U.S. FOOD & DRUG ADMINISTRATION

507 SUMMARY RESPONSE LETTER

DDTBMQ000039

May 6, 2019

AnaBios Corporation
Attention: Dr. Jack A. Reynolds
93 Randi Drive
Madison, CT 06443
Phone: (203)710-0280
Email:jreynolds@anabios.com

Dear Dr. Reynolds:

We are issuing this 507 Summary Response Letter to AnaBios Corporation on the proposed qualification project (DDT BMQ000039) submitted to the Center for Drug Evaluation and Research (CDER) Biomarker Qualification Program (BQP). We have completed our review of the Legacy Transition Status Update received on May 20, 2018 and its amendment received on March 27, 2019. We support and encourage your ongoing study for development of the safety biomarker for preclinically identifying the pro-arrhythmia risk of drugs, with specific focus on Torsade de Pointes (TdP) type arrhythmias.

Based on our review of the transition summary, the qualification review team (QRT) has agreed to invite this biomarker project to the next stage, Qualification Plan (QP), which is the second of the three stages in the 507 DDT qualification process. Please prepare a Qualification Plan (QP) submission that addresses the scientific issues and the recommendations outlined below. A QP contains details of the analytical validation of the biomarker measurement method, detailed summaries of existing data that will support the biomarker and its context of use (COU), and descriptions of knowledge gaps and how you propose they will be mitigated. If future studies are planned, please include detailed study protocols and the statistical analysis plan (SAP) for each study as part of your QP submission.

In addition to the qualification effort, we encourage further study of your biomarker including collection of specified exploratory information from the proposed clinical trials. When evaluating biomarkers prospectively in clinical trials, sponsors are encouraged to submit study data using Clinical Data Interchange Consortium (CDISC) standards to facilitate review and utilization of data. Data sharing and the capability to integrate data across trials can enhance biomarker development and utilization.

The QRT offers the following comments and recommendations for your preparation of the QP submission.

1. Clarification on drug development needs: Please describe how this new tool may overcome existing gaps, supplement evidence, and accelerate drug development.

2. Comparison with other emerging techniques in the same space: Please summarize the benefits or unique attributes over currently available assays, e.g., iPS cardiomyocytes or animal models. Do you have any data from direct comparisons?

3. Decision tree: Please provide a rationale how evidence generated from your assays aligns with your current risk management and decision-making practices or paradigm, e.g. as a follow up study after an initial integrated risk assessment under ICH S7B? We recommend you use a flow diagram or decision tree to describe your rationale.

4. Alignment with efforts of the Comprehensive in vitro Proarrhythmia Assay (CiPA) and International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH): Please describe how your efforts align with CiPA and the proposed ICH S7B and E14 Q&A.

5. Clarification on assays: How are your multifaceted assays—action potential, contractility, imaging, mitochondrial, or other mechanisms of action—combined to derive a single pro-arrhythmia score? Are they always combined to create a single decision point in the overall risk assessment scheme or used separately at multiple decision points? How does the score inform clinical development/study design? How is the *in silico* model constructed and tested? Are the assays always conducted at the cardiomyocytes level or also at the tissue level?

6. Assay/model performance criteria and recommendations: Any assays that generate nonclinical data and translate the data into a TdP risk prediction can be treated as proarrhythmia risk prediction models. The following six principles are recommended to evaluate the accuracy of TdP risk assessment of all such models.

    a) A unified endpoint is needed for consistent evaluation of all models. It is recommended that the CiPA TdP risk categories (28 drugs, High/Intermediate/Low risk) should be used as the endpoint of the model.
    b) The risk scoring or classification algorithm should be unambiguous. All the parameters in such algorithms should be transparent. The training and validation data being used for model development should be made available.
    c) The model should have a defined domain of applicability. This includes clearly defined experimental protocol(s) that all training, validation, and new drugs should follow. And the type of proarrhythmia mechanisms (e.g. type of ion channels; direct block vs trafficking, etc.) the model and experimental protocols can cover should also be clearly defined.

d) A stringent strategy to assess predictivity. A prospective design should be taken to pre-split the 28 drugs into a training set and a validation set. Experimental protocol optimization, scoring/classification algorithm adjustment, and biomarker/metric selection should be performed based on training data. After that the "frozen" assay and model should be used to predict the risk categories in the validation set. After training and before validation, a pre-validation document needs to be generated to specify the experimental protocol, model parameters, biomarker/metric, classification thresholds, as well as targeted validation performance. Such a document will likely need to be approved by the Agency before validation begins.
e) A mechanistic interpretation of the biomarker/metric being used to assign a risk score or classify a drug into a risk category needs to be provided.
f) Appropriate uncertainty quantification. The cell-to-cell, or experiment-to-experimental variability in the assay will need to be quantified and translated into the uncertainty of risk prediction following robust statistical methodology.

When you prepare for your QP submission, please use the attached outline and follow the instructions within. Please contact **CDER's Biomarker Qualification Program (BQP)** (**CDER-BiomarkerQualificationProgram@fda.hhs.gov)** should you have any questions (refer to DDT **BMQ000039** in the subject line). We look forward to working with you on this beneficial project.

Sincerely,

Christopher L. Leptak -S

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Christopher Leptak
Director, CDER Biomarker Qualification Program

Norman L. Stockbridge -S

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Date: 2019.05.06 09:40:10 -04'00'

Norman Stockbridge
Division Director, OND Division of Cardiorenal Products

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov