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NOTICE

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Release of final Health Canada document: Health Canada Question and Answer Document Regarding the ICH S7B and E14 Guidances

On April 5, 2006, Health Canada adopted the following two International Conference on Harmonisation (ICH) guidances:

- ICH S7B: The Non-clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals
- ICH E14: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs

Health Canada has developed the following regional guidance documents to support the interpretation and implemention of these guidances:

- Health Canada Question and Answer Document Regarding the ICH S7B and E14 Guidances
- Guide for the Analysis and Review of QT/QTc Interval Data
- QT/QTc Interval Prolongation: Guidance for Product Monograph Content

The Health Canada document entitled *Health Canada Question and Answer Document Regarding the ICH S7B and E14 Guidances* is intended to clarify our regional regulatory expectations with regard to the ICH S7B and E14 guidances.

This document replaces the draft document of the same name. Comments and suggestions received from the consultation on the draft version of the guidance were reviewed and considered in the finalization of this document. A tabulation summarizing the comments received during the external consultation and the outcome of the Health Canada discussion of these comments is available on request.

Should you have any questions or comments regarding the content of this guidance, please contact :

Bureau of Policy, Science and International Programs
Therapeutic Products Directorate
1600 Scott Street
Holland Cross, Tower B
2nd Floor, A.L. 3102C5
Ottawa, ON K1A 0K9

Fax: (613) 941-1812
E-mail: Policy_Bureau_Enquiries@hc-sc.gc.ca

Health Canada Question and Answer Document Regarding the ICH S7B and E14 Guidances

Question 1: *What is the position of Health Canada regarding the timing of the S7B core battery studies (i.e., hERG/I_{Kr} assay and in vivo QT assay) in relation to first in human clinical trials?*

Answer 1: The results of the *in vitro* hERG/I_{Kr} assay and the *in vivo* QT assay should be available to support Clinical Trial Applications for first in human testing of investigational drugs that fall within the scope of the ICH S7A and S7B guidances (see Sections 1.3 of the ICH S7A and S7B guidances and Section 2.9 of the ICH S7A guidance).

Question 2: *If the ICH S7B safety pharmacology studies do not provide evidence of cause for concern, would this influence the position of Health Canada regarding the need to perform a thorough QT/QTc study in humans?*

Answer 2: A clinical pharmacology study dedicated to assessing effects on the electrocardiogram (ECG), as described in Section 2.2 of the ICH E14 guidance, will be expected for almost all drugs, even if the non-clinical safety pharmacology studies that assess the potential for delayed ventricular repolarization do not provide evidence of cause for concern.

Question 3: *The ICH E14 guidance contains the following statement: "a negative 'thorough QT/QTc study' is one in which the upper bound of the 95% one-sided confidence interval for the largest time-matched mean effect of the drug on the QTc interval excludes 10 ms." How does Health Canada intend to apply this threshold?*

Answer 3: The 10 ms threshold for the upper bound 95% one-sided confidence interval for the largest time-matched mean effect is intended for use in judging the intensity of the ECG safety evaluation during later stages of drug development. This threshold would be considered only for treatment arms receiving substantial supratherapeutic exposures, not therapeutic exposures or low multiples thereof. Ideally, the exposure achieved at the supratherapeutic dose in the ECG assessment study should cover and exceed the maximum anticipated clinical exposure in the target patient population and subjects with compromised elimination (e.g., drug-drug interactions, poor metabolizers, elderly, renal impairment, hepatic impairment). If the testing of sufficiently high exposures is not possible for reasons of safety, tolerability, or saturating absorption, the failure to observe drug-related ECG changes in the thorough QT/QTc study would not be entirely reassuring and the sponsor would be expected to pursue a careful assessment of ECG safety in phase II and III clinical trials.

When a potential for QT/QTc prolongation has been identified in clinical trials, regulatory decisions regarding approval and prescribing information will be based on a thorough assessment of relevant data from all stages of drug development, with appropriate attention to dose-dependency, concentration-relationship, and trend-over-time; central tendency analyses of magnitude of effect (e.g., means and confidence intervals); categorical analyses of outlier values; morphological abnormalities; discontinuations and dosage reductions due to QT/QTc prolongation; and pre- or post-marketing adverse events suggestive of proarrhythmia.

The magnitude of the QT/QTc prolongation effect determined for a drug treatment in a particular study is dependent on many factors, including, but not limited to, the following:

- the doses studied
- the exposure achieved (e.g., C_{max}, AUC)
- the subject population (e.g., demographic characteristics)
- the time points at which the ECGs were acquired
- the electrocardiographic equipment
- the methodology of ECG reading
- the method(s) used for defining the baseline QT/QTc interval
- the endpoint(s) used for describing maximum QT/QTc prolongation
- the heart rate correction method(s)

The magnitude of effect that serves as a threshold for regulatory concern may therefore vary depending upon the experimental conditions and the methods used for the acquisition, reading, and analysis of the data.

Question 4: *The ICH E14 guidance contains the following text: "If the 'thorough QT/QTc study' is negative (see section 2.2), the collection of baseline and periodic on-therapy ECGs in accordance with the current investigational practices in each therapeutic field is almost always sufficient evaluation during subsequent stages of drug development." How does Health Canada interpret this statement?*

Answer 4: Evidence of QT/QTc interval prolongation will be an important consideration in determining the intensity of ECG monitoring in subsequent clinical trials. Factors other than QT/QTc prolongation that might also be influential in this regard include, but are not limited to, known or suspected pharmacodynamic effects on heart rate, blood pressure, cardiac conduction, thrombosis, certain laboratory parameters (e.g., electrolytes, lipids, glucose), or cardiac ion channel expression or regulation.