NOTICE

Release of final Health Canada document: Guide for the Analysis and Review of QT/QTc Interval Data

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 implementation 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 *Guide for the Analysis and Review of QT/QTc Interval Data* provides advice relating to the reporting and evaluation of QT/QTc interval data. This document replaces the draft guidance document of the same title. 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:

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Canada

GUIDANCE DOCUMENT
Guide for the Analysis and Review of QT/QTc
Interval Data

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Health Products and Food Branch

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FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada mandates and objectives should be implemented in a manner that is fair, consistent and effective.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document *may be* acceptable provided they are supported by adequate justification. Alternate approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidance documents.

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1.   INTRODUCTION

1.1   Background

The QT interval of the surface electrocardiogram (ECG) consists of the QRS complex, which represents depolarization within the His-Purkinje system and ventricles, and the JT interval, which reflects ventricular repolarization. The QT interval is measured from the initiation of the QRS complex to the termination of the T wave. Because of its inverse relationship to heart rate, the measured QT interval is routinely transformed by means of various heart rate correction formulae into a variable known as the corrected QT interval (QTc) that is intended to be independent of heart rate.

Excessive prolongation of the QT/QTc interval creates an electrophysiological environment that is conducive to torsade de pointes, a polymorphic ventricular tachyarrhythmia that can result in syncope or progress to ventricular fibrillation and sudden cardiac death. Torsade de pointes appears on the ECG as continuous twisting of the QRS complex around the isoelectric line.

ECG data should be analysed for the QT/QTc, PR and RR intervals and the QRS duration. Various alternative ECG repolarization parameters have been suggested, such as the T-end interval (the interval between the peak and the end of the T wave), the JT interval (the difference between the QT interval and the QRS duration), the area under the T wave, and the root mean square T wave. Although clinical experience is presently inadequate to establish the predictive value of these measurements, the use of alternative ECG parameters for exploratory analyses is encouraged.

1.2   Objectives

This document is intended to provide guidance to the pharmaceutical industry, the Therapeutic Products Directorate, and the Biologics and Genetic Therapies Directorate concerning the analysis and review of QT/QTc interval data. This document should be used in association with the following guidelines:

*   International Conference on Harmonisation E14 Guideline: The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. May 12, 2005.

*   Health Canada Guidance Document: QT/QTc Interval Prolongation: Guidance for Product Monograph Content. September 6, 2006.

1.3 Scope

The recommendations contained in this guidance document are applicable to the submission and review of QT/QTc data contained in New Drug Submissions and Supplemental New Drug Submissions.

2. EXPOSURE DATA

A clinical pharmacology study dedicated to the assessment of ECG safety is an expected component of the development programme for almost all new drugs. This dedicated ECG assessment study should investigate both therapeutic and supratherapeutic doses, unless precluded by considerations of tolerability, absorption, or safety. The premise underlying the ECG assessment study is that exposure of healthy volunteers to sufficiently high concentrations of an investigational drug is likely to disclose QT/QTc prolongation that might be observed in patients with risk factors for proarrhythmia. Evidence of dose- and concentration-dependency is, of course, a powerful argument for a treatment relationship; however, unusual dose-response curves (*e.g.*, flat or bell-shaped) have been reported for some QT/QTc-prolonging drugs.

The supratherapeutic dose selected for the ECG assessment study should be the maximal dose that can be administered with acceptable safety and tolerability or the dose at which absorption becomes saturated. The exposure (C_{max}, AUC) achieved in the ECG assessment study should be compared with corresponding values in the target patient population and subjects with compromised elimination (*e.g.*, drug-drug interactions, phenotypic/genotypic poor metabolizers, elderly, renal impairment, hepatic impairment). For example, a summary figure could be provided in which C_{max} and AUC data for the ECG assessment study and other relevant trials are presented as parallel box plots to facilitate comparisons of exposure. The figure could include simulations of exposure in situations of combined risk factors (*e.g.*, renal impairment and CYP3A4 inhibition). Similar figures should be provided for metabolites of interest.

