International Drug Regulatory Standards

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In 1990, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) was created to harmonize global regulatory standards (Algonquin College, 2020 - a). The ICH is comprised of quality, safety, efficacy, and multidisciplinary guidelines (Algonquin College, 2020 - a). Quality guidelines are based on Good Manufacturing Practice (GMP) risk management assessments and the harmonization of breakthrough research on stability studies as well as minimum acceptable quantities for the testing of impurities (Algonquin College, 2020 - a). Safety guidelines involve the identification of associated risks including reproductive, genetic, carcinogenic, and cardiac toxicities (Algonquin, 2020 - a). Efficacy guidelines are based on how the clinical trial is designed, conducted, manages safety, as well as the reporting of results (ICH Guidelines, 2022 - a). These guidelines also extend to the development of novel agents using biotech as well as genomic and pharmacogenetic procedures (ICH Guidelines, 2022 - a). Multidisciplinary guidelines include ICH Medical Terminology (MedDRA), the Common Technical Document (CTD), and developing the Electronic Standards for the Transfer of Medical Information (ESTRI) (ICH Guidelines, 2022 - a). This paper will focus on the efficacy guidelines involved with the clinical evaluation of a cardiovascular adverse effect called QT/QTc prolongation. The impact of this guideline on Mutual Recognition Agreements (MRAs), and how adoption of these guidelines may facilitate joint reviews between Canada and the United States Regulatory Cooperation Council (RCC) will also be discussed.

**ICH Efficacy Guidelines**

The efficacy guidelines consist of sections E1 to E21, where the clinical evaluation of QT/QTc is detailed in section E14 (ICH Guidelines, 2022 - a). The QT interval indicates the duration of ventricular depolarization and repolarization (ICH Guidelines, 2022 - a). When this repolarization is delayed it results in a prolonged QT interval that is measured on an electrocardiogram (ECG) (ICH Guidelines, 2022 - a). The QT interval is dependent on heart rate, but it is often corrected to a value called the QTc that is less dependant on heart rate, so the interval is typically referred to as the QT/QTc interval (ICH Guidelines, 2022 - a). This is an important area because among adverse events, it is the identification of the risk for QT/QTc interval prolongation that is responsible for the most withdrawal of drugs from the market (ICH Guidelines, 2022 - a). Section E14 contains the following documents:

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| **E14 Clinical Evaluation of QT** | |
| E14 | The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs |
| E14 Q&As (R3) | Questions & Answers: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs |
| E14/S7B IWG | Questions & Answers: Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential |

The E14 guidance document on the clinical evaluation of QT/QTc interval prolongation and the proarrhythmic potential for non-antiarrhythmic drugs is divided into sections that elaborate on conducting a thorough QT/QTc study in clinical trials, analysis of ECG data, adverse events, and regulatory implications, labelling and risk management strategies (ICH Guidelines, 2022 - b). This document serves as a guide to evaluate the QT/QTc prolonging effects of a study drug during the clinical trial process. The key sections of the document are summarized below.

