other important factors involved, such as the method of granulation or mixing the drug, the choice of inert ingredients used in combination with the active ingredient, and the product design which prevents impurities and defects from entering into the final product. All the above factors may influence the final availability of the active ingredients to the patient.

Physiological availability is, therefore, on essential quality characteristic that is not spelled out in any existing book of standards.

Specific examples can be pointed out which substantiate the contention that adherence to official standards does not guarantee clinical efficacy.

In testimony delivered earlier before this Committee by Congressman Durward Hall, reference was made to a Department of Defense experience with a drug of "supposed generic equivalency".

The drug mentioned was diphenylhydantoin which is used in the treatment of epilepsy. The Government had purchased at least three lots from three different producers other than Parke, Davis & Company. Documented complaints ensued from various military hospitals concerning the serious side effects elicited by patients taking the drug. Congressman Hall quoted a letter from the Chief Neurologist of one of the hospitals who recommended that:

"It has been my experience that patient response is significantly more erratic with diphenylhydantoin supplied by other than Park-Davis. Therefore, all further procurements of this drug should be made from Park-Davis."

Our product is now being procured by the Defense Supply Agency.

This difference in therapeutic effect between supposedly equivalent products is one of the reasons which led the military medical procurement agency of the Defense Department to require clinical testing data on the physiologic and pharmacologic efficacy of products offered for contract.

I believe that this testimony corroborates the stand we have taken. The firm I work for, Parke, Davis & Company, developed diphenylhydantoin, and through its many years of experience has been able to control the variables that are inherent in the production of this complex and useful medicine.

The FDA in the "1966 Drug Potency Study" announced in a published list that Parke-Davis' Thyroid Tablets were assayed and did not fall within the United State Pharmacopeia standard range.

The company was deeply concerned, and since FDA did not at first disclose the particular lot number of thyroid sample tested, it was of even greater concern. However, through inquiries, the company was finally able to ascertain the lot number of the thyroid tablets that were tested by the Food and Drug Administration. As it turned out, the lot of thyroid tablets tested by the Food and Drug Administration was not the company's USP Thyroid Tablets, but rather was their Thyroid *Strong* Tablets, a product that is labeled to contain 1½ times the USP potency.

The particular sample of thyroid tablets, tested by the FDA was indeed within our labeled potency range. A letter of apology from the FDA was later sent to the company.

Another example of failure of analysis in controlling the quality of medicinal preparations can be illustrated by the recall of a lot of tetracycline syrup distributed by a number of generic manufacturers a few years ago.

Tetracycline, as you know, is an antibiotic and subjected to batch-by-batch testing and certification by the Food and Drug Administration.

The recall of the tetracycline suspension involved a problem of subpotency. The question that arises here is—was the test performed by the Food and Drug Administration on the sample *before distribution* adequate to determine this lack of stability? On the other hand, if the product was potent when it left the manufacturer's plant, why did the product lose its potency in less than one year after distribution. The minimum shelflife of this product, as established by regulation, is 18 months.

Analysis at the time of manufacture, therefore, cannot assure that a product will be stable or retain its labeled and tested potency for an extended length of time.

This is another important point which a total quality control program contains. Total quality control manufacturers test and study their products to determine the length of time that their products can be assured to maintain the labeled potency.