Cardiosafety Testing Based on CiPA - at Scale with SyncroPatch 384 and Genedata Screener

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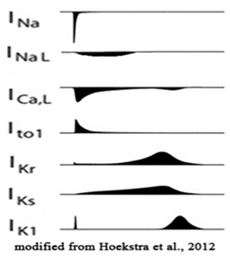
As part of the *Comprehensive In Vitro Proarrhythmia Assay* (CiPA) initiative, the FDA and other medical agencies have collaborated with pharma companies, academics, CROs, and device companies to develop a more comprehensive, robust, mechanism-based in vitro assessment of arrhythmia risk for new drugs. The CiPA protocols consist of panels of standardized in-vitro assays, incorporating defined tests against major cardiac ion channels, and thus enable large-scale, early discovery screens for liability prediction. Here we present a tailored solution for upscaled and traceable cardiac safety studies performed according to the CiPA guidelines. A combination of automated patch clamp assays run on Nanion SyncroPatch 384 instruments with automatic processing of the resulting data in the Genedata Screener software enables comprehensive cardiac risk assessment on potentially thousands of compounds per week, following CiPA experimental and analysis guidelines. This integrated, efficient workflow enables collection of high-quality electrophysiological data, their rigorous analysis, and their collation with non-APC assays (e.g. impedance data) for final panel assessment. We demonstrate this using hERG and $Na_v1.5$ assays conducted in compliance with CiPA recommendations on experimental procedures. Data processing, use of control data, data normalization, visualization of recording quality over time and other quality control metrics, assay end results and cross-assay safety scores are all combined in a result package that provides a clear path for putative submission to regulatory authorities. The automation technology presented enables large-scale cardiac safety assessment of candidate molecules, comprehensive in quality and dimensionality and authoritative by virtue of data integrity and accessibility, to eliminate risks earlier in the process of therapeutic development.

CiPA - the future of Cardiosafety testing

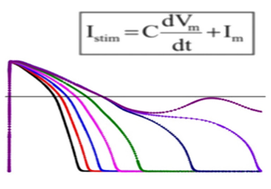
Comprehensive In Vitro Proarrhythmia Assay

Four components

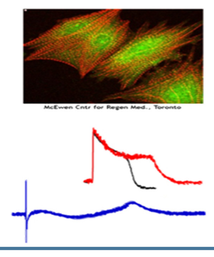
- Drug Effects on Multiple Human Cardiac Currents



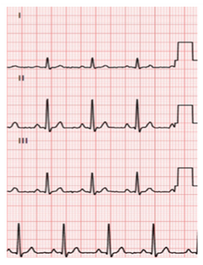
- In Silico Reconstruction of Human Ventricular Cellular Electrophysiology



- In Vitro Effects on Human Stem-Cell Derived Ventricular Myocytes



- Clinical Evaluation: Unanticipated EP Effects



A current goal of CiPA is to determine requirements and protocols to deliver robust, reliable and reproducible ion channel data in a high throughput screening (HTS) environment using high throughput automated patch clamp (APC) systems.

Reference Compounds Designated by the CiPA Initiative ("CiPA Compounds, May 10, 2016")

- Bepridil
- Chlorpromazine
- Cisapride
- Diltiazem
- Mexiletine
- Ondansetron
- Quinidine
- Ranolazine
- Sotalol
- Terfenadine
- Verapamil

SyncroPatch 384 and Screener Integration

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SyncroPatch 384, 384i, 768

High throughput APC

JSON

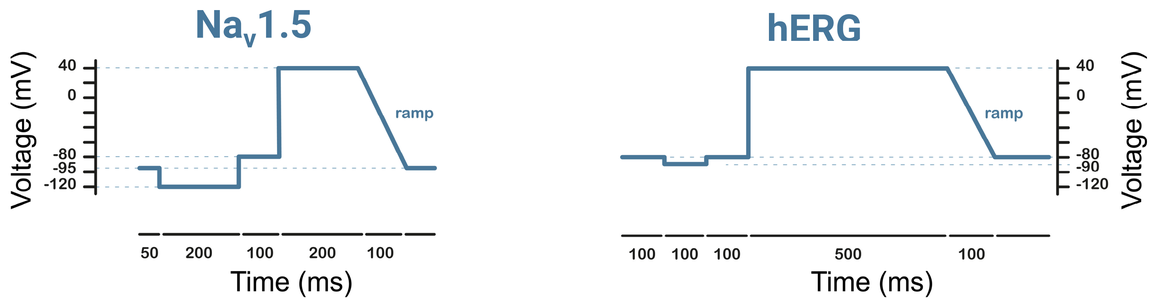
- Raw channel recordings
- Compound mapping
- Operational parameters

