

you do any toxicity studies in humans before a drug is released for general use?

Dr. MINCHEW. Toxicity observations or observations for toxicities in humans would be a routine part of investigational phases of the drug. Even though a similar product in the form of other tetracyclines would have been marketed previously, this being a new molecule, it would technically have a phase I period when it was first introduced into man, so that during the phase I, phase II and phase III studies, observations would be made for human toxicity.

The competitive situation in tetracycline marketing is intense. The company sought to include in the labeling for Vibramycin features that would emphasize its safety and effectiveness in comparison with established products. To do this, Pfizer sought to feature the lower, once-a-day dosage, a broader antibiotic spectrum, and an advantage in not causing tooth discoloration—a side effect particularly important for pediatric age groups.

Senator NELSON. When you are referring to tooth discoloration, are you referring to permanent deposits of color?

Dr. MINCHEW. The teeth that would be discolored, Mr. Chairman, would be dependent upon which teeth were being calcified at the time the drug was administered. If the drug were being administered at a time when permanent teeth were in fact calcifying, then the permanent teeth could be discolored.

Senator NELSON. Permanently?

Dr. MINCHEW. The observations on this are not so sound that one can say unequivocally permanently, but certainly they have persisted for as long as some people have been observed.

Senator NELSON. Is this a very dramatic coloration?

Dr. MINCHEW. Yes, sir; it is. It is a very noticeable cosmetic defect. It is not the same in every person, and probably depends upon how much of the drug is deposited and combined with the calcium as the calcification occurs. It is certainly a noticeable and disadvantageous cosmetic defect.

Senator NELSON. And this is a characteristic of all tetracyclines?

Dr. MINCHEW. Yes, in general that is true. I can't say that unequivocally for each and every molecule of the tetracyclines that are available it has been specifically observed. Our position is that until proven otherwise, any tetracycline is capable of causing tooth discoloration because they all will combine with calcium this way.

Senator NELSON. Are there any preparations of tetracycline that has any noticeably less effect than others?

Dr. MINCHEW. I don't know that any studies have been done in terms of the actual incidence of tooth discoloration with each particular dosage form of tetracycline that would give a sound answer to your question.

Our conclusion was that the antimicrobial spectrum of this drug was very similar to that of the other tetracyclines, that the small differences in antibiotic sensitivity were of no practical significance, that the animal studies should be called to the prescriber's attention, and that the drug had the single advantage of less frequent dosage.

Labeling changes were requested—to delete a sentence implying greater effectiveness against *Staphylococcus aureus*, and to modify a claim for efficacy in treatment of genitourinary infection to state