If the Secretary finds that the above provision, and others, do not apply, "he shall issue an order approving the application."

The 1962 Amendments also added the following definition of the term "substantial evidence":

"[T]he term 'substantial evidence' means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or the proposed labeling thereof." *Ibid.*

There has been some discussion in these hearings about the meaning of the terms "substantial evidence" and "adequate and well-controlled investigations" which were introduced by the 1962 amendments.

The testimony of Dr. William M. O'Brien has particularly focused upon these statutory terms. Dr. O'Brien, in his prepared statement at page 2, stated that:

"The 1962 Kefauver-Harris amendments specifically stated that a manufacturer must support claims of efficacy of a drug with 'subtantial evidence.' The law defines this as 'adequate and *well controlled* investigation by experts qualified by scientific training and experience to evaluate effectiveness.'

"I define the word control as a standard of comparison for checking inferences in an experiment—in other words, in testing a drug one group is treated, and its response is compared to the response of an identical group which receives a standard of comparison—a standard treatment or a dummy (placebo). I believe this was the exact intent of Congress in the 1962 amendments. . . ."

Furthermore, at page 5 of his prepared testimony, Dr. O'Brien stated that:

"The only scientifically sound method for drug testing is the controlled double blind trial which eliminates both positive and negative bias and uses a comparison—either a placebo or a standard drug."

Dr. O'Brien's views on the meaning of the pertinent statutory terms were underscored in his oral testimony before this committee, in response to a quetion by Mr. Gordon.

"Mr. GORDON. Is it your opinion, then, as I understand it, that before a drug is approved by the FDA, controlled double blind studies should be conducted by objective sources? Is that correct?"

"Dr. O'BRIEN. Well, apparently it is not only my opinion but this is what the 1962 amendments said. . . ."

Although Dr. O'Brien conceded in his oral testimony that the 1962 amendments did not specifically require double blind investigations, it is apparent that Dr. O'Brien reads the statutory terms "adequate and well-controlled investigations" as synonomous with, and only with, controlled double blind studies. Dr. O'Brien also concludes that "substantial evidence" can only be produced by controlled double blind studies.

The words in the 1962 amendments of course do not state so precisely what constitutes an adequate and well-controlled investigation. We submit that the lack of such exactitude in the statute was deliberate, and that Congress intended flexibility in interpretation of the statutory terms.

As this submission will show, Congress was well aware of several important points when it enacted the terms "substantial evidence" and " adequate and well-controlled investigations" in 1962. Throughout the legislative debate, it was clear that these terms could have different content, depending upon the kind of disease under consideration. Rheumatoid arthritis received particular attention as a disease about which there is great dispute as to proper methods of diagnosis and treatment. The professional witnesses who testified in the Senate and House hearings did not suggest that there was any particular or exact way to measure the effectiveness of any particular drug. The entire course of the hearings instead established that a wide range of adequate and well controlled investigations and of professional opinion about what they prove can exist with regard to any drug, and that the 1962 amendments were not intended to require an either-or choice between differing schools of thought.

LEGISLATIVE HISTORY

As introduced by Senator Kefauver on April 12, 1961, S. 1552 would have required the Secretary to refuse to approve a new drug application if he had insufficient information to determine whether the drug is "efficacious in use" under the conditions prescribed, recommended, or suggested in the proposed