



November 15, 2002

Mark D. Kramer
Director, Combination Products Program
Office of the Ombudsman
Food and Drug Administration
5600 Fishers Lane (HF-7)
Rockville, MD 20857

Dear Mr. Kramer:

I am writing on behalf of VIVUS, Inc. in response to FDA's request for comments from stakeholders about combination products issues and suggestions for improvement.

Combination products are good medicine. During the development program of any combination product, the FDA can obtain more detailed and specific information about the interaction of drug/drug or drug/biologic or drug/biologic/device combinations that is difficult to obtain in any other way. In addition, combining two drugs, for example, might result in the patient receiving less of either drug for better efficacy and with fewer side effects.

The consensus at VIVUS about combination products is that there is a compelling need for a clear guidance that would define not only what a combination product is but also clearly stipulate how said product should be evaluated for efficacy and safety. This guidance should apply to both CDER and CBER and should be applicable to all reviewing Divisions within each of these Centers. The guidance should be worded such that there would be little room for interpretation about standards of efficacy and safety for combination products for both reviewers and sponsors.

It has been the experience of VIVUS that this current lack of clear definition and steps for evaluating the efficacy and safety of combination products, has resulted in a disturbing discrepancy in policy interpretation at FDA and that said discrepancy has led to inconsistency in the application of combination policy between reviewing Divisions for the same product.

Such an experience describes the development program for a VIVUS combination product that began in the Cardio-Renal Division and was later transferred to the Division of Urologic and Reproductive Drug Products during a CDER reorganization. Plans that were developed and agreed upon by the former Division, early in the product development program, were not readily understood and accepted by the latter Division at the time of NDA submission and review. In addition since one component of the product in question was a low dose of a marketed product that was approved for titration of dosage, reviewers had confusion about how to apply the guideline that the combination product had to demonstrate a definite safety and efficacy advantage over the individual components of the combination. While one Division interpreted this to mean that the combination product should be more effective than the dosage of the approved single-agent contained within the combination the other required that the combination product be better than the maximum approved dosage of the single agent.

02N-0445

C2

A well thought-out guidance that clarifies exactly how sponsors must demonstrate combination product efficacy and safety ---and especially for those products that have a component with a number of dose levels that are used for patient titration ---would greatly enhance the efficiency of a drug development program and allow patients to receive new drugs sooner. It would also decrease review time since both parties, the reviewers and the sponsor, would have clarity on what would be required for approval.

We at VIVUS believe strongly in the inherent benefits of combination drug products and appreciate the opportunity to address our comments on the critical need for additional workable guidance that is standardized for CDER and CBER for the development of combination drug products.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Carol Zoltowski". The signature is fluid and cursive, with a large initial "C" and "Z".

Carol Zoltowski, VMD
Vice President, Regulatory Affairs