the risk-to-benefit ratio is less than—or the benefit-to-risk ratio, putting it the other way around—is less than the ratio for the single ingredient of the combination.

Does that answer your question?

Mr. DUFFY. If I understand you correctly, then, we are really concerned here about the safety features of fixed combination drugs.

Dr. LEY. One must always bear in the back of one's mind, when considering drug actions of any sort, certain aspects of safety. It is impossible to totally disassociate safety and efficacy. Although we may say that prior to 1962 we did not consider efficacy—we didn't as a formal requirement—there were still situations in which efficacy was a feature even in the safety consideration of the drugs administration. I think it is legally proper perhaps to say that you cannot disassociate these two features of drug evaluation. Medically and pharmacologically, there is always a little bit of one along with the other.

Mr. DUFFY. Did I understand you correctly a moment ago—to say that in an NAS/NRC study did not touch on the issue of safety.

Dr. LEY. They were asked not to approach safety, but to approach efficacy. Now, even in that case, although their charge was efficacy, there were in many recommendations comments on safety. Again, it is totally impossible to disassociate these two factors totally from the other. The majority, 95 to 99 percent of the Academy recommendations, are concerned with efficacy. But where the panels have felt it appropriate to call our attention to certain safety hazards, there are comments on safety.

It is appropriate that it be so.

Mr. DUFFY. The action that you are taking with respect to fixed combination drugs is directed more toward their safety?

Dr. LEY. It is directed to both. There is no substantial evidence that there is any benefit from such combinations in a fixed ratio, none whatsoever.

I will be pleased to consider such evidence when it is submitted. But as of this time there is nothing that meets the definition of substantial evidence.

Mr. DUFFY. Mr. Goodrich, do you understand perhaps what I am driving at now? I am trying to understand the legal considerations that are going to obtain when and if these matters get to that stage?

Mr. GOODRICH. These matters have already reached that stage.

Mr. DUFFY. They may have reached that stage. And I just query the advisability of us debating them if they are in fact before the courts. Maybe there is another tribunal that should be deciding.

Mr. GOODRICH. Perhaps so. I understand that the Upjohn Co. will be filing suit today. And if you don't want to discuss it, it is perfectly OK with me.

But to address myself to your issues, as I said a few minutes ago, the claim for Panalba is that it is better than tetracycline, that it broadens the spectrum, that it is useful for unique type of mixed infections in which neither drug separately works as well as the combination. These claims are false, unsupported by substantial evidence. And this is the basis on which—one basis on which the Academy found the drug ineffective as a fixed combination.