DETERMINATION LETTER

Mark J. Evans, PhD
Pfizer Global Regulatory Affairs
500 Arcola Road
Collegeville, PA 19426-3982

Dear Dr. Evans:

Please refer to the submission by *Pfizer* received on April 21, 2021 and responses to information requests received on September 28, 2021, December 15, 2021, and April 4, 2022, intended to support the use of the 'Empirically Based Bayesian Emax Models for Dose Response Design and Analysis' as a statistical methodology for dose finding studies. We have completed our review of your submission and have determined it is fit-for-purpose in the context outlined in this letter.

Goal and Intended Applications

Although dose selection is a critical component in drug development, inadequate design and analysis of dose finding studies continues to plague many development programs. Inadequate dose exploration due to limited understanding of the dose-response relationship can lead to failed late-stage trials. To address the need for better informed dose selection, *Pfizer* submitted a proposal for the use of 'Empirically Based Bayesian Emax Models for Dose Response Design and Analysis'. Statistical methods and supporting software are proposed to improve the design and analysis of clinical trials whose primary purpose is to characterize the relationship between efficacy and dose to guide the dose selection for further development.

FDA Assessment

A multidisciplinary team, with representation from both the Office of Biostatistics and the Office of Clinical Pharmacology in the Office of Translational Sciences within the Center for Drug Evaluation and Research, has reviewed all aspects of the submission. The review team finds that the proposed empirically-based Bayesian Emax model, including the goodness-of-fit (GOF) statistic, can be designated fit-for-purpose under the following conditions:

(1) component studies for a new compound are homogeneous

(2) the proposed GOF statistic is applicable

(3) the model is identifiable

(4) study-specific information is considered for dose selection

Additionally, the following are noted:

1. The applicant assumed an identical treatment effect across multiple studies. In that sense, the proposed method could be applicable in situations where component studies are comparable in terms of study population, randomization allocation scheme, primary endpoint assessment timelines, etc.

2. The applicant used predictive probability for non-monotonicity as a GOF statistic. In general, this proposed test statistic appears reasonable. However, the GOF statistic is not universally useful under all possible scenarios. One example of an applicable scenario for the proposed GOF statistic may be dose-finding studies with a high-signal design.

3. The applicant proposed potential decision criteria for an optimal dose based on two sets of simulation studies. The supporting evidence may not be sufficient to generalize the proposed decision criteria because the decision criteria for thresholds of the posterior probabilities of the target efficacy and futility could be compound-specific and may be dependent upon the study design.

4. When one study cannot fully inform the proposed Bayesian Emax model to ensure all model parameters are identifiable, additional studies – either historical or prospective – are needed to make best use of the R package. Otherwise, alternative model and/or methods should be considered and selected based on the data available.

This determination is based on the applicant's original submission, the applicant's responses to information requests and the relevant statistical literature.

General Comments

The importance of adequately understanding the dose-response relationship is well-recognized in drug development. Dose finding studies, however, are often designed with a small number of doses and a narrow dose range using suboptimal analysis techniques. The 'Empirically Based Bayesian Emax Models for Dose Response Design and Analysis' approach seeks to motivate better design and analysis of dose-finding studies. The use of 'Empirically Based Bayesian Emax Models for Dose Response Design and Analysis' is supported under specific conditions; however, our support does not preclude the availability and application of other methods for dose finding studies. In practice, the specific study design characteristics when choosing candidate methods for a dose finding clinical trial should be carefully considered; and when deciding on the trial design, the

applicability of the candidate methods in the context of the intended application should be carefully evaluated.

Sincerely,

Sylva Collins, Ph.D.
Director, Office of Biostatistics
Office of Translational Sciences
Center for Drug Evaluation and Research

Issam Zineh, PharmD, MPH
Director, Office of Clinical Pharmacology
Office of Translational Sciences
Center for Drug Evaluation and Research