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Mr. GORDON Now, in discussing the variability in response to different formulations of bishydroxycoumarin, you stated that the source of manufacture is as important as the choice of the drug itself. Evidence already in the hearing record, which was brought out in an article by Dr. Gerhard Levy, shows that bishydroxycoumarin tablets have shown a major variation in clinical response between two separate lots of that drug produced by the same manufacturer. Consequently, while there may be some evidence that a very few drugs such as this one you have mentioned are sensitive to variations in their formulation, even two lots from the same manufacturer may not be exactly the same.

I would like this to be part of the record, too.

(The document referred to follows:)

(Excerpts from Competitive Problems in the Drug Industry, Part 1, Page 438)

PHARMACEUTICAL FORMULATION AND THERAPEUTIC EFFICACY

(Gerhard Levy, Ph. D., Buffalo and Eino Nelson, Ph. D., San Francisco)

There is a mistaken belief among many that the active constituent as a chemical entity is the sole basis for the pharmacological effectiveness of a pharmaceutical product. It is the purpose of this review to show that the physiological response to the administration of a given drug product is frequently a function of both the pharmaceutical formulation of the particular dosage form as well as of the active ingredient. Certain variables related to pharmaceutical formulation will be discussed with respect to the manner in which they may modify therapeutic response in the hope that the examples cited may lead to the recognition that the choice of dosage form and of brand can be just as important as the choice of the actual therapeutic agent.

In general, differences in therapeutic efficacy among different generically identical drug products, while sometimes caused by lack of stability or by contamination, are most frequently due to differences in the rate at which the active ingredient or ingredients become available for absorption. This may modify the onset intensity, and duration of the desired physiological response. Furthermore, the efficiency, the biological availabliity (e.g., the completeness of absorption), as well as the incidence and intensity of side effects and toxic reactions from he drug may be affected.

A dramatic example illustrating differences in intensity of action of a drug as a result of dosage form modification has been given by Lozinski. His company found it desirable to increase the physical size of their bishydroxycoumarin (Dicumarol) tablets to facilitate breaking the tablets for administration of half doses. Patients who switched from the smaller to the new larger tablets required larger doses in order to maintain prothrombin levels in the therapeutic range. Laboratory studies undertaken to explain this difference indicated that