Commentary

ICH E14 Q & A (R1) document: perspectives on the updated recommendations on thorough QT studies

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The International Conference on Harmonization (ICH) guidance ICH E14 provides recommendations, focusing on a clinical 'thorough QT/QT_c (TQT) study', to evaluate the QT liability of a drug during its development. An Implementation Working Group (IWG) was also established to assist the sponsors with any uncertainties and clarify any ambiguities. In April 2012, the IWG updated its June 2008 version of the Questions and Answers document to address additional issues. These include the gender of the study population, a reasonable approach to evaluating QT_c changes in late stage clinical development and the recommended approach to correcting the measured QT interval. This commentary provides our observations and, when appropriate, recommendations, on these issues. We review briefly evidence that suggests that (i) the greater QT effect observed in females is not entirely related to differences in drug exposure and (ii) the Fridericia correction of measured QT interval is adequate for a majority of TQT studies. Until further evidence suggests otherwise, we recommend balanced gender representation in TQT studies, unless warranted otherwise, and for positive studies, subgroup analysis of key data by common demographic variables including the gender and ethnicity. We provide a general scheme for ECG monitoring in late phase clinical trials and consider that while intensive monitoring and centralized reading of ECGs in late phase clinical trials is the norm when a TQT study is positive, there are other circumstances that also call for high quality ECG reading. Therefore, locally read ECGs should only be acceptable as long as accurate high quality ECG data can be guaranteed.

Introduction

Under the auspices of International Conference on Harmonization (ICH), the regulatory authorities of the European Union (European Medicines Agency), Japan (Pharmaceutical and Medical Devices Agency) and the United States (Food and Drug Administration, FDA) adopted in May 2005 two internationally harmonized guidance notes, ICH S7B and ICH E14 [1, 2]. Whereas ICH S7B provides guidance on preclinical strategy, ICH E14 deals with the strategy for the clinical evaluation of the QT_c liability of a drug. ICH E14 focuses on the need during drug development to conduct a 'thorough QT/QT_c study', popularly referred to simply as a TQT, which is typically conducted in healthy volunteers as the primary method for evaluating the potential effect of non-cardiac agents on cardiac repolarization [2]. To allow some flexibility, the guidance adopted in 2005 is deliberately not overtly too prescriptive. Recognizing that with advances in science and experience, the ICH E14 guidance may require revision, the ICH Steering Committee also established an Implementation Working Group (IWG). Although the identities of some of original members have

changed with time, the current members of IWG nominally represent ICH Expert Working Groups that drafted the original ICH S7B and ICH E14 guidance notes. This includes representatives from the industry organizations and regulatory authorities of the three ICH regions. This group later issued a Questions and Answers (Q & A) document in June 2008, providing clarity on some aspects of the guideline that were ambiguous and responding to others on which there were uncertainties [3].

Recently in April 2012, the Q & A document has been updated further [4] to include responses to four new questions. These concern (i) the gender of the subjects enrolled and whether the study should be powered to detect gender-related susceptibility, (ii) the sponsor's approach to incorporating new technology or validating new methodology into the measurement and/or analysis of TQT, (iii) whether there was now a reasonable approach to evaluating QT_c changes in late stage clinical development when QT prolongation has been detected prior to late phase studies and (iv) any recommended approach to correction of the measured QT interval that may be different from that recommended in the original ICH E14 guidance.

Based on our experience, review of a large number of TQT studies and published literature as well as review documents available on the FDA website, this short commentary provides our observations and, when appropriate,

*The views expressed in this paper are those of the authors and do not necessarily reflect the views or opinions of their affiliates, any regulatory authorities or any of their advisory bodies.

recommendations, on the IWG responses to the above four questions. The commentary concludes by identifying other equally important issues that require the attention of the IWG.

Gender-related QT susceptibility

The updated Q & A document points out that post-pubertal males have shorter QT_c intervals than do pre-pubertal males or females generally. It goes on to explain that (i) because women are generally smaller than men, their exposure to a given fixed dose of a drug will generally be higher, and, if a drug prolongs QT, it can be expected to prolong it more in women because of the higher exposure, (ii) it is not settled whether and how often there are gender differences in response to QT-prolonging drugs not explained by exposure alone and (iii) it is unlikely that any of a variety of baseline demographic parameters would introduce a large difference in QT response to a drug in subpopulations defined by age, co-morbidity and gender. Therefore, the IWG encourages, but does not mandate, sponsors to include both men and women in the TQT study and analyses of concentration–response relationship by gender in cases where there is evidence or mechanistic theory for a gender difference. If the primary analysis is negative and if there is no other evidence suggesting gender differences, subgroup analysis by gender is not expected. It emphasizes that the primary analysis of a thorough QT study should be powered and conducted on the pooled study population.