Ideally, the exposure achieved at the supratherapeutic dose in the ECG assessment study should cover and exceed the maximal anticipated clinical exposure in patients with compromised elimination. 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 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. In some cases in which gastrointestinal tolerability or absorption proves to be exposure-limiting, the co-administration of metabolic inhibitors can be used to achieve supratherapeutic concentrations if the investigational drug is a sensitive substrate for a particular drug-metabolizing enzyme (*e.g.*, CYP3A4 or CYP2D6). This approach will be suitable only when major metabolites of the parent compound do not have an important role in contributing to the QT/QTc prolongation effect. Use of pharmacological inhibitors has the possible disadvantage of introducing confounding effects on the parameters of interest, whether through effects of ion channel function or haemodynamics.

Exposure-response modelling is encouraged and can often be of assistance in interpreting the results of the ECG assessment study; however, concentration-effect relationships can be complex when metabolites contribute to QT/QTc prolongation, when the drug affects multiple cardiac ion channels, or when there is a hysteresis effect due to delayed tissue penetration or interference with ion channel trafficking.

3.   HEART RATE CORRECTION

The QT interval has an inverse relationship to heart rate. For this reason, various formulae are used to correct the QT interval for the influence of heart rate. Ideally, a scatter plot of the derived QTc versus RR values should generate a horizontal linear regression line (slope=0), indicating independence of the QTc intervals from the RR values. The scatter plot should be constructed from ECG data collected during the drug-free state. For a crossover study, this would be the placebo data and possibly baseline data. For a parallel arm study, baseline data should be used in the scatter plot, but not placebo data, as inclusion of placebo data would result in an unequal representation of the subjects in the study population.

The heart rate correction formula currently used in clinical practice is Bazett's formula:

$$QTc=QT/RR^{0.5}$$

Unfortunately, this formula provides an underestimation of the QTc interval at low heart rates and an overestimation at high heart rates.

Fridericia's formula is now recognized to be a more suitable choice of heart rate correction formula:

$$QTc=QT/RR^{0.33}$$

Although Fridericia's formula yields QTc values that exhibit less heart rate dependency than those computed using Bazett's formula, both of these formulae share the limitation of assuming that a constant heart rate correction coefficient can be applied to diverse populations and individuals.

Population- and individual-specific regression models are sophisticated approaches to correcting the QT interval for heart rate. These methods involve applying linear or non-linear regression modelling to scatter plots of drug-free QT and RR data. In the population-specific regression model, a single scatter plot is generated, using QT and RR pairs from all subjects in a specific study or group of studies. In the individual-specific regression model, a scatter plot of QT and RR pairs is generated for each subject.

The slope parameters (m) determined from these plots are then used as population- or individual-specific coefficients for heart rate correction of the baseline and on-treatment data for each subject according to the following models:

linear regression model: $QTc = QT + m(1 - RR)$

 or

non-linear regression model: $QTc = QT/RR^m$

For the individual-specific regression approach to be reliable, the range of heart rates during active treatment should match that observed during the drug-free period. A very large set of drug-free QT-RR measurements (*e.g.*, 400 QT-RR pairs) should be available for each study participant, with the RR values covering a wide range (*e.g.*, 600 to 1000 ms). Sponsors using this approach should be prepared to demonstrate the extent to which these criteria were met in their studies. In the setting of a clinical pharmacology laboratory, where ECGs are collected from resting subjects, the range of heart rate values is often not adequate to support this heart rate correction method.

The RR bin method of controlling for heart rate involves distributing QT values according to their preceding RR interval into 'bins' encompassing a pre-defined range. For example, the QT_{1000}, determined from the 995-1004 ms RR bin, is an estimate of the QT interval at 60 bpm. By averaging values collected over a range of time points, this approach results in under-estimation of the maximum QT/QTc prolongation effect. Furthermore, the RR bin method is not amenable to the examination of time course or concentration-effect relationships and is therefore suitable only as an auxiliary analysis.

For any given study, the QT data set should be corrected for heart rate using Fridericia's formula and Bazett's formula, as well as additional methods chosen by the sponsor. The endpoints of interest should be computed for each of the resulting QTc data sets. The methods used to correct or control for heart rate can lead to considerable differences in the apparent magnitude of the effect. Explanations should be offered for any discrepancies in results between the different heart rate corrections.

