

*A newsletter dedicated to keeping our colleagues informed of progress and changes  
at WIL Research, as well as scientific and regulatory matters of interest.*

## **UPDATE: Safety Pharmacology**

# **Integrated Risk Assessment Addresses ICHS7B**

In October 2005, the FDA adopted the International Conference Harmonization (ICH) Draft Guidance, Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals (S7B). The document provides guidance for a testing strategy designed to evaluate the potential effects of pharmaceuticals on ventricular repolarization and proarrhythmic risk. This draft has been recommended for adoption by the regulatory bodies of the European Union, Japan and the United States. Europe was the first regulatory body to require these assessments to be performed as GLP components of an IND submission and this has been followed by the United States and Japan.

The guideline extends and complements the ICH guidance Safety Pharmacology Studies for Human Pharmaceuticals (ICHS7A) and applies to new chemical entities for human use and for marketed pharmaceuticals where indications of adverse clinical events, new patient population or new route of administration raises concerns not previously addressed.

A delay in ventricular repolarization associated with QT interval prolongation increases the risk of ventricular tachycardia, which has the potential to lead to lethal situations such as torsade de pointes. Ventricular repolarization is a complex multichannel physiological process with the rapid and slow-activating components of the delayed rectifier potassium currents, IKr and IKs, apparently having the most influential role on the action potential and, therefore, the QT interval. Inhibition of the channel responsible for IKr is the most common mechanism by which pharmaceuticals can evoke QT interval prolongation. In order to fully assess the proarrhythmic risk and the potential of pharmaceuticals to evoke effects on ventricular repolarization, the guidance recommends an integrated risk assessment. This strategy effectively consists of evaluating effects both in vitro and in vivo, along with consideration of the chemical/pharmacological class and relevant nonclinical and clinical information.

WIL Research staff have many years of experience in the assessment of potential cardiac safety issues through our program of Safety Pharmacology studies designed to address the issues raised in ICHS7A. We are, therefore, in a position to offer solutions to our clients with regard to the ICHS7B document by our approach to the integrated risk assessment process.

The Safety Pharmacology Department at WIL Research has extensive experience in conducting QT assays designed to satisfy the in vivo portion of the integrated risk assessment. The in vivo system possesses the full complement of molecular, biochemical and physiological systems, which allow evaluation of parent substance and metabolites in order to establish safety margins. Cardiovascular studies can be conducted in either canines or primates, surgically implanted with telemetry transmitters (arterial pressure and electrocardiographic waveforms), and placed in dedicated animal rooms. The arterial and ECG waveforms are collected, via receivers and a data exchange matrix, using the Dataquest A.R.T. Gold™ data acquisition and analysis software suite. Our staff can remotely monitor the data as it is being collected in our central control suite. Following collection, the ECG waveform data is analyzed using Physiostat™ ECG analysis software. The actual ECG waveforms are qualitatively reviewed by our trained staff for abnormalities. Any abnormalities that are detected can be referred to our veterinary cardiology consultant for assessment of cause.

WIL Research has a collaborative agreement with ChanTest, Inc., a leading provider of electrophysiology-based ion channel safety testing and it is through this relationship with ChanTest that we are able to offer GLP whole-cell patch-clamp hERG assays.

Please contact us if you have any questions regarding our approach to the integrated risk assessment or other safety pharmacology services.