Rechanneling the Current Cardiac Safety Paradigm:
Synopsis of the July 23, 2013 FDA/CSRC/HESI Think Tank Meeting Held at the FDA

A FDA/CSRC/HESI-sponsored Think Tank was convened at FDA Headquarters on July 23rd, 2013 to discuss a potential new approach to assessing drug-induced proarrhythmic risk. The current paradigm (implemented circa 2005) does not directly assess the endpoint of primary clinical concern, namely ventricular proarrhythmia. Instead, it provides a regulatory framework for the detection of delayed ventricular repolarization, as represented by the nonclinical focus on block of hERG (the delayed rectifier repolarizing current) and the clinical cardiac safety biomarker of QTc interval prolongation.

While the current paradigm has largely eliminated the unanticipated presence of new torsadogenic drugs entering the market, important limitations have been noted. Block of hERG alone is often insufficient in predicting delayed repolarization (itself a surrogate marker of proarrhythmia), and increases in the QTc interval are highly sensitive but not very specific for the prediction of ventricular proarrhythmia risk. Second, sponsors have often come to regard the hERG repolarizing ionic current assay (in early nonclinical development) and QTc interval prolongation (in later nonclinical and clinical development) as gatekeepers for the continued development of a new chemical entity, an unfortunate occurrence that has likely led to the inappropriate discontinuation of development programs for drugs with potentially high public health benefits. Given these concerns, the bulk of the presentations and discussions at the Think Tank revolved around the following proposition:

> *Might a new cardiac safety paradigm utilizing a novel array of nonclinical proarrhythmia assessments, in silico predictive modelling, and Phase 1 ECGs make drug development more efficient, move the major clinical/regulatory analysis concerning arrhythmogenic potential earlier in the drug discovery and development continuum, enhance the accuracy with which existing and/or new drugs are labelled relative to actual proarrythmic risks, and increase the output of new chemical entities that become marketed drugs that benefit patients?*

Such a new paradigm would be expected to result in the removal of proarrhythmia risk labelling from some marketed drugs that have modest QTc effects.

The proposed new paradigm, the Comprehensive *In vitro* Proarrhythmia Assay (CIPA), is based on mechanistic understandings of ventricular arrhythmias via investigations on overexpressed human cardiac currents, computer models of ventricular myocyte electrophysiology, and isolated IPS-stem cell derived cardiomyocytes. The assessment of multiple ionic currents that influence the human ECG potentially includes I_{CaL}, I_{Kr}, I_{Ks}, I_{K1}, $I_{Na(fast)}$, and $I_{Na(late)}$. *In silico* modeling focusing on the propensity to manifest early afterdepolarizations and increased proclivity of depolarization during phase 3 repolarization, and a complementary cell-based arm of CIPA were proposed as a means to integrate the in vitro data into a prediction relevant to drug effects on human ventricular myocytes.

Methods, advantages, and concerns associated with new approach in general and with human induced pluripotent stem cell-derived cardiomyocytes and *in silico* modeling were therefore discussed. Clinical evaluations would remain part of the new paradigm, likely focused on careful ECG assessment in Phase 1 studies in order to evaluate a drug's effects on ECG intervals in general, atrioventricular conduction, heart rate, and to determine if there are findings that were not anticipated based on nonclinical testing (which would then need to be understood).

With this new paradigm in place, the Thorough QTc study would no longer be a necessary component in drug development.

The proposal was met with a large amount of productive discussion, spanning a wide range of viewpoints (technical challenges that will need to be addressed, the added benefits of such an effort, etc.), from academics, pharmaceutical developers, CRO representatives, and members of regulatory agencies that should prove useful to guide further progress. FDA proposed the goal of efficiently performing the additional work so that the new paradigm would be ready for implementation in two years.

It should be emphasized that the Think Tank was not designed to propose and then seek consensus endorsement of a fully defined and vetted new paradigm that is ready for immediate implementation. Its goals were to suggest components of such a paradigm, facilitate transparent stakeholder input and discussions, propose potential member organizations of a collaborative program to develop the specifics that would needed, and consider the first pragmatic steps. These goals were accomplished and such next steps are underway.