4.   ANALYSES OF CENTRAL TENDENCY FOR QT/QTc INTERVAL DATA

For all treatment arms, the QT/QTc value at each time point should be expressed in terms of a mean, a mean change from baseline (ΔQT), and a standard deviation. To facilitate assessment of a possible time course relationship, both tabular and graphical presentations of these data should be provided. ECGs should be collected from resting, supine subjects. The QT/QTc interval should be computed on the basis of multiple complexes from replicate (≥ 3) ECG recordings within a time period of ≤ 4 minutes,

encompassing each nominal time point. For parenterally administered drugs that result in rapid changes in the QT/QTc interval, the averaging of results from replicate ECGs may not be appropriate.

The new drug will be compared to the placebo and active control treatments in terms of the differences of means at serial post-dose time points. A small mean increase in the QT/QTc interval, which appears not be clinically significant in itself, may nonetheless signal an enhanced risk with the investigational drug, if not matched by a corresponding change in the placebo control group. The magnitude of the effect is determined as the difference between the time-matched, baseline-adjusted QT/QTc values for the drug and placebo treatments. This point estimate should be accompanied by the two-sided 90% confidence interval.

Many different methods are currently in use for computing the baseline QT/QTc value, including, but not limited to, the following:

- time-matched baseline: baseline QT/QTc values from replicate ECGs recorded at time points scheduled to match the on-treatment recordings for each treatment arm during the 24 hour period preceding treatment administration

- time-averaged baseline: average of all baseline values, usually recorded at time points scheduled to match the on-treatment recordings for the treatment arm, during the 24 hour period preceding treatment administration

- pre-dose baseline: baseline value obtained on day of treatment initiation (*e.g.*, average from ECGs at several time points during the hour preceding treatment administration on the first day of treatment)

In a crossover study, period-specific baseline values are needed to provide information on possible carryover effects. Use of a pre-dose or time-averaged baseline assumes that there is no diurnal pattern in QT/QTc changes; whether this is adequately compensated for, in a crossover study, by a time-matched placebo-adjustment is not known. Use of time-matched baselines assumes that diurnal variations in the QT/QTc are reproducible from day to day within individuals.

In a parallel group study, a full day of time-matched replicate baseline values is usually preferred to account for within-subject diurnal patterns; however, in situations where diurnal patterns in the placebo group do not appear to be reproducible, a time-averaged baseline might be more suitable.

In some cases, adjustment of the same data set using a variety of methods for the baseline computation has been found to yield quite different results for the endpoints of interest. The method(s) used for a given study should be prospectively defined and justified with a convincing rationale.

4.1   Endpoints for Analyses of Central Tendency in Clinical Pharmacology Studies

The primary endpoint of interest will be the maximum increase in the QTc interval. The optimal approach for quantifying peak QT/QTc prolongation is not a simple matter and may in fact be dependent on the pharmacokinetic and pharmacodynamic characteristics of the investigational drug in question. The recommendations in this section are intended primarily for clinical pharmacology studies in which multiple replicate ECGs have been collected over the course of a dosing interval.

4.1.1   Maximum Mean QT/QTc Increase from Baseline

When time profile plots of the change in the QT/QTc interval show an obvious trend-over-time relationship, an appropriate estimate of the maximum QT/QTc prolongation effect can often be obtained at the time point at which the placebo-adjusted increase from baseline is greatest for each treatment arm (*i.e.*, the mean placebo- and baseline-adjusted QT/QTc value at the time point when the one-sided 95% confidence interval upper bound is maximal). The time point at which this increase occurs may be different for each treatment arm and should be specified. Time-matched placebo adjustments of this endpoint can be performed with comparable ease for both crossover and parallel arm studies.

To support the use of this endpoint for a drug that shows a trend-over-time for QT/QTc prolongation, the sponsor should be able to demonstrate that the time of maximum effect for individual subjects generally coincides with the time of maximum effect for the treatment arm, for example by using a frequency distribution analysis of the number of subjects who experienced maximum QT/QTc prolongation at each time point. Erroneous conclusions could result if the time course of QT/QTc prolongation is subject to considerable inter-individual variation, perhaps due to variable rates of absorption, distribution, and/or production of active metabolites between study participants. Furthermore, conclusions based on such an endpoint might be misleading if an isolated, spurious, suprathreshold spike occurs at a single point on an otherwise rather flat time profile plot, with no obvious concentration relationship.

