on the basis of which it can fairly and responsibly be concluded by qualified experts that the drug is safe and effective for such uses". Amended regulations covering the same subject contain substantially the same provision.

Relying on the record so established, the companies proceeded to submit such material as they had reasonable grounds to believe were required.

Virtual silence on this subject followed, until the FDA announced its desire in 1966 to turn the massive task of reviewing the evidence over to the NAS/NRC. The industry commended FDA for this decision, incidentally, and gave its full cooperation to the planning and implementation of the arrangement, contrary to the implication of your letter. The NAS/NRC Report specifically acknowledges "the unrestrained but unobtrusive cooperation of the FDA and of the pharmaceutical industry. Both have responded quickly and sensitively to all requests for information but have never been importunate".

The efficacy review consumed two years, and one of the most interesting general conclusions arrived at lends additional credence to the view that certainty as to the meaning of the law is lacking. Let me quote from the portion of the NAS/NRC Drug Efficacy Study, discussing the definition of "substantial evidence":

> "*The Legal Definition of Substantial Evidence of Effectiveness.*—The definition in the law is an exacting one. Had the panels adhered rigidly to it, a great many claims would have been rejected on the grounds that they were not supported by substantial evidence based on 'well-controlled investigations . . . by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved.'
>
> "In a number of areas of drug action (e.g., psychotherapeutic effects), there is no agreement on what constitutes a well-controlled investigation. More generally, the many imponderables of clinical investigation influence the validity of studies that may appear to be well-controlled methodologically and statistically. If one reviews the hearings on the Bill that led to the Amendments, it becomes evident that it was the intent of Congress to be permissive in the application of the wording of the law. Specifically, Congress did not intend that the word 'substantial' should be read to mean 'predominant'. It is clear from the debates that claims for effectiveness should be accepted if a substantial amount of well-documented favorable evidence is presented, even though there may also exist a weighty body of inconclusive or negative evidence. In the words of Alanson W. Willcox*, General Counsel, Department of Health, Education, and Welfare:
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> > This provision states that there must be a bona fide, responsible and adequately based medical judgment in support of efficacy before a drug may be put on the market, but if this condition is met, a minority opinion may prevail.
>
> It should be emphasized that the law relates primarily to new drugs that have been submitted for approval on the basis of only limited premarketing clinical trials. The drugs that have been reviewed in the Study, on the other hand, have been on the market for 5 to 30 years. In many cases, no reports on well-controlled studies of their efficacy for the claims cited for their use could be found in the presentations of the manufacturers or in the medical literature, and yet many of them have received wide acceptance in medical practice. This situation presented the panels with a very difficult problem. How much weight should they give to the opinion of the marketplace? The final arbiter of the value of a drug is the consensus of the experience of critical physicians in its use in the practice of medicine over a period of years. Approval of a new drug for release to the market is only a license to seek this experience. When the panels were faced with this situation, they have sought to grant liberty but to restrain license by assigning a rating of 'Probably effective' or 'Possibly effective' on the basis of their own clinical experience with the drug and their evaluation of the opinions of their peers."

Does not this suggest that the firms might reasonably have concluded that the efficacy evidence in hand, together with the clinical record, though certainly not of 1971's sophistication, might constitute "well documented" evidence, as the NAS/NRC Report put it, or "bona fide, responsible and adequately based" evi-

*Charles Wesley Dunn lecture, Law School of Harvard University, Cambridge, Massachusetts. 15 March 1963.