A New Perspective in the Field of Cardiac Safety Testing through the Comprehensive In Vitro Proarrhythmia Assay (CiPA) Paradigm


According to lead author Bernard Fermini, Ph.D., of the Department of Global Safety Pharmacology at Pfizer (Groton, CT) and colleagues from the Ion Channel Working Group (composed of members from pharma industry, universities and contract research organizations), the current approach suffers from acknowledged limitations. While it provides a regulatory framework for the detection of delayed cardiac repolarization by focusing on the inhibition of a single, essential, cardiac ion channel (hERG), and in vivo assessment of QT prolongation, it doesn’t assess the endpoint of clinical concern (namely ventricular arrhythmias), and needs revision.

Termed Comprehensive in vitro Proarrhythmia Assay (CiPA), this novel initiative represents one of the most important revisions to happen in cardiovascular safety since the implementation of the current international regulatory guidelines more than a decade ago. It is based on the fundamental mechanistic understanding of the integrated role of ion channels in ventricular repolarization and alterations leading to cardiac instability and arrhythmogenesis. It comprises two distinct series of tests: 1) in vitro evaluation of drug effects on multiple ion channels (not just hERG), and incorporation of these effects in an in silico model of a human ventricular action potential, and 2) confirmation of these results using cardiomyocytes derived from human induced pluripotent stem cells.

This initiative is the next logical step following the review and analysis of a decade of data obtained using current guidelines related to hERG inhibition and QT prolongation. It represents a visionary strategy that will likely require several years of testing before coming to fruition, but may revolutionize cardiovascular risk assessment.

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Specifically, JALA explores ways in which scientists adapt advancements in technology for scientific exploration and experimentation. In direct relation to this, JBS reports how scientists use adapted technology to pursue new therapeutics for unmet medical needs, including assay development, identification of chemical probes and target identification and validation in general.


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