In these cases, it would be preferable to consider summary statistics based on data that were collected at time points which can vary between subjects depending on the pharmacokinetic and pharmacodynamic characteristics of the drug in each individual.

4.1.2   QT/QTc Change at the Subject-Specific C_{max}

Computation of the mean change in the QT/QTc interval at the subject-specific peak plasma concentration (C_{max}) involves determining the C_{max} for each subject, then identifying the change from baseline in the QT/QTc interval at the time point that coincides with or immediately follows the C_{max} value. In a crossover study, a time-matched, within-subject placebo adjustment would be performed. The baseline- and placebo-adjusted change in the QT/QTc at C_{max} would then be averaged for all subjects in the treatment arm. In a parallel group study, the median T_{max} for each active treatment arm could be used to select the time point in the placebo arm to use for the adjustment.

This endpoint will be useful only if the maximum increase in the QT/QTc interval coincides with peak plasma concentrations. Results will be misleading if there is a substantial lag phase between the peak plasma concentration and maximum QT/QTc prolongation due to the contribution of active metabolites, delayed distribution to myocardial tissue, or effects on ion channel trafficking or expression. To support the use of this endpoint, the sponsor should be able to demonstrate a strong temporal correlation between peak plasma concentration and maximum QT/QTc prolongation for means and individual subject data, using superimposed time profile plots for plasma concentration and change in QT/QTc or hysteresis plots of concentration versus change in QT/QTc.

4.1.3   Maximum Individual QT/QTc Increase from Baseline

Another commonly used endpoint is the mean of individual maximum QT/QTc interval increases (or minimum decreases for individuals who did not experience an increase, *i.e.*, the placebo- and baseline-adjusted QT/QTc that is closest to zero). This approach involves examining the on-therapy placebo- and baseline-adjusted QT/QTc values for all time points for each individual and selecting the upper limit of the range to use in computing the mean maximum increase for the treatment arm. This endpoint is suitable for crossover studies in which time-matched, within-subject placebo adjustment is possible. Despite the upward biasing inherent in selecting extreme values, this approach might be appropriate for some drugs that have considerable inter-individual variability in the time course of QT/QTc prolongation and a substantial delay between

the C_{max} of the parent compound and the peak QT/QTc prolongation, such that alternative endpoints lead to an under-estimation of the magnitude of the effect. An inspection of QTc time profile plots and hysteresis plots of concentration versus QT/QTc may be useful in determining whether the observed individual maximum values show a time- and concentration-relationship that is consistent with a drug effect. The selection of extreme values would, of course, be expected to result in higher variability than for other endpoints.

4.1.4   QT/QTc Change at the Pharmacokinetic T_{max} for the Population

Another endpoint that has been used in some ECG assessment studies is the placebo- and baseline-adjusted change in the QT/QTc interval at a protocol-defined time point, representing the observed or expected pharmacokinetic T_{max} for the population. This approach is discouraged, as it will yield erroneous results if there is substantial inter- individual variability in the pharmacokinetic T_{max} or a lag phase between peak plasma concentrations and maximum QT/QTc prolongation. As the T_{max} often varies between studies, choice of this time point on the basis of experience with previous clinical trials is inappropriate, especially when applied indiscriminately to treatment arms receiving other drugs or doses.

4.1.5   Time-Averaged QT/QTc Intervals

Analyses of the mean time-averaged change in the QT/QTc interval are of limited value for clinical pharmacology studies in which multiple ECGs have been collected over the course of a dosing interval. Time-averaging involves computing an average of all baseline- and placebo-adjusted QT/QTc values over a range of time points. Time- matched placebo adjustment of this endpoint can be performed with comparable ease for both crossover and parallel group studies. However, the time-averaging approach ignores concentration-effect and time course relationships and under-estimates the magnitude of the drug effect. With time-averaging, the summary statistic obtained will be critically dependent on the scheduling of the ECG recordings, such that very different means could be computed for the same treatment, depending on the time points studied. For example, the scheduling of several recordings near or subsequent to the offset of the effect would dramatically reduce the average computed.

