

Pfizer Inc
Worldwide Regulatory Affairs and Quality Assurance
50 Pequot Avenue
New London, Connecticut 06320



Global Research & Development

February 15, 2005

Division of Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, Maryland 20852

Re: **ICH Draft Guidance on E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs**
[Docket No. 2004D-0377, 69 *Federal Register*, 55163-55164, September 13, 2004; extension for comment published January 5, 2005]

Dear Dockets Management:

Pfizer Inc submits these comments on the ICH Draft Guidance on E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs, published originally in the *Federal Register* on September 13, 2004 and then re-opened for comment on January 5, 2005. Please note that these comments supplement the Pfizer response to the ICH Draft Guidance on E14 submitted electronically on December 13, 2004, followed by a hardcopy submission.

It should be noted that these comments are in response to the Agency's request to provide support for the utility of exposure-response modeling to characterize drug-related effects on QT.

We thank you for this opportunity to comment and would invite direct dialogue with the Agency if you would consider the opportunity valuable.

Sincerely,

William R. Murphy/PIP

William R. Murphy, Ph.D.
Director
Pfizer Global Research and Development

2004D-0377

C13

Utility of Exposure-Response Modeling in QT Assessment

In order to fully understand and predict the pharmacologic behavior of an NCE, it is important to quantify the time course of the QT/QTc effects in relation to the plasma drug concentrations using exposure-response modeling through PK/QTc modeling. This approach is a powerful tool, used to quantify drug related effects on the QT interval, aid in establishing a therapeutic index and extrapolation of expected effects on QT interval under different treatment conditions (multiple dose, drug-drug interaction, special populations) and/or following unexpected exposure increases (drug overdose or physiologic events altering PK).

This approach to assessment of drug related effects on QT accounts for between subject variability in exposure by assessing concentration-response and the mixed-effects modeling-based methods allow for inclusion of all concentration and QT data from all subjects collected in the study. The slope of the exposure-response relationship is the primary endpoint and can be used to determine the expected increase in QT (if any) at the projected efficacious and maximum tolerated exposure. A 95% confidence interval constructed about the slope provides a measure of precision in the population slope. The interval bounds of the slope confidence interval and relevant average concentration can then be used to generate an expected population prolongation interval. Finally, a statement can then be made of the extreme responders by evaluating the distribution of slopes in the population and the relevant average maximum concentration. Additionally, extreme response can be evaluated through simulation, performing a categorical analysis of the simulated QTc data.

Simulations presented at recent meetings have demonstrated the lack of bias, and good precision with appropriate exposure-response modeling unlike the currently proposed metric in the E-14 (largest time-matched difference relative to placebo) which was shown to be biased and thus can lead to false conclusions. An additional benefit of exposure-response modeling is related to *a priori* assessments of study design through simulation. Given a proposed study design, a determination of the precision and bias of the exposure-response model slope estimate under assumed conditions of an "effect" and a "no effect" can be explored.

Absence of evidence of exposure (parent and/or metabolite) related changes in QT (i.e., slope not differentiated from zero) should be considered as supportive evidence of lack of drug related effects. The 'causality' or link between parent and/or metabolite plasma concentration is strengthened for compounds with a negligible contribution of metabolism to overall elimination or for a compound where all drug related material in plasma is accounted for by monitoring both parent and metabolite concentrations. For cases in which concentrations of an unknown metabolite drive QT prolongation, hysteresis may be evident when plotting individual QTc vs. parent concentration, and mean QTc across time data would suggest that parent concentration was not directly related to effect. Proper inspection of individual plots of QTc vs. concentration and mean effect across time become paramount to appropriate analysis of the data.

In summary, appropriate exposure-response modeling is essential to the proper evaluation and interpretation of QT results from clinical studies and has important advantages over the currently recommended metric in the draft guidance.