There are not many published studies that specifically address the reasons for gender differences in QT effect of a drug. The vast majority of these studies show the QT response in females is greater but do not correlate this finding with any possible differences in exposure if any, namely, exposure–response (E–R) relationships in the two genders. What evidence is available argues for and against the presence of such a difference at a pharmacodynamic level.

In a study with intravenous infusion of moxifloxacin, the post-infusion peak $\Delta\Delta\text{QT}_c$ values (corresponding to maximum plasma concentrations) were not statistically different in women (16.1 ± 6.5 ms) and men (15.1 ± 5.3 ms). Although the population mean $\Delta\Delta\text{QT}_c$ changes closely followed mean plasma concentration kinetics ($4.8 \text{ ms } \mu\text{g}^{-1} \text{ mL}^{-1}$), the individual post-infusion peak $\Delta\Delta\text{QT}_c$ was not related to individual peak plasma concentrations but was strongly related to body mass index [5]. In a pooled analysis of data on oral moxifloxacin from 20 TQT studies, women had a statistically significant larger moxifloxacin-induced QT prolongation compared with men, although there were no differences in E–R slope estimates between men and women [6]. These differences in $\Delta\Delta\text{QT}_c$ were explained on the basis of gender-related differences in drug exposure since women had about 40% higher observed maximum moxifloxacin concentrations. Pharmacokinetic

modelling indicated that body weight alone explained these observed differences in pharmacokinetics. One early study with intravenous d-sotalol reported that there were no detectable differences between genders in Hill coefficient, concentration at half the maximal QT_c prolongation from baseline or maximum prolongation from baseline, nor were there differences in the pharmacokinetics of the drug between men and women, suggesting that the longer QT_c intervals observed in women after administration of d-sotalol might have resulted from their longer baseline QT_c interval rather than increased pharmacologic sensitivity [7]. Consistent with this, a more recent E–R study, also with intravenous sotalol, reported that (i) QT_c and serum sotalol concentration strongly correlated and (ii) an upward shift of the regression line in females indicated a longer QT_c at any concentration [8]. In this study, males had greater body weight and body surface area than females but neither correlated with QT_c or predicted QT_c prolongation. These four studies appear to rule out a true gender-related pharmacodynamic difference in QT response. However, an explanation based solely on differences in exposure does not entirely explain why moxifloxacin-induced greater QT prolongation in females is more marked in crossover studies than it is in parallel design studies [9].

Sex hormones have profound influences not only on the pharmacokinetics of some drugs but also on cardiac repolarization and therefore, we would caution against a general application of conclusions from the above studies to all other drugs. The overall pharmacological evidence that may explain longer baseline QT_c intervals, and also the presence of a true pharmacodynamic QT susceptibility, in females is briefly summarized below:

- Females seem to have diminished repolarization reserve compared with males. Male and female human hearts have been reported to have significant differences in ion channel subunit composition, with female hearts showing decreased expression for a number of repolarizing ion channels [10], thus predisposing them to greater effects. Physiological concentrations of 17 β -oestradiol have been reported to suppress partially IKr current and hERG channel. Mutagenesis studies have revealed the common drug-binding residue at the inner pore cavity of hERG channel (F656) is critical for this effect. Furthermore, 17 β -oestradiol enhanced both hERG suppression and QT_c prolongation by E4031 [11].
- Progesterone has been reported to disrupt hERG trafficking [12] whereas testosterone is thought to increase IKr current and suppress L-type calcium currents.
- Oestrogen is reported to account for the QT interval prolongation in several studies conducted with hormone replacement therapy in post-menopausal women. In healthy post-menopausal women, hormone replacement therapy with oestrogen alone usually produces a prolongation of QT interval, while oestrogen plus progesterone has no significant effects on QT interval [13].