4.1.6 Integration of Data Regarding Magnitude and Time Course of QT/QTc Prolongation

Two drugs might have similar maximum effects on QT/QTc prolongation, but differ in terms of the rate of increase or the duration of time over which the increase is sustained. Conceivably, such considerations might provide a partial explanation for apparent differences in proarrhythmic potential between drugs or administration routes, despite similar maximum effects on QT/QTc prolongation. Therefore, in addition to comparing peak effects between treatment arms, attention should be directed to features of the time-effect curve, such as the range of time points over which the QT/QTc interval is prolonged in relation to the placebo treatment.

An integrated approach to quantifying the magnitude and duration of the effect is calculation of the area under the QT/QTc interval time curves (AUCs) for on-therapy versus pre-therapy measurements. Successful use of the AUC is dependent on synchronization of the ECG measurement schedule for both the baseline and treatment phases. Experience with this approach is limited and interpretation of QT/QTc AUC values is complicated by the absence of well-recognized criteria for distinguishing clinically relevant absolute or delta values. Therefore, AUC computations in drug submissions are considered subsidiary to more established data analyses.

4.1.7 General Considerations

As the optimal endpoint for quantifying peak QT/QTc prolongation will vary depending on the pharmacokinetic and pharmacodynamic characteristics of the drug, the sponsor should provide placebo- and baseline-adjusted results for the maximum mean increase (see Section 4.1.1) and the mean change at the subject-specific C_{max} (see Section 4.1.2). To enable an appreciation of the worst case scenario, the mean of the maximum individual QT/QTc increases should be provided as a follow-up analysis when the aforementioned endpoints suggest cause for concern (see Section 4.1.3). A discussion of possible explanations for any discrepancies between the different endpoints should be provided. Confidence in an outcome will be increased when multiple analyses yield congruent results and when positive control agents produce signals of a magnitude that corresponds closely with expectations based on historical experience with the drug and dose in question. Complex situations can be anticipated, in which the effects of the investigational drug are better described by one of the aforementioned endpoints, while another endpoint more appropriately characterizes the effects of the positive control or reference agent(s).

Sub-group analyses based on age, gender, or poor/extensive metabolizer status often prove to be informative.

Quality control/quality assurance reports from the central laboratory that performs the ECG readings should be provided as appendices to the study reports.

4.1.8   Interpretation of Magnitude of Effect

The estimate of maximum QT/QTc interval prolongation for a treatment in a given study is dependent on many factors, including, but not limited to, the following:

- the subject population (*e.g.*, demographic characteristics)
- the dose and duration of treatment
- study conditions (*e.g.*, duration of resting period, schedule of food ingestion)
- the exposure achieved (*e.g.*, C_{max}, AUC)
- the choice of time points
- the electrocardiographic equipment used
- the methodology of ECG reading
    - the lead(s) selected
    - the use of raw or superimposed complexes
    - the conventions used for determining T wave offset
    - the inclusion or exclusion of large U waves in the interval measurement
- the aptitude of the ECG readers
- the method(s) used for defining the baseline QT/QTc value
- the endpoint(s) used for determining maximum QT/QTc prolongation
- the heart rate correction method(s)

The unavailability or inconsistent quality of data on the magnitude of peak QT/QTc prolongation for drugs of known proarrhythmic potential presents a problem when making regulatory judgements concerning small signals near the limit of study sensitivity. Even drugs that produce relatively modest prolongation of the QT/QTc interval at therapeutic doses or low multiples thereof have been associated with events of torsade de pointes when used in patients with underlying risk factors. Regulatory judgements concerning QT/QTc prolongation potential are based on the evaluation and integrative interpretation of the pattern of results across several groups of measures.

4.2 Analyses of Central Tendency for QT/QTc Data in Phase II and III Clinical Trials

For therapeutic clinical trials in which ECGs were collected at periodic time points over the course of extended treatment, an analysis of change from baseline should be presented for all time points at which ECG assessments were performed. The active treatment groups should be compared with the concurrent placebo treatment group, with attention to the point estimate and the upper bound of the two-sided 90% confidence intervals at each time point. Comparisons with active control treatments are also important, especially if a placebo group is unavailable. The mean of the maximum individual on-therapy increases from baseline in each treatment group should also be computed. Presentation of an analysis of the mean time-averaged change from baseline would be acceptable only for studies in which the ECG recordings were obtained during fixed dose treatment under steady-state conditions, with no evidence for a sustained increase or decline in the effect over the course of continued treatment. In some cases, conclusions based on data for a particular time point might be acceptable, if supported by a convincing rationale (*e.g.*, single dose parenteral use; short duration of treatment, with only one ECG assessment performed at steady-state; or very long duration of treatment, such that ECGs at late time points are unlikely to be comparable to baseline ECGs due to progression of the underlying disease process). QT/QTc data that are limited to the change from baseline to final evaluation are of little value if they include ECGs collected after the last day of treatment with the study drug.

Quality control/quality assurance reports from the central laboratory that performs the ECG readings should be provided as appendices to the study reports.

5. CATEGORICAL ANALYSES OF QT/QTc INTERVAL DATA

In addition to analyses of central tendency, categorical analyses should be performed to gain an impression of the proportion of study participants who exceed predefined upper limit values. Categorical analyses can also be useful to characterize the susceptibility of certain population sub-groups (*e.g.*, females, poor metabolizers). Outlier thresholds can be defined in terms of absolute QTc intervals or change from baseline (delta) values. Absolute interval flags are QTc values in excess of some specified threshold value. Delta flags occur when the change from baseline in the absolute QTc interval is greater than some predefined value.

The interpretation of categorical analyses of absolute interval and delta flags presents certain challenges. The absolute QTc interval for a particular cardiac cycle will be highly dependent on the methods used for reading the interval and performing heart rate correction. For example, a QT interval reading method that determines the interval on the basis of earliest QRS onset to latest T wave offset in any of twelve simultaneously displayed leads would be expected to yield more absolute interval outlier flags for a given data set than a method using only one lead.

Delta values have the advantage of being less dependent on reading method. Interpretation of categorical analyses for delta flags is, however, complicated by regression toward the mean. Regression toward the mean is a measurement phenomenon, resulting from imperfect correlation between the baseline and post-dose measurements, such that individuals having baseline QTc intervals above the mean will tend to have smaller increases from baseline than individuals with baseline QTc intervals below the mean, regardless of a treatment effect. This phenomenon is occasionally exploited inappropriately as apparent evidence that individuals with high baseline QTc values are less susceptible to drug-induced QTc prolongation than those with lower values. Use of baseline values that are calculated from multiple measurements, rather than single readings, can reduce the effects of regression toward the mean.

For both absolute interval and delta flags, the incidence of noteworthy outlier values will be dependent on the number of ECGs recorded over the treatment period and their scheduling in relationship to the time course of QTc prolongation. Comparisons with concurrent placebo and active control treatments are important to place these findings in a meaningful context. Analyses should be provided for the number and percentage of subjects with suprathreshold values (*i.e*., # subjects with outlier values/total # subjects per treatment arm). Analyses of the number and percentage of ECGs that exceeded threshold values (*i.e.*, # outlier ECGs/total # ECGs per treatment arm) are often informative as well.

Consensus within the scientific community concerning the choice of thresholds for absolute QTc intervals and change from baseline values has remained elusive. While lower limits increase the background rate of abnormal findings, higher limits increase the risk of failing to detect a signal. Multiple analyses using different threshold values are a reasonable approach to this controversy:

Absolute QTc Interval Thresholds

> QTc >450 ms
> QTc >480 ms
> QTc >500 ms

Change from Baseline (Delta) Thresholds

> QTc increase from baseline >30 ms
> QTc increase from baseline >60 ms

These threshold values for outlier analyses are based on experience with Bazett's corrected QTc data. Unfortunately, QTc data corrected by Bazett's formula often do not correspond closely to QTc values corrected using other formulae currently in use. Owing to concerns about the inaccuracy of Bazett's correction, especially at low or high heart rates, corresponding outlier thresholds for data corrected using Fridericia's formula would be highly desirable.

As noted previously, the incidence of abnormal values will also vary with the methods used to read the QT interval. While it is difficult to declare any particular reading method superior to another, a standardized approach for regulatory purposes would facilitate the identification of outlier thresholds that could be applied consistently between studies and drug development programmes.

Sample size determinations for the dedicated ECG assessment studies are computed based on the ability to exclude a predefined change in the mean QTc interval. As these studies are not powered to detect outliers, the absence of extreme values should not necessarily be considered reassuring.

6. ANALYSES OF ECG MORPHOLOGY

Morphological abnormalities in the ECG waveform should be described and the data presented in terms of the number and percentage of subjects in each treatment arm who had changes from baseline that represented the appearance or worsening of the morphological abnormality. When a treatment-emergent effect is evident for abnormal U waves or T waves, an analysis of the number and percentage of abnormal ECGs might also be informative.

Attention should be directed to the appearance of abnormal U waves and changes in T wave morphology that might be indicative of delayed repolarization, such as double humps ("notched" T wave), indistinct terminations (TU complex), delayed inscription (prolonged isoelectric ST segment), widening, flattening, and inversion. T wave alternans (beat-to-beat variability in the amplitude, vector, and/or morphology of the T wave) is considered to be a harbinger of ventricular arrhythmias.

While the predictive value of morphological analyses is not well characterized, shifts in the incidence of abnormalities between treatment arms have proved to be informative.

7. INTEGRATED ANALYSES OF ECG DATA

When cause for concern has been identified on the basis of the dedicated ECG assessment study or other ECG or adverse event data, integrated analyses can provide useful information on the adequacy of the ECG safety database in terms of the total number of patients receiving ECG evaluations, as well as overall estimates of mean changes and the incidence of outlier values. Analyses of pooled ECG data from several clinical trials are appropriate, provided that the assessment procedures were of comparable rigour. Standardization of the ECG collection schedule (*e.g.*, number and frequency of visits, timing of ECG recordings in relation to dosing) for similar studies within a clinical trial programme will facilitate pooled analyses. The clinical trials used in the generation of such analyses should be clearly identified and their inclusion justified. The data from certain trials or treatment groups may be inappropriate for pooling, if the study conditions were not representative of the proposed clinical use. For example, if the pooling results in the inclusion of data from many patients receiving sub-therapeutic doses of the drug, the magnitude of QT/QTc prolongation and the incidence of outliers at the recommended therapeutic doses would be underestimated. To avoid variability introduced by

investigators operating from different regions and centres, the ECGs used for the integrated analysis should be assessed by a central laboratory where a uniform methodology for reading and interpretation can be enforced. If the reading method has a computerized component, the same algorithm for ECG interval readings should be used across all studies.

Sub-group analyses of the pooled QT/QTc data from the phase II and III clinical trials are desirable for drugs that delay ventricular repolarization. Sub-group analyses for gender, age (e.g., <18 years, ≥65 years), cardiac co-morbidities, hepatic impairment, renal impairment, and other special patient populations are recommended. Such sub-group analyses should be provided for both analyses of central tendency and categorical analyses. For many special populations, such as renal and hepatic impairment, the number of patients in phase II and III trials will often be too small to permit meaningful sub-group analyses. The inclusion of intensive ECG monitoring in the pharmacokinetic studies performed in these special populations will often provide the best opportunity to examine drug-disease interactions affecting QT/QTc prolongation.

8.   CONCLUSIONS

Regulatory decision-making concerning drugs that cause QT/QTc prolongation should be based on a careful assessment of relevant data from all stages of drug development, with appropriate attention to evidence of dose-dependency, concentration-relationship, and trend-over-time; central tendency analyses of magnitude of effect; 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. This process involves the evaluation and integrative interpretation of the pattern of results across several groups of measures and multiple clinical trials.

The acquisition, reading, and analysis of QT/QTc data are currently subjects of intensive discussion and research activity. The recommendations contained in this guidance document might undergo modification in the future to reflect new developments in these areas.