Analysis and Reporting Pipeline for Cardiac Ion Channel Pharmacology Data: HESI BAA case example

Manni Mashaee[1,2], Claudia Alvarez-Baron[2], Donglin Guo[1], Wendy Wu[2], Jose Vicente Ruiz[1],

[1]FDA/ CDER/OND/OCHEN/DCN

[2]FDA/CDER/OTS/OCP/DARS

Abstract

In vitro cardiac ion channel data are critical for clinical decision-making in drug development. The HESI BAA Ion Channel Patch Clamp Study includes data generated by 5 manual and 4 automated patch clamp laboratories around the world. To enable the timely review and interpretation of results from this large dataset and any subsequent studies, it was crucial to unify the data formats, build an automated analysis pipeline, and standardize reports.

We designed a pipeline to automatically analyze large volumes of data with robust validation steps and improved report layouts, enabling easier intra- and inter-laboratory comparisons.

This unified approach not only streamlines the evaluation process but also supports meta-analyses to assess assay variability using data from all experiments and labs. The use of the unified data format and the analysis and reporting pipeline significantly reduced the time required for performing analyses from several days to few hours, thereby increasing efficiency and ensuring reproducible results of analysis of this type of data as well as enabling more time for the scientists to evaluate and interpret the results.

Introduction

ICH E14/S7B Q&As describe how nonclinical data, including in vitro cardiac ion channel pharmacology data, generated following best practices can be used to support clinical interpretation of QT studies as a part of an integrated proarrhythmic risk assessment. The evolving regulatory landscape illustrates how knowledge gained regarding the cellular of clinical risk could lead to increasing use of nonclinical strategies to support clinical decision-making. However, reproducibility of the hERG assay (or variability in hERG results) either within or across laboratories remains incompletely understood. To better understand variability in hERG and other cardiac ion channels, a Health and Environmental Sciences Institute (HESI)-coordinated international effort funded by Broad Agency Announcement (BAA) Award from the FDA was launched in 2019 to collect data by 5 manual and 4 automated patch clamp laboratories to determine the potency of 28-30 clinical drugs with different cardiac risk. To share these data and since no open data format existed, we implemented the Tabulated Experimental Data (TED) format, a spreadsheet-based and human-readable format developed and utilized by FDA electrophysiology lab at CDER. An automated analysis and reporting pipeline was developed to streamline the evaluation of these data and enable scientists to focus on interpretation of results.

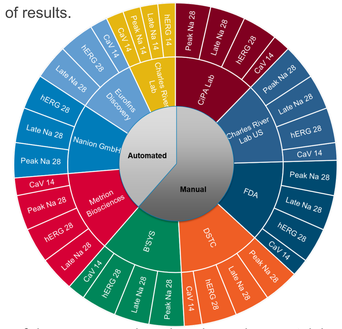

Figure 1. Number of drugs assessed per ion channel current, lab and platform.

Materials and methods

We developed the Tabulated Experimental Data (TED) format, a spreadsheet-based template intended to serve as a bridge to the CiPA Open Data (COD) format with a tabular data model while remaining human-readable for ease of use. TED is a tabular data model inspired by manual patch clamp experiments and includes metadata tables for experimental conditions and results, as well as raw waveforms stored in text or CSV files. It was designed to facilitate dataset review and sharing. This format has been utilized by the FDA electrophysiology lab at CDER for various experiments (e.g., Mashaee et. al. FDA Science Forum 2021, Alvarez-Baron et al. J Pharmacol Toxicol Methods 2022).

Building upon the TED format, we developed an automated analysis pipeline capable of handling large volumes of recorded data from each participant lab. This pipeline incorporates robust data validation and interactive reports to support quantitative and qualitative evaluation of results.

For each drug, the pipeline generates detailed reports that include plots of raw waveforms, current-time plots, current inhibition tables, and concentration-inhibition relationships. Additionally, it indexes measurements generated during the analysis of each dataset, providing a comprehensive overview of cellular properties under control and drug conditions across all labs. The pipeline's modular design and standardized I/O at each step enable it to produce various data subsets for additional analyses without the need to rerun the entire process. This functionality facilitates fast and high-quality evaluations of data consistency and reliability.

