

next 2 weeks. The Pharmaceutical Manufacturers Association has asked that we look at what they suggest, which we will do with them the latter part of this week.

In essence what we are saying is that in any combination drug, the various ingredients of the combination must be shown to exert some effect on the total effect of the drug.

Mr. GORDON. You mean an additive effect or more than an additive effect?

Dr. EDWARDS. Well, that any ingredients of a combination must in fact have some effect on the ultimate or total effect of the drug. Dr. Simmons, do you want to add to that?

Dr. SIMMONS. That no drug should be present in a fixed dose combination unless its presence clearly enhances safety or efficacy. And unfortunately, most combination drugs to this point have not developed that type of efficacy.

Mr. GORDON. But convenience is not sufficient.

Dr. EDWARDS. I think convenience is a factor. It certainly has to be considered all else being equal. I think, for instance, in pediatric drug therapy convenience frequently can come into play, but it certainly is not a factor upon which we would base our decision.

Senator NELSON. I am puzzled about that. If it is a fixed dosage form, are you saying that adequately controlled studies would have to be submitted to demonstrate that the combination of these drugs is additive or synergistic?

Dr. SIMMONS. That is right. Mr. Chairman, maybe the simplest way I might be able to explain it would be that if you put two drugs together to treat pain, we would expect you to provide evidence that you get a better result with those two than you would with either of the active ingredients if that particular drug were used in an adequate dose. This is basically what we wish to have provided to us.

Senator NELSON. But here you are reciting the case of an analgesic.

Dr. SIMMONS. Yes.

Senator NELSON. You are not talking, then, about establishing some rules to permit fixed combinations of anti-infectives?

Dr. SIMMONS. Yes. That would follow the same rule, that you do not put two antibiotics together unless you can show that those two provide a better result than either one of the ingredients, either a better result in increased safety or increased efficacy.

Senator NELSON. In order to put two antibiotics together in a fixed dosage form, do you mean to say that both of these antibiotics must be effective against the target organism?

Dr. SIMMONS. That is right.

Senator NELSON. So that you would not permit the situation that occurred in the fixed combination of novobiocin and tetracycline which was Panalba.

Dr. SIMMONS. No, we would not. There are two parts to the combination policy, one, that there should be evidence that both contribute to the therapeutic effect, and two, that that specific formulation can be used rationally. In other words, where you must increase the dose of one antibiotic to take care of a certain organism, you do not carry along with it an increase in the dose of the other for which there is no indication to increase the dose. So, there are two requirements in our combination policy.