Five additional studies since my original testimony have also confirmed the existence of a significant positive slope for the dose-response curve of propoxyphene using various graded doses of the hydrochloride salt from 32 to 200 milligrams and/or the equivalent doses of the napsylate salt of 50 to 300 milligrams.

In my opinion, the above cited studies alone and in conjunction with those I have previously reviewed, prove beyond any doubt that propoxyphene hydrochloride in doses of 65 milligrams and higher or propoxyphene napsylate in doses of 100 milligrams and higher have some analgesic activity in patients with pain of a wide variety of etiologies.

Indeed, since propoxyphene produces narcotic-like responses in all pharmacologic tests with which I am familiar, can produce drug dependence of the classic narcotic type and produces an overdose syndrome characteristic of narcotics, I would find it impossible to explain how the drug could possibly *not* be an effective analgesic at some dose level.

Now, several double-blind studies which ostensibly meet the minimum criteria for a controlled clinical trial of analgesic efficacy have not demonstrated a statistically significant difference between the analgesic effect of 65 milligrams of propoxyphene hydrochloride and a placebo treatment. There are a number of possible explanations for this state of affairs, and most of them hinge on an understanding of the concept of assay sensitivity as it applies to clinical trials of analgesics.

Because of the multiplicity of known and unknown variables which affect the course of a patient's pain and its response to analgesics, and because there is no satisfactory measure of a patient's pain other than the patient's own subjective reports of this experience, analgesic clinical trials vary greatly in their ability to demonstrate the efficacy of even known effective analgesics. That is, they vary widely in their assay sensitivity. Therefore, unless an analgesic clinical trial contains an internal measure of assay sensitivity that demonstrates that the trial is capable of measuring an analgesic effect of the magnitude anticipated to result from administration of the test drug, for example propoxyphene, a negative finding concerning the efficacy of the test drug has no meaning.

Most of the clinical trials which did not distinguish propoxyphene from placebo either did not contain a measure of assay sensitivity or were clearly insensitive in that they also could not distinguish known analgesics, for example, codeine or aspirin from placebo.

Furthermore, since single doses of propoxyphene 65 milligrams are almost certainly less effective than the usually used doses of the mild analgesic standards, codeine 65 milligrams, aspirin 650 milligrams, acetaminophen 650 milligrams or two APC tablets, an oral mild analgesic study may have adequate assay sensitivity to demonstrate a statistically significant difference between one or more of these standards and the placebo, while still not being able to identify the less substantial analgesic effect of propoxyphene 65 milligrams as statistically significant. That is my interpretation of the results of Dr. Moertel's study which was presented in the New England Journal of Medicine and which he discussed yesterday at these hearings.