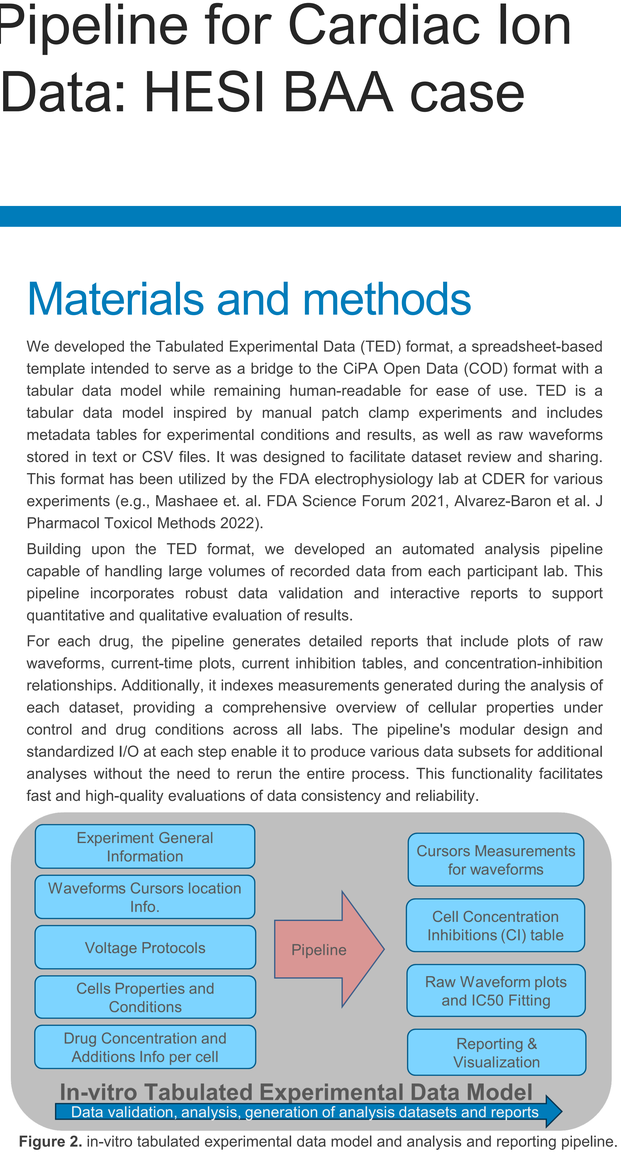

Figure 2. in-vitro tabulated experimental data model and analysis and reporting pipeline.

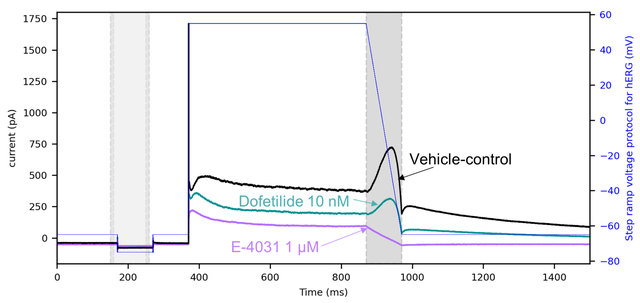

Figure 3. Average recorded waveforms during a patch clamp experiment. Blue trace is the voltage protocol. Highlighted regions (gray) are cursors' location for measurements used in the analysis.

Results and discussion

- HESI BAA manual patch clamp data were generated in two phases of 14 drugs each and four ion channel currents for each drug.
- All manual patch clamp labs and one automated lab provided their raw data in TED format.
- Two automated labs provided their raw data in COD format. There are ongoing efforts to export the data from the remaining automated lab to either TED or COD format.
- The entire manual patch clamp data were processed using the pipeline and for each drug on each channel a comprehensive report with visualization including raw waveforms and current-time (IT) plots per cell (Figure 4). Fractional inhibition tables were generated, and data were fit to a hill equation for calculation of the concentration inhibiting 50% of the current (IC_{50}) (Figure 5)
- (Figure 5)
- A total of 426 reports were generated for manual data.