Genedata solutions in silico

SCREENER

Automated analysis

CiPA Voltage Protocols

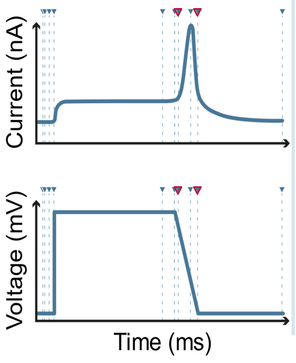


Workflow for Cardiosafety Analysis

Normalized, Quality Results per Sweep

Import Recordings & Metadata, Normalize

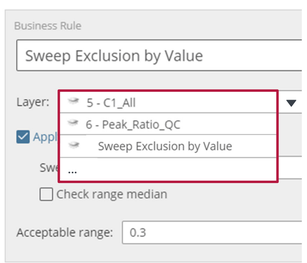
Traces with cursors



Normalization to CiPA-defined reference compounds and control wells

Define criteria for automated QC

Automated quality control according to CiPA guidelines



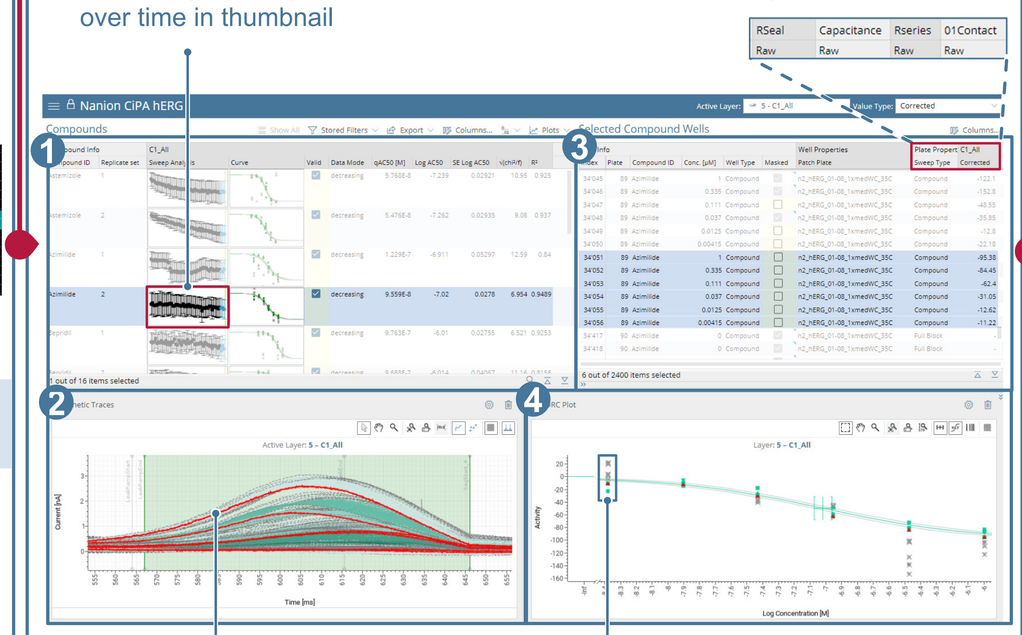
Compound Results per Assay

Individual well information and final compound results

1 Compounds | 2 Traces | 3 Wells | 4 Titration Response

Curves and peak amplitude over time in thumbnail

Sweep & well information



Individual trace

Interactively mask of outlier replicates

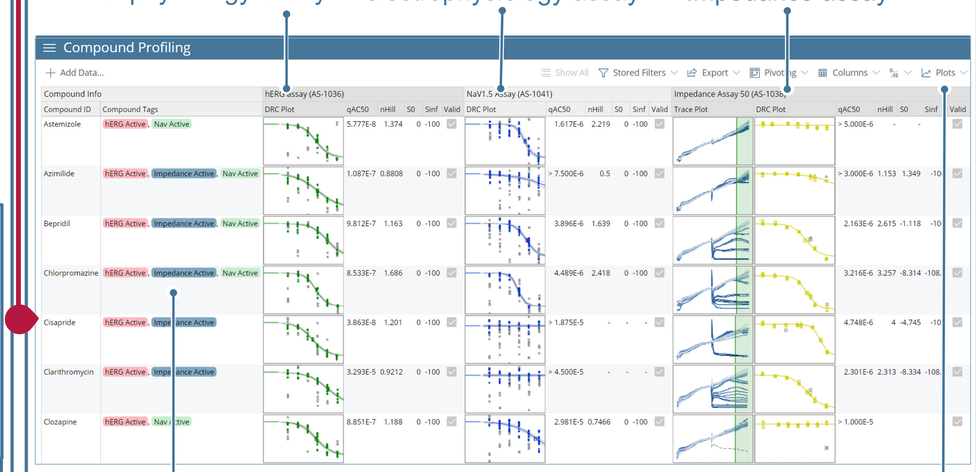
Make Decisions – And Share and Report Them

Collation of the CiPA assays on multiple ion channels and final safety assessment

Results from hERG electrophysiology assay

Results from $Na_v1.5$ electrophysiology assay

Results from Impedance assay



Automated flagging of compounds active in multiple-assays

Create further summary visualizations (e.g. scatter plots)

Creation of detailed reports; export of recordings, final results, and assessment decisions to data warehouses

For internal or external sharing

The direct interaction between the Nanion SyncroPatch 384 instrument and Genedata Screener enables seamless, rigorous analysis of hERG, Nav1.5, and other CiPA-mandated ion channel assays in an automated workflow. It makes it easier to consistently apply CiPA guidelines to large-scale, early discovery screens and incorporate them as part of standard operating procedure, including full data traceability and reporting. Thus, it helps organizations pave the way towards scalable, early safety assessment to increase discovery success and prepares them for a CiPA-mandated process including *in silico* models and exports into open, eCTD-compliant data formats currently in development by the FDA and industry.