FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Pharmaceutical Science and Clinical Pharmacology Advisory Committee (PSCP) Meeting
Omni Shoreham Hotel, The Ballroom
2500 Calvert St., NW, Washington, District of Columbia
March 15, 2017

QUESTIONS

Morning Session:

1. **DISCUSSION:** What information should be included in a physiologically-based pharmacokinetic (PBPK) submission to the FDA to ensure adequacy of an analysis for its intended purpose? Should these recommendations be universal or should there be different recommendations depending on the purpose for which the PBPK submissions will be used (e.g., to inform clinical study planning vs. labeling or regulatory decision making). What are the principles or criteria that should be considered?

2. **DISCUSSION:** Based on the proposed workflows as examples, please discuss:

    a. What criteria should be used to determine that the model is adequately verified for the intended purpose?

    b. When the model needs modification, what considerations should be given related to modifications of model structure and/or parameter estimates?

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QUESTIONS (cont.)

Afternoon Session:

Comprehensive *in vitro* Proarrhythmia Assay (CiPA) is a fit-for-purpose assay that will utilize an in silico computational model of the human ventricular cardiomyocyte to serve as the primary prediction of proarrhythmic risk with an additional preclinical check to ensure that drug effects on repolarization are not missed. Electrocardiograms (ECGs) will still be assessed in Phase 1 clinical studies with exposure-response modeling to determine if there are unexpected ion channel effects that were not observed in the preclinical assessments.

1. **VOTE:** For a QT prolonging drug, will this mechanistic, model-based approach be fit for the following 2 applications:

    a. Determining whether ECGs need to be collected in Phase 3

    b. Informing proarrhythmic risk language in drug labeling

2. **VOTE:** Does the committee agree with the proposed approach for validating the new paradigm that involves assessing 28 drugs classified into low, intermediate and high risk by an expert panel?
    a. **DISCUSSION:** If not, what else should be done?

3. **VOTE:** As this new mechanistic, model-based approach is implemented, should FDA collect the world's experience (i.e. digital waveform data from *in vitro* experiments) to facilitate future enhancements as was done by the FDA with the ECG warehouse for QT studies?