![CERTARA / Simcyp logo]

# Cardiac Safety Simulator

**The Cardiac Safety Simulator (CSS) is a systems biology-driven, modeling and simulation-based platform for the assessment of the pro-arrhythmic potency of drugs, new chemical entities, and other xenobiotics within the targeted clinical population**

Drug-induced cardiovascular adverse events are one of the leading causes of drug withdrawals from the market and of drug label restrictions. As a result, biopharmaceutical companies are keen to identify new drug candidates with a propensity to cause arrhythmias, or the heart to beat with an abnormal rhythm, early in the R&D cycle.

## Biosimulation and TQT study

ICH E14 guidance, which was introduced in 2005, required biopharmaceutical companies to conduct a "Thorough QT/QTc study (TQT)" to assess the likelihood of a new drug candidate

### Highlights

- Visualize and analyze simulation results with a flexible, Excel®-based tool

- Account for inhibition of multiple ion channels

- Predict population variability and drug triggered physiology modifications

- Evaluate up to 7 chemical species simultaneously (drugs, metabolites and other exogenous xenobiotics and endogenous substances) interacting at the ion channel(s) level

- Assess various ECG related outputs/ endpoints such as QT/ QTc, QRS, J-Tpeak, and Tpeak-Tend

Virtual Population
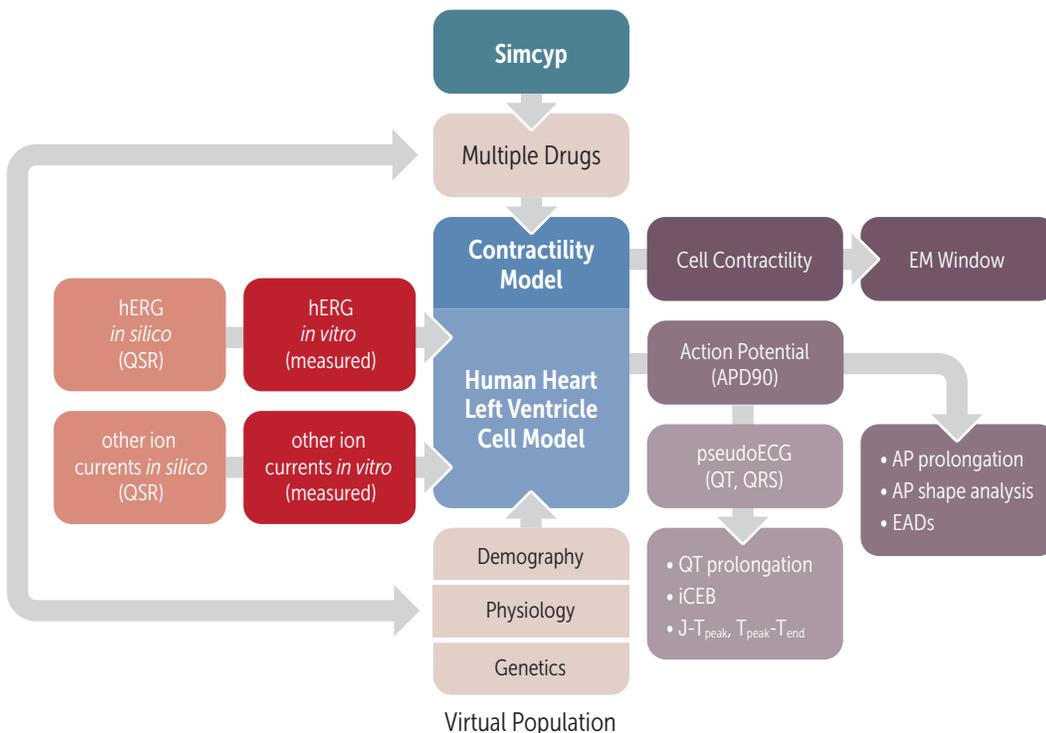
- Save time learning complex software: CSS is designed to be intuitive and easy for non-modelers to use

- Maximize investment in software: CSS is connected to the Simcyp Simulator allowing use of the leading platform for population-based *in vitro-in vivo* (IVIVE)/ physiologically-based pharmacokinetics (PBPK)

- Enable early assessment of cardiac liability: Enhanced QSAR models enable assessment of drug triggered ion channel current inhibition even when *in vitro* data are not available

- Comprehensive cardiac safety assessment: Use demographic, physiological and genetic information to evaluate a drug's risk of cardiac toxicity

producing lethal ventricular arrhythmias. A TQT study requires a new drug candidate to be given to healthy volunteers in escalating doses, often up to the maximally-tolerated dose. The participant's response to the drug is then monitored using high quality electrocardiograms (ECGs) to gain more understanding about its potential cardiotoxicity.

However, TQT studies are expensive and time-consuming. They may also result in the development of some drug candidates being stopped prematurely before the drug's entire clinical profile has been evaluated. By enabling early cardiotoxicity risk to be measured more precisely, Certara's CSS allows biopharmaceutical companies to make more informed go/no go decisions regarding their new drug candidates. In the next few years, TQT studies will likely be replaced with properly-designed first-in-patient studies combined with *in silico* modeling.

## CSS: Value across drug discovery cycle

The CSS platform can inform decision-making at every stage of drug development. In pre-clinical development, it brings together quantitative structure activity relationship (QSAR) and *in vitro* physiological measurements, generating early information on cardiac safety without incurring additional cost. During clinical development, *in vivo* data can be combined with CSS to enable a more robust assessment of cardiac risk with a focus on the impact of population variability.

CSS uses drug-triggered cardiac ion-current disruption data in combination with predicted *in vivo* drug exposure data to evaluate the factors influencing potential cardiac risk. It can account for the inhibition of multiple cardiac ion channels to assess pro-arrhythmic potency. CSS also uses demographic, physiological and genetic information (and parameter variability) to evaluate risk of cardiac toxicity. Finally, it can measure the influence of multiple drugs on ventricular ion currents and simulated ECGs.

While CSS version 2.0 is now a standalone product, it can also be used with the Simcyp Population-based Simulator, which simulates *in vivo* drug concentration – time data and their associated population variability. Combining knowledge gained from the Simcyp Simulator and CSS enriches the assessment of pro-arrhythmic potential and facilitates the design of clinical studies. Available early phase clinical studies results with robust QT assessment can be used for the simulation approach validation and extended to real life situations via virtual scenarios testing.
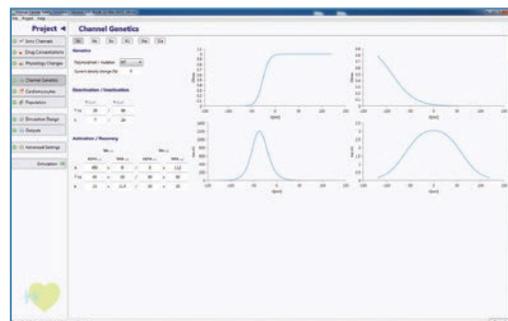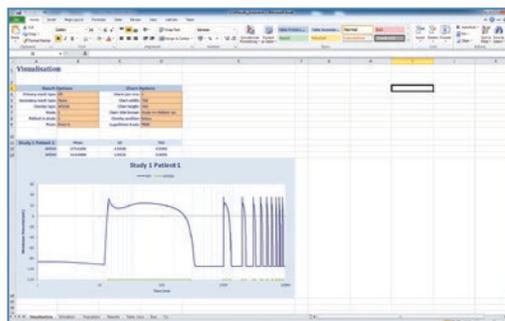
# Evaluating the factors that influence drug cardiotoxicity

CSS uses models of human heart ventricular cells to mathematically describe cardiac cell electrophysiology. In addition to single cell simulations, CSS includes a one-dimensional (1D) fibre model that incorporates transmural heterogeneities in ionic currents between endocardial, mid-myocardial and epicardial cells. The output from the single cell model is an action potential describing membrane dynamics. Results from the one-dimensional fibre model are used to generate a virtual ECG for automatic calculation of its derivatives, including QRS, QT, J-$T_{peak}$, and $T_{peak}$-$T_{end}$.

CSS can also be used in early stage drug development as a screening tool, even in situations where no *in vitro* data are available. Four independent models are available for the prediction of the inhibition of *in vitro* ion channels. All of the models for the IKr, IKs, INa and ICa currents were developed with artificial neural networks in conjunction with novel enhanced QSAR methodology. The latter combines molecular descriptors of the compound of interest with parameters relating to the *in vitro* assessment of a specific ion channel's inhibition.

Virtual clinical populations are generated to account for the impact of multiple demographic, physiological and genetic parameters. Default parameters are listed below; these can also be modified by the user.

| Parameter | Sex Dependent | Age Dependent | Circadian Variability |
| --- | --- | --- | --- |
| Cardiomyocyte volume | No | Yes | No |
| Cardiomyocyte electric capacitance | No | Yes | No |
| Sarcoplasmic reticulum volume | No | Yes | No |
| Left ventricle free wall thickness | Yes | Yes | No |
| Heart rate | Yes | Yes | No |
| $K^+$ plasma concentration | Yes | Yes | Yes |
| $Na^+$ plasma concentration | Yes | Yes | Yes |
| $Ca^+$ plasma concentration | Yes | Yes | Yes |
| hERG channel genetics | No | No | No |
| Maximum current density | Yes | No | No |

## CSS v2.0 offers new features including:

- Enhanced QSAR models for predicting drug-triggered IKr, IKs, INa and ICaL current inhibition based on automatically-calculated physical chemistry data (when *in vitro* data are not available)

- Prediction of population variability and drug-triggered physiology modifications

- Assessment of the potential impact of disease and genotype on ionic currents at the channel level

- An additional human left ventricular muscle cell model allowing for contractility assessment

- Up to seven chemical species (drugs, metabolites and other substances) can be simultaneously evaluated for interaction at the ion channel(s) level

- A new flexible, Excel-based tool to enhance visualization and analysis of simulation results

## Recent Publications

**Glinka A, Polak S.**
QTc modification after risperidone administration – insight into the mechanism of action with use of the modeling and simulation at the population level approach. *Toxicology Mechanisms and Methods*, 2015; accepted for publication.

**Wisniowska B, Mendyk A, Szlęk K, Kołaczkowski M, Polak S.**
Enhanced QSAR models for drug-triggered inhibition of the main cardiac ion currents. *Journal of Applied Toxicology*, 2015; accepted for publication.

**Mishra H, Polak S, Jamei M, Rostami-Hodjegan A.**
Interaction Between Domperidone and Ketoconazole: Toward Prediction of Consequent QTc Prolongation Using Purely In Vitro Information. *CPT Pharmacometrics Syst Pharmacol.*, 2014; 3, e130.

**Fijorek K, et al.**
Model of the distribution of diastolic left ventricular posterior wall thickness in healthy adults and its impact on the behavior of a string of virtual cardiomyocytes. *Journal of Cardiovascular Translational Research*, 2014; 7(5): 507-517.

**Glinka A, Polak S.**
The Effects of Six Antipsychotic Agents on QTc – an attempt to mimic clinical trial through simulation including variability in the population. *Computers in Biology and Medicine*, 2014; 7:20-26.

**Wisniowska B, Mendyk A, Fijorek K, Polak S.**
Computer-based prediction of the drug proarrhythmic effect – problems, issues, known and suspected challenges. *Europace*, 2014;16:724-735.

**Polak S, Wisniowska B, Fijorek K, Glinka A, Mendyk A.**
In vitro-in vivo extrapolation of drug-induced proarrhythmia predictions at the population level. *Drug Discovery Today*, 2014; 19:275-281.

**Fijorek K, Püsküllüoglu M, Polak S.**
Circadian models of serum potassium, sodium and calcium concentrations in healthy individuals, and their application to cardiac electrophysiology simulations at individual level. *Computational and Mathematical Methods in Medicine*, 2013; Article ID 429037, 1-8, 2013; doi:10.1155/2013/429037.

## About Certara

Certara is a leading provider of decision support technology and consulting services for optimizing drug development and improving health outcomes. Certara's solutions, which span the drug development and patient care lifecycle, help increase the probability of regulatory and commercial success by using the most scientifically advanced modeling and simulation technologies and regulatory strategies. Its clients include hundreds of global biopharmaceutical companies, leading academic institutions and key regulatory agencies.

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