Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Meeting of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee
March 15, 2017

Location: Omni Shoreham Hotel, The Ballroom, 2500 Calvert St., N.W., Washington, District of Columbia.

Topic: The use of model-informed drug development (MIDD) for new and generic drugs has significantly increased over the past several years. The committee discussed strategies, approaches, and challenges in MIDD with specific focus on two areas. During the morning session, the committee discussed approaches and evidentiary information needed for applying physiologically-based pharmacokinetic (PBPK) modeling and simulation throughout a drug's lifecycle. During the afternoon session, the committee discussed mechanistic model-informed safety evaluation with a focus on drug potential for causing arrhythmias. The Comprehensive in Vitro Proarrhythmia Assay was discussed as an exemplar.

These summary minutes for the March 15, 2017, meeting of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee of the Food and Drug Administration were approved on May 4, 2017.

I certify that I attended the March 15, 2017, meeting of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/
Jennifer Shepherd, RPh
Designated Federal Officer, PSCP

/s/
Scott Waldman, MD, PhD
Chairperson, PSCP

Summary Minutes
Pharmaceutical Science and Clinical Pharmacology Advisory Committee Meeting
March 15, 2017

The following is the final report of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee meeting held on March 15, 2017. A verbatim transcript will be available in approximately four weeks, sent to the Office of Clinical Pharmacology and the Office of Generic Drugs, and posted on the FDA website at:
https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/ucm535520.htm

All external requests for the meeting transcripts should be submitted to the CDER Freedom of Information Office.

The Pharmaceutical Science and Clinical Pharmacology Advisory Committee (PSCP) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on March 15, 2017 at the Omni Shoreham Hotel, The Ballroom, 2500 Calvert St., N.W., Washington, District of Columbia. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA. The meeting was called to order by Scott Waldman, MD, PhD (Chairperson, Clinical Pharmacology). The conflict of interest statement was read into the record by Jennifer Shepherd, RPh (Designated Federal Officer). There were approximately 450 people in attendance. There were two Open Public Hearing speakers in the morning session, and one Open Public Hearing speaker in the afternoon session.

Issue:
The use of model-informed drug development (MIDD) for new and generic drugs has significantly increased over the past several years. The committee discussed strategies, approaches, and challenges in MIDD with specific focus on two areas. During the morning session, the committee discussed approaches and evidentiary information needed for applying physiologically-based pharmacokinetic (PBPK) modeling and simulation throughout a drug's lifecycle. During the afternoon session, the committee discussed mechanistic model-informed safety evaluation with a focus on drug potential for causing arrhythmias. The Comprehensive in Vitro Proarrhythmia Assay was discussed as an exemplar.

Attendance:
PSCP Members Present (Voting): Jeffery M. Carrico, PharmD, BCPS; James C. Cloyd, PharmD; Tonglei Li, PhD (afternoon session only; via phone); Patricia W. Slattum, PhD, PharmD, GCP; Duxin Sun, PhD; Scott A. Waldman, MD, PhD (Chairperson, Clinical Pharmacology)

PSCP Members Not Present (Voting): Gregory E. Amidon, PhD (Chairperson, Pharmaceutical Science); Donald E. Mager, PharmD, PhD; Kathleen A. Neville, MD, MS; Anne S. Robinson, PhD

PSCP Members Present (Non-Voting): Walid M. Awni, PhD (Industry Representative); Jack Cook, PhD (Industry Representative)(via phone); Srini Tenjarla, PhD (Industry Representative)(via phone)

Temporary Members (Voting): Bonnie Arkus, RN (Acting Consumer Representative)(via phone); Jessie L-S Au, PharmD, PhD; Jerry M. Collins, PhD; James E. Polli, PhD; Dan M. Roden, MD; Alexander A. Vinks, PharmD, PhD, FCP; Albert L. Waldo, MD, PhD (via phone)

Guest Speakers: Morning Session: Anna Nordmark, PhD; Neil Parrott, PhD; Afternoon Session: Gary Gintant, PhD; Gary Mirams, PhD

