# GLP hERG Screening

**Metrion Biosciences provides screening services against hERG using the conventional whole-cell patch-clamp technique. These services have been audited and approved by the UK Medicines and Healthcare products Regulatory Agency (MHRA) and are performed in accordance with the FDA best practice guidelines.**

## An Introduction to GLP hERG Screening

The ICH S7A and ICH S7B guidelines provide regulatory guidance on performing safety pharmacology studies for human pharmaceuticals. Most Investigational New Drug (IND) applications for small molecules include pharmacological assessments against the human *ether-à-go-go related* gene (hERG) potassium channel, which should be conducted in compliance with GLP principles.

## Why Perform hERG Screening?

The hERG potassium channel encodes the pore forming subunit of the rapidly activating delayed rectifier potassium current ($I_{Kr}$), which plays an important role in contributing to the repolarisation of ventricular cardiomyocytes.

The action potential duration of ventricular cardiomyocytes corresponds to the QT-interval of the electrocardiogram; therefore, inhibition of $I_{Kr}$ can lead to prolongation of the cardiac action potential and the QT interval. Prolongation of the rate corrected QT interval beyond 440 ms is associated with an increased risk of arrythmias, such as the polymorphic ventricular tachycardia, Torsade de Pointes (TdP).

Several drugs have been withdrawn from the market, or had their use severely restricted, due to their proarrhythmic liability. All of those drugs have been identified as hERG blockers and, consequently, ICH S7B guidelines were introduced that include guidance on evaluating the effect of new chemical entities against hERG using GLP principles. The implementation of hERG screening in drug discovery has had a significant contribution in reducing the development of proarrhythmic drugs.

GLP compliant hERG screening is mandatory under the ICH S7B guidelines, which states that *in vitro* $I_{Kr}$ and *in vivo* QT assays described in Sections 2.3.1 and 2.3.2 when performed for regulatory submission should be conducted in compliance with good laboratory practice (GLP).

## Metrion's GLP hERG Assay

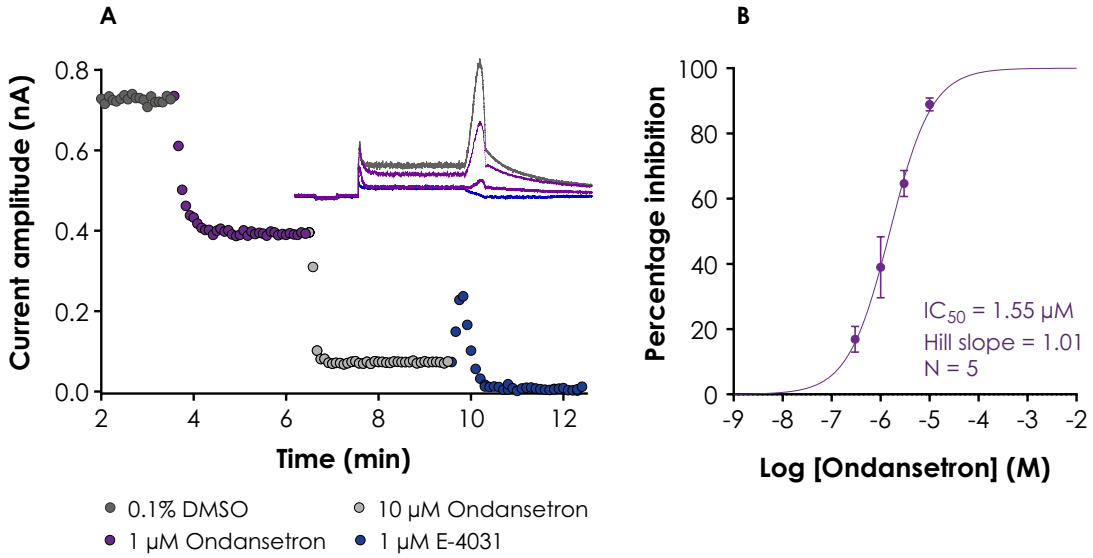
Metrion provides screening services against hERG using the conventional whole-cell patch-clamp technique. These services are performed in accordance with the FDA's best practice guidelines and in compliance with:

1. UK GLP Regulations, SI 1999 No 3106; amendments, SI 2004 No. 994 2. OECD No 1 Principles on Good Laboratory Practice and Monographs.

The experiments are performed using the FDA's recommended voltage protocol and experimental solutions at physiological temperature. Concentration verification via chemical analysis of dosing formulations (Dose Formulation Analysis, DFA) is an obligatory requirement for GLP studies submitted in IND filings and is performed by Metrion's preferred GLP compliant partner.

**Figure 1.**
A. Graph showing current plotted against time for a representative cell treated with 1 and 10 µM ondansetron followed by 1 µM E-4031. The inset figure shows representative current traces in 0.1% DMSO, ondansetron and E-4031.

