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Chapter 4 The Mechanisms Underlying Cardiac Arrhythmias
Introduction; Mechanisms Underlying Cardiac Arrhythmias; Abnormal Automaticity; Early and Delayed After depolarizations; Re-entry; Transmural Dispersion of Repolarization; How does Action Potential and QT Prolongation Generate Arrhythmias?; Does the M-Cell Play a Role in Arrhythmia Induction in Humans?; Using Mouse Models to Study Arrhythmia Mechanisms; Experimental Studies Exploring the Relationship Between Changes in Transmural Repolarization Gradients and Arrhythmias in Mouse Hearts
Arrhythmia Mechanisms and Novel Antiarrhythmic Approaches Identified Using the Hypokalemic Mouse Model Summary; References;
Chapter 5 The Mechanisms Underlying Drug-Induced Arrhythmias; Introduction; The Classical Model of Drug-Induced QT Prolongation and Proarrhythmia: HERG Blockade; Additional Mechanisms Contributing to Drug-Induced Arrhythmias; Drug-Induction Activation of Depolarizing Ion Channels; Drug-Induced Changes in Ion Channel Expression; Drug-Induced Sodium Channel Dysfunction; Summary; References;
Chapter 6 Assessing Cardiac Safety in Drug Development; Introduction
Preclinical Evaluation of Cardiac Drug Safety The ICH S7B Guidelines; Single Cell Safety Studies; The Purkinje Fiber Model; The Ventricular Wedge Model; Isolated Heart Models; In Vivo Models; The Impact of Species-Related Differences in Cardiac Electrophysiology on Preclinical Drug Safety Assessment; Methods to Provoke Arrhythmias in Preclinical Studies; Programmed electrical stimulation; Reductions in the extracellular K⁺ concentration; Clinical Evaluation of Cardiac Safety; The Thorough QT study; Thorough QT study design; Additional Biomarkers to Detect Drug-Induced Proarrhythmia
Variability of repolarization

Sommario/riassunto

Ensuring the safety of new medical products remains a major challenge for the pharmaceutical industry. Cardiac safety, particularly drug-induced heart rhythm abnormalities, remains an important cause of pipeline attrition and has resulted in countless major product recalls or label changes. The risk of encountering this major adverse event continues to shape the drug development and regulatory landscape. Extensive research over the past decade has shed light on the root causes of arrhythmias that are triggered by medications and has helped drive, and optimize, drug safety testing. However,