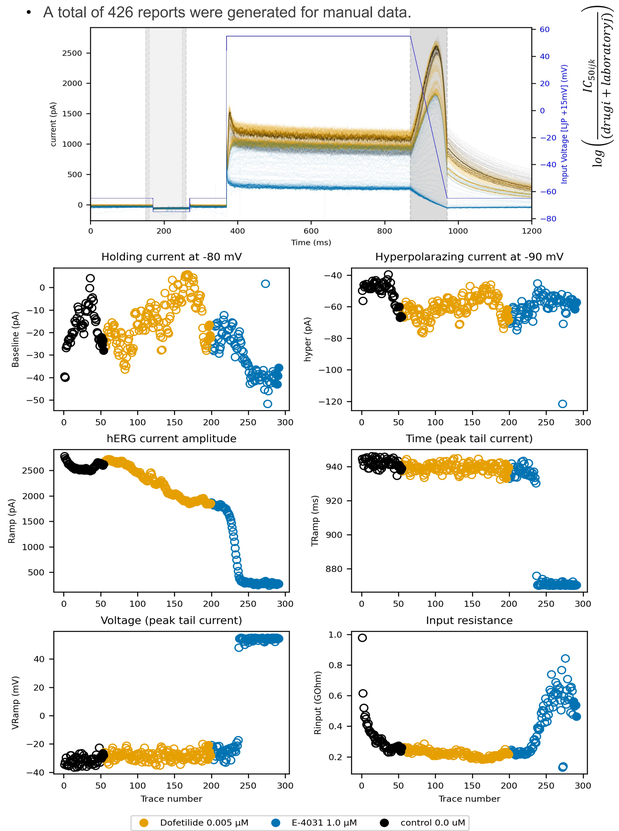

Figure 4. Recorded waveforms (top panel) and corresponding IT plots. IT plots show cursors measurement in different waveform regions (gray in top panel). Solid dots are used in analysis calculations and the open circles are used for qualitative review. These plots are from 1 out of the 29 cells tested for dofetilide by FDA lab. Waveforms and IT plots for each cell are available in the full report.

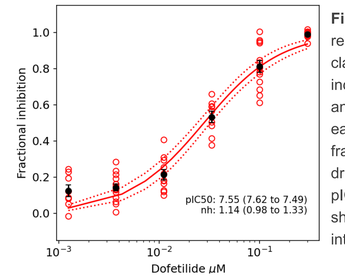

Figure 5. Dofetilide dose inhibition relationship from an automated patch clamp lab. Open red circles show individual data points. Solid black circles and error bars show mean and SE for each concentration tested. Y-axis shows fractional inhibition, and X-axis shows drug concentration in logarithmic scale. pIC50 and hill coefficient values are shown together their 95% confidence intervals on the bottom right of the figure.

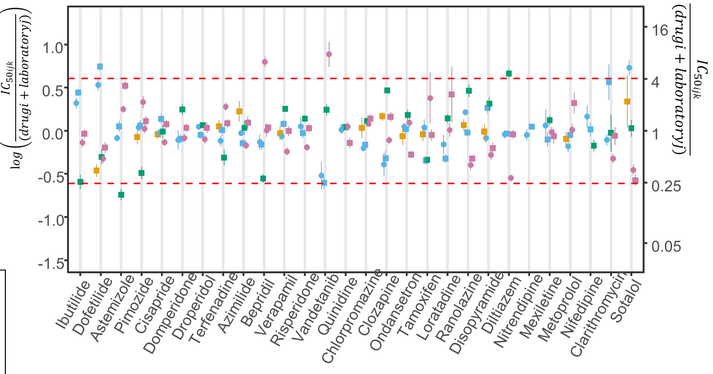

Figure 6. Example of a meta-analysis of the hERG pIC50 values from the four automated laboratories (four datasets acquired at ambient temperature and two datasets acquired at near physiological temperature). The y-axis shows the pIC50 values adjusted by the model-predicted values for each drug and lab combination. Error bars represent the 95% confidence intervals. Dashed red lines indicate the variability factor derived from the meta-analysis model. This analysis aggregates data to provide an estimate of variability in hERG block potency (see poster #051-A Safety Pharmacology Society 2024 Annual meeting for additional details).

Conclusion

- TED format provides a "user friendly" approach to gather and share data from patch clamp experiments. The files can be easily used with existing data validation, analysis and reporting tools without need for additional transformation.
- The analytical and reporting pipeline significantly reduced the time required for common as well as subsequent analyses from several days to few hours, thereby increasing efficiency and ensuring high-quality, reproducible results.
- This approach represents a substantial step towards enabling data sharing to foster research as well as to streamline the analysis and review of cardiac electrophysiology data to support clinical decision-making.

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