FDA Participants (Non-Voting): Issam Zineh, PharmD, MPH; Kathleen Uhl, MD; Shiew-Mei Huang, PhD; Liang Zhao, PhD (morning session only); Ping Zhao, PhD (morning session only); Robert Lionberger, PhD (morning session only); David Strauss, MD, PhD (afternoon session only); Christine Garnett, PharmD (afternoon session only); Zhihua Li, PhD (afternoon session only)

Designated Federal Officer (Non-Voting): Jennifer Shepherd, RPh

Open Public Hearing Speakers: Morning Session: Klaus Romero (Critical Path Institute); Amin Rostami (University of Manchester); Afternoon Session: Sebastian Polak, PhD (Certara, Simcyp)

The agenda proceeded as follows:

Call to Order and Introduction of Committee	**Scott A. Waldman, MD, PhD** Chairperson, PSCP
Conflict of Interest Statement	**Jennifer Shepherd, RPh** Designated Federal Officer, PSCP
Introduction and Background	**Shiew-Mei Huang, PhD** Deputy Director, Office of Clinical Pharmacology (OCP) Office of Translational Sciences (OTS), CDER, FDA

Morning Session: Role for Physiologically-based Pharmacokinetic (PBPK) Modeling and Simulation in Drug Development and Regulation

Towards Consistent Regulatory Assessment of Physiologically-based Pharmacokinetic (PBPK) Modeling to Support Dosing Recommendations	**Ping Zhao, PhD** PBPK Lead, Division of Pharmacometrics OCP, OTS, CDER, FDA
Absorption PBPK Modeling and Applications to Support Formulation and Generic Drug Development	**Liang Zhao, PhD** Director, Division of Quantitative Methods & Modeling Office of Research and Standards Office of Generic Drugs (OGD), CDER, FDA

PBPK Submissions and Review Experience in EMA and EMA Draft PBPK Guideline	**Anna Nordmark, PhD** Pharmacokinetic Assessor Medical Products Agency, Sweden Member of the Modelling and Simulation Working Group, European Medicines Agency (EMA) Rapporteur of the EMA PBPK Guideline
Experience, Opportunity, and Challenges in Submitting PBPK Analyses to Regulators, and Comments to EMA and FDA Draft PBPK Guidance Documents	**Neil Parrott, PhD** Distinguished Scientist Roche Pharma Research and Early Development Roche Innovation Center Basel, Switzerland Leader, The Innovation & Quality (IQ) Consortium Working Group on PBPK Guidances

Clarifying Questions

Break

Open Public Hearing I

Questions to the Committee and Committee Discussion I

Lunch

Afternoon Session: Comprehensive *in vitro* Proarrhythmia Assay (CiPA)

Overview of the ICH E14 Guideline and its Implementation within FDA	**Christine Garnett, PharmD** Clinical Analyst and QT Lead Division of Cardiovascular and Renal Products Office of Drug Evaluation I, Office of New Drugs, CDER, FDA
The Need for and Overview of the Proposed Comprehensive In Vitro Proarrhythmia Assay	**Gary Gintant, PhD** Senior Research Fellow Department of Integrative Pharmacology Abbvie
Background and Rationale for Mechanistic Cardiac Electrophysiology Models	**Gary Mirams, PhD** Sir Henry Dale Fellow Centre for Mathematical Medicine and Biology University of Nottingham., United Kingdom
CiPA In Silico Modeling Development Strategy and Results	**Zhihua Li, PhD** Staff Fellow Division of Applied Regulatory Science (DARS) OCP, OTS, CDER, FDA
Phase 1 ECG Analysis under CiPA, Integration of All CiPA Components, and Potential Implementation Strategy	**David Strauss, MD, PhD** Director, DARS, OCP, OTS, CDER, FDA

Clarifying Questions

Break

Open Public Hearing II

Questions to the Committee and Committee Discussion II

Concluding Remarks	**Kathleen Uhl, MD** Director OGD, CDER, FDA

Adjournment

Questions to the Committee:

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?