Clinically, other studies also contradict a purely exposure-related explanation. In a study investigating the effect of low dose intravenous ibutilide, maximum increase in QT_c interval was greater in females than in males, despite a lack of gender-related difference in plasma ibutilide concentrations [14]. Similarly, after a single oral dose of quinidine, maximum prolongation of QT_c interval was significantly greater in women (33 ± 16 vs. 24 ± 17 ms) although there were no gender differences in the pharmacokinetics of the drug [15]. In this particular study, maximum quinidine concentrations in females were slightly lower than in males (871 ± 57 vs. 997 ± 56 ng ml⁻¹, respectively). Furthermore, one published study has reported on quinidine-induced gender differences by analysis of E–R relationship. This approach eliminates the effect of any differences in exposure. The slope of this relationship was 44% greater in women than in men (mean 42.2 vs. 29.3 ms μg^{-1} ml⁻¹) [16]. Vemurafenib is a tyrosine kinase inhibitor with mild to moderate QT-prolonging potency (largest mean $\Delta\Delta\text{QT}_c$ effect of 11.9 ms with 90% confidence intervals of 9.1 to 14.8 ms). In an E–R analysis of vemurafenib-associated QT_c effect by gender, the mean slope was about 30% greater in female patients compared with male patients [17].

The IWG acknowledges that it is not settled whether and how often there are gender differences in response to QT-prolonging drugs not explained by exposure alone. Therefore, we believe that it would be unwise at present to dismiss the probability of gender-related differences in QT response. It is intuitive that difference in QT response between two subgroups may be more evident during high intensity situations such as high doses or greater potency of the QT-prolonging drug. Since the data available at present are limited, there is a need to investigate this issue further by careful analysis of data for gender-related difference in E–R relationships. Whilst such an analysis will be unrewarding in most cases since the majority of drugs have little effect on QT_c interval, this subgroup analysis should be routinely pursued when the TQT is positive. Since the outcome of a TQT cannot be known in advance, a TQT should be well balanced at the outset in terms of gender enrolment unless the preclinical toxicology of the drug or its indication dictates otherwise.

New technologies and analytical methods

We fully endorse the view of the IWG that the ICH process is better suited to the determination of regulatory policy once the science in a particular area has become more or less clear and that in general, it is not well-suited to the qualification or validation of new technology.

We are, however, disappointed to note that the Q & A document suggests that 12-lead continuous recording devices have largely supplanted cart recorders in TQT

studies without a formal validation process. Collaboration between a core ECG laboratory, Pharmacia Phase I unit and Mortara Instruments and the Cardio-Renal Division of the FDA allowed for the conduct of a trial that employed a QT prolonging agent in healthy volunteers with dual snap electrodes to record ECGs by both recording methods simultaneously and to subject them to different analysis methods. This study showed that the manual ECG measurements by both recording techniques produced identical results for heart rate and QT duration data across a wide range of QT measurements, thus validating the use of this new technology to make possible the robust determinations required in the TQT [18].

We fully support the IWG for maintaining their previous position that although automated methods have the advantage of being consistent and reproducible, they can yield misleading results in the presence of noise or when dealing with abnormal ECG rhythms, low amplitude T waves or overlapping U waves. As the Q & A document explains, the techniques used for construction and measurement of representative waveforms and global waveforms vary between different computerized algorithms and between different software versions within individual equipment manufacturers. As a result, between-algorithm and within-manufacturer variability of fully automated measurements can confound serial comparisons when the equipment or algorithm is not constant. Kasamaki *et al.* compared the QT intervals of all leads for a selected single heart beat between automated measurement with the new software from Fukuda Denshi and manual measurement [19]. These investigators reported that variability was related to the T wave amplitude and to setting the baseline and tangent in the tangent method of determining the offset of T wave. Drift, low amplitude recordings and T wave morphology were problems for both methods they compared. Tyl *et al.* have also reported that newer automated algorithms for QT measurements are highly reliable in normal tracings, although electrocardiogram abnormalities increased the risk of QT measurement errors [20].

Since QT interval is one of the many parameters that reflect changes in ventricular repolarization, we would encourage sponsors to include an exploratory analysis (with no regulatory consequences if accepted by the regulatory authority) of the effect of a drug on these novel parameters such as T wave morphology combination score (MCS), T wave alternans, Tpeak-Tend (Tp-Te) interval, Tp-Te:QT ratio and early and late T wave vectors. As it concerns validation of new techniques and methodologies, the main tool for validation is the use of a positive control. Thus, if a sponsor intends to use newer approaches in phase III studies, a TQT provides an opportunity of validating these approaches using the positive control. However, there is no simple means of studying whether the positive control provides a high enough hurdle for reliable and robust validation to enable the routine use of these novel approaches.

ECG monitoring in late phase clinical trials

We believe three issues need addressing with regard to ECG monitoring in late phase clinical trials. These are (i) intensive vs. routine monitoring, (ii) automated vs. manual readings and (iii) local vs. central reading of ECGs. Having already discussed above the limitations of automated readings, we discuss the other two issