# Publication

## Supplemental Studies for Cardiovascular Risk Assessment in Safety Pharmacology: A Critical Overview

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*Abstract*

Safety Pharmacology studies for the cardiovascular risk assessment, as described in the ICH S7A and S7B guidelines, appear as being far from sufficient. The fact that almost all medicines withdrawn from the market because of life-threatening tachyarrhythmias (torsades-de-pointes) were shown as hERG blockers and QT interval delayers led the authorities to focus mainly on these markers. However, other surrogate biomarkers, e.g., TRIaD (triangulation, reverse-use-dependence, instability and dispersion of ventricular repolarization), have been identified to more accurately estimate the drug-related torsadogenic risk. In addition, more attention should be paid to other arrhythmias, not related to long QT and nevertheless severe and/or not self-extinguishing, e.g., atrial or ventricular fibrillation, resulting from altered electrical conduction or heterogeneous shortening of cardiac repolarization. Moreover, despite numerous clinical cases of drug-induced pulmonary hypertension, orthostatic hypotension, or heart valvular failure, few safety investigations are still conducted on drug interaction with cardiac and regional hemodynamics other than changes in aortic blood pressure evaluated in conscious large animals during the core battery mandatory studies. This critical review aims at discussing the usefulness, relevance, advantages, and limitations of some preclinical in vivo, in vitro, and in silico models, with high predictive values and currently used in supplemental safety studies.