B. Concentration-response curve for ondansetron (data points ± SD).




## GLP hERG Assay Overview

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|---|---|
| **Platform** | Manual patch-clamp |
| **GLP hERG test system** | CHO |
| **Temperature** | 35 ± 2 °C |
| **Number of test concentrations** | 4 |
| **Positive control** | Ondansetron |
| **Required for IND submission?** | Yes |
| **Dose-formulation Analysis (DFA)** | Yes, using a GLP Compliant Partner |

## Why Choose Metrion?

Metrion has extensive experience of providing high quality biology services for ion channel targets. Our team offers:

- Exceptional ion channel electrophysiology and drug discovery expertise
- A team of experienced cell biologists to create novel cell lines
- High quality, cost-effective compound screening
- Detailed characterisation of lead compounds in a range of high quality assays
- Translational services including confirmation of efficacy in stem cell and other phenotypic models
- Rapid reporting and data interpretation by highly experienced ion channel scientists.

## Our Experts

Metrion has a strong global reputation as a world leading provider of ion channel drug discovery services; our team of predominantly PhD qualified biologists have a considerable amount of experience working on a wide range of ion channel targets during their careers.

Our staff have worked at various leading pharmaceutical companies, CROs and Universities. This experience has enabled them to develop their knowledge and expertise in ion channel drug discovery and become market leaders in the use of different electrophysiology platforms to drive ion channel drug discovery programmes.

For more information on GLP compliant hERG screening, please visit: **www.metrionbiosciences.com/GLP-herg-screening**

**Contact us:**
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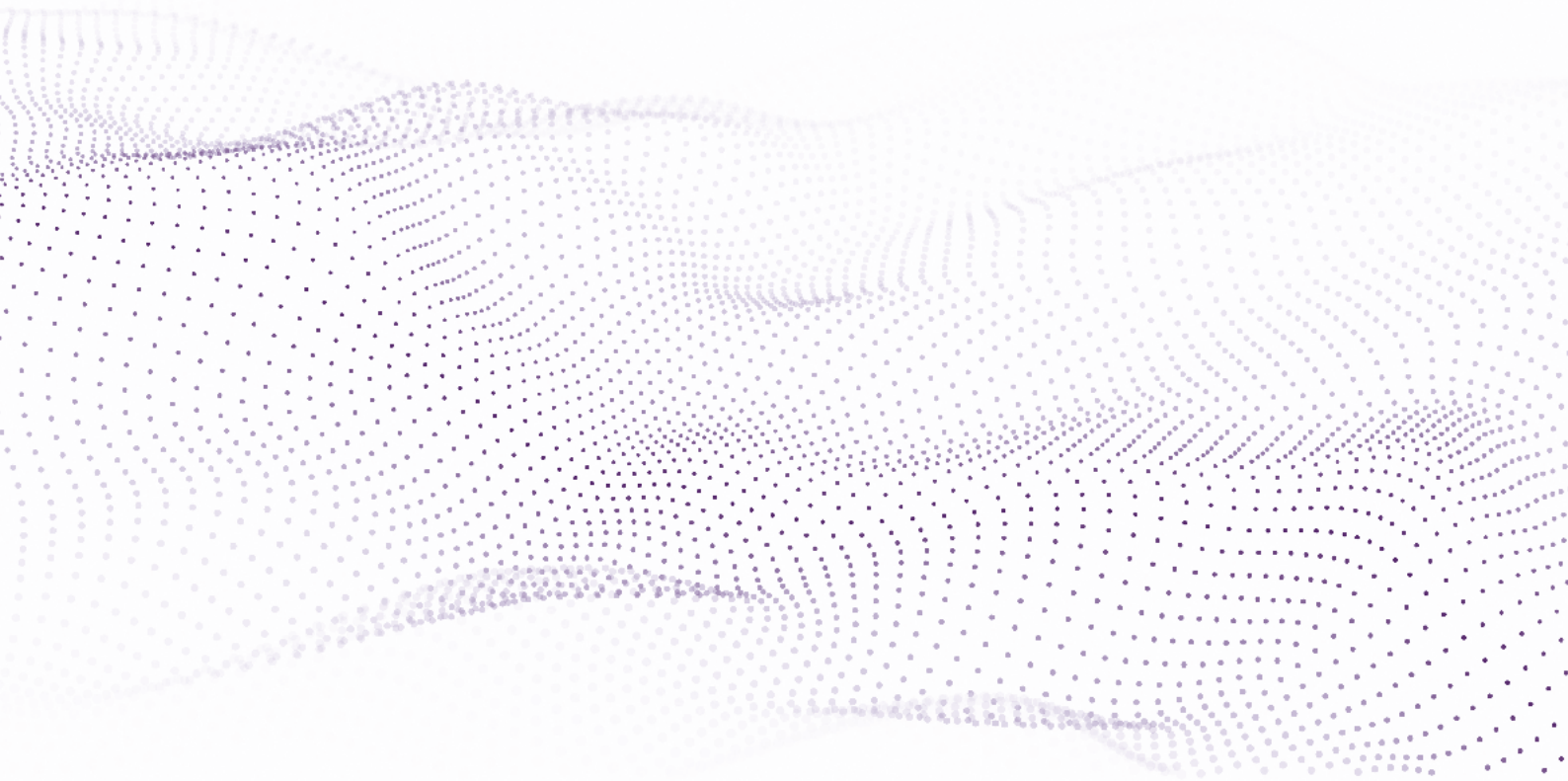

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