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11, May 1988

Dear Professor Endrenyi

Enclosed please find the requested reprints. As you can see in the paper published in the J. Am. Pharm. Ed. 51, 29 (1987), I acknowledge your DLP method as a method of choice when the assumption of equal variance for the error structure is violated.

Relying on our mutual interest, I am taking the liberty to renew my proposal for collaboration being now more precise and specific.

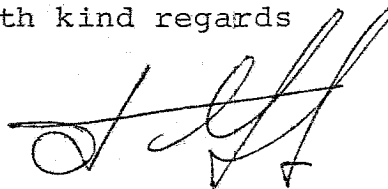
I think that the methodology (computerized) described in my paper published in Bioph. Drug Disposition 8, 387 (1987) can be easily adapted to your DLP method. Thus, a robust method suitable for the analysis of linear one compartment model with comparable values of rate constants can be developed. This method should be superior to nonlinear regression techniques if the assumptions for the error structure of the regression are not true.

To the best of my knowledge the only nonparametric method suitable for the analysis of this model has been published by P. Shelver and J. Farris, J. Pharm. Sci. 72, 1218 (1983). However, their simulated data were generated by assigning a very high ratio of rate constants i.e. $K_a/K_e = 10$. I have doubts about the performance of this method in cases where $K_a \approx K_e$. I think that the simultaneous solution of Eqs 5 and 6 of Shelver and Farris' paper is questionable when $K_a \approx K_e$. A study based on simulated

data can be used to compare the two methods.

Hoping that you will find my proposal interesting, I look forward to hearing from you at your earliest convenience.

With kind regards

A handwritten signature in black ink, appearing to be 'P. Macheras', written in a cursive style.

Dr P.Macheras

P.S. It is highly probable to spend a 4-months sabbatical, starting on 1, September 1988, in U.S.A. I would be delighted to visit your Department during my stay in U.S.A.