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| **Clinical Trails** | Drugs are evaluated for their effects on cardiac repolarization in the early stages of clinical trials (ICH Guidelines, 2022 - b). This section describes the process used for evaluating drug effects on the QT/QTc interval. Exclusion criteria for subject enrollment are discussed such as a baseline prolonged QT/QTc interval of > 450 milliseconds (ms) identified through ECG, having a history of risk factors for a serious arrhythmia called torsade de pointes, or the use of concurrent medications that prolong the QT/QTc interval (ICH Guidelines, 2022 - b). Clinical trials establish safety monitoring parameters and the criteria for a subject to be discontinued from the study. Repeat ECG measurements demonstrating a clinically significant prolonged QT/QTc interval > 500 ms or 60 ms over baseline is a criterion for discontinuing the use of a study drug in the subject (ICH Guidelines, 2022 - b).  A thorough QT/QTc study is undertaken using a 12-lead surface ECG to determine the minimum threshold for QT/QTc prolongation in healthy volunteers based on a set increase over baseline (ICH Guidelines, 2022 - b). For example, drugs that prolong the mean QT/QTc interval by > 20 ms are more likely to be proarrhythmic (ICH Guidelines, 2022 - b). The minimum threshold determines how much ECG data will be collected in later stages of drug development and whether expanded ECG safety data should be collected (ICH Guidelines, 2022 - b). The document also addresses the problem of intrinsic variability in ECG data resulting from extraneous factors in subjects such as activity level, food intake, etcetera (ICH Guidelines, 2022 - b). The importance of obtaining multiple baseline ECG measurements before undertaking the study on drug effects on QT/QTc prolongation is recommended so that more reliable baseline data is available (ICH Guidelines, 2022 - b). The study also examines drug dose and concentration effects on ECG, considering above therapeutic doses of the drug and the tendency to cause QT/QTc prolongation (ICH Guidelines, 2022 - b). The drug concentration at the time of ECG requires measurement to establish this relationship (ICH Guidelines, 2022 - b). In addition, drug-drug as well as drug-food interactions may inhibit enzymes involved in drug metabolism resulting in increased drug concentrations that effect the QT/QTc interval (ICH Guidelines, 2022 - b). The ECG results should be obtained when the drug is at its maximum concentration considering how long the drug remains in the body before elimination (ICH Guidelines, 2022 - b). |
| **Analysis of ECG Data** | This section details how ECG data is interpreted from test results based on correction formulas used to correct for the effects of variations in heart rates and rapid heart rate changes on ECG results (ICH Guidelines, 2022 - b). Clinical risk assessment is based on analysis of central tendencies and median values on ECG interval data (ICH Guidelines, 2022 - b). |
| **Adverse Events** | Certain adverse events may signal the proarrhythmic potential of the study drug such as torsade de pointes, sudden death, ventricular tachycardia, ventricular fibrillation, and flutter (ICH Guidelines, 2022 - b). Data on the premature discontinuation of the drug or dose reductions due to prolonged QT/QTc interval are noted, as well as post marketing adverse events indicating abnormal ECG findings (ICH Guidelines, 2022 - b). |
| **Regulatory Implications, Labelling and Risk Management Strategies** | A drug that displays QT/QTc prolonging effects may not be approved or have its development halted if there is no clinical advantage compared to other available therapies (ICH Guidelines, 2022 - b). If adequate assessment of the QT/QTc prolonging potential of the drug is not undertaken, then this may result in a delay or denial in receiving market authorization (ICH Guidelines, 2022 - b). A risk benefit assessment based on overall benefit of the drug verses the clinical significance of the abnormal ECG will determine the utility of the drug compared with alternative agents (ICH Guidelines, 2022 - b).  Special labeling requirements exist for drugs that prolong the QT/QTc interval (ICH Guidelines, 2022 - b). The document makes several recommendations concerning what information should be included in the labelling (ICH Guidelines, 2022 - b):   * A warning label about the risk * Dosage recommendations * A summary of the design and results of the trials investigating the drug effect on the QT/QTc interval as well as information on absence of a QT/QTc prolonging effect * A list of comorbidities known to cause clinically significant increase in QT/QTc interval prolongation * A precaution describing the increased risk if co-administering the study drug with another agent known to prolong the QT/QTc interval or drug interactions that increase this risk * Recommendations to monitor ECG results and management strategies if abnormal ECGs are observed |

**How ICH Efficacy Guidelines may Impact MRAs Between Canada and Partner Countries**

The ICH guidelines provide the framework to assess for efficacy based on the design, conduct, safety, and reporting of clinical trials (ICH Guidelines, 2022 - a). Health Canada is an official member of the ICH that is engaged in adopting and implementing the ICH guidelines (Government of Canada, 2022 - b). Health Canada is also responsible for MRAs that allows for the recognition of regulatory practices by their partner countries’ regulatory authorities (Algonquin College, 2020 - b). MRAs facilitate harmonization through regulatory cooperation between countries that have formal agreements in place (Government of Canada, 2021).

Health Canada has adopted ICH guidance document E14 (Government of Canada, 2006). When countries that have MRAs with Canada also adopt the ICH efficacy guidelines for obtaining ECG data, then they have accepted these regulatory guidelines as part of the clinical trial process for premarketing surveillance of this adverse event. This will allow partnering countries to accept drug products because they have been developed based on mutually recognized compliance with efficacy guidelines and according to the Good Manufacturing Practices Compliance Programme. This agreement helps reduce the regulatory burden on industries at the international level (Government of Canada, 2021).

**ICH Guidelines and the Canada-United States RCC**

The RCC allows regulators from Canada and the United States to work together to reduce regulatory barriers and to facilitate regulatory cooperation through several technical work plans such as the regulatory cooperation statement for pharmaceutical and biological products (Government of Canada, 2022 - a). This work plan states that Health Canada and the U.S. Food and Drugs Administration work together to harmonize their pre and post marketing surveillance requirements and standards (Government of Canada, 2022 - a).

The efficacy guidelines for analysis of ECG data for non-antiarrhythmic drugs during clinical trials and the establishment of thresholds for the identification of clinically significant QT/QTc prolongation is important for applying consistency in standards to identify drugs that result is cardiac dysrhythmias. Adoption of these guidelines by both countries will facilitate a joint review process that will make data analysis and interpretation of results easier to apply when discussing regulatory approval between the Canada and United States through the RCC. As a result, there will be confidence in the regulatory process that may expedite the approval in Canada of a drug developed in the United States, and vice versa.

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