   Committee Discussion:
   Many committee members discussed that flexibility was very important when considering the type of information that should be included in a PBPK submission and that it may be useful to present the timeline of the evolution of the model (data, assumptions, etc.) with appropriate annotations to support the modeling and conclusions from the modeling. The committee generally felt that the specific requirements for model submissions to the FDA should consider whether the model is intended to inform drug development or regulatory decisions making (e.g., approvability, labeling, waiving a clinical study). In addition, it was discussed that special populations (e.g., pediatrics, elderly, patients with various organ dysfunction) should be considered and that the guiding principles should be the interpretation of the applications and the modeling should be in the context of the population being considered for the intended use. During the discussion, differences in data sources supporting PBPK model qualification for new and generic drugs were recognized, as PBPK models to support generic drug development can rely on a larger dataset accumulated over the product life cycle. For generic drugs, product category specific guidelines, e.g., for locally acting and complex drug products, were also suggested. Please see the transcript for details of the Committee discussion.

2. **DISCUSSION:** Based on the proposed workflows described 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?

Committee Discussion:
The committee discussed that since the science is so new and evolving, it is hard to anticipate what is going to be needed to be provided in the future as technology and models evolve. As a general framework, the committee seemed to emphasize the need for a clear description of the data, model assumptions, intended use of the model, and results of sensitivity analyses. The committee emphasized that models should be fit for their intended purposes and that the range of model acceptance criteria should be defined up front for a given intended use as appropriate. The committee discussed that collaboration with the Agency would be helpful in the absence of understanding exactly what information is going to be needed. It may be helpful to present the thought process, logic, and rationale for information provided in sponsor submissions and in the development of products. The committee also discussed that harmonization of these processes with regulatory bodies worldwide will be useful. Please see the transcript for details of the Committee discussion.

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. 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, does the committee think that this mechanistic, model-based approach will be fit for the following 2 applications:

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

VOTE: **YES 11** **NO 2** **ABSTAIN 0**

   b. Informing proarrhythmic risk language in drug labeling

VOTE: **YES 11** **NO 2** **ABSTAIN 0**

Committee Discussion:
The majority of the committee voted "Yes", that for a QT prolonging drug, the committee believed that the mechanistic, model-based approach will be fit for 2 applications: determining whether ECGs need to be collected in Phase 3 and informing proarrhythmic risk language in labeling. The committee members discussed that the CiPA paradigm has utility, but it is limited in that it currently doesn't consider other

attributes of patient pathophysiology (e.g., intrinsic/extrinsic factors, comorbidities, concomitant meds). The committee did eventually clarify that the intent of CiPA is not to predict individual patient risk or risk in subpopulations, but rather to describe the intrinsic risk of a molecule. The committee also stated that the vote that was taken was a conditional vote with the caveat that more work needs to be done for the paradigm to be ready for use. Those voting "No", stated that their vote was conditional on the fact that additional data available in the future may change their vote. One committee member suggested that monitoring may be useful in high risk patients. Please see the transcript for details of the Committee discussion.

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?

VOTE: YES 10 NO 3 ABSTAIN 0

Committee Discussion:
The majority of the committee members voted "Yes", indicating that they agreed 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. Several committee members stated that they believe that the 3 categories of drugs and 28 drugs included are good, but that additional drugs are needed to fine tune the paradigm. Those voting "No", stated that there is a need for additional drugs with emerging mechanisms to be included on the list. Please see the transcript for details of the Committee discussion.

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?

VOTE: YES 13 NO 0 ABSTAIN 0

Committee Discussion:
The committee voted unanimously that as this new mechanistic, model-based approach is implemented, FDA should 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. Many committee members stated that the collection of this data is beneficial, and the FDA stated that work is underway to standardize the data output that is submitted to the agency. Please see the transcript for details of the Committee discussion.

The meeting was adjourned at approximately 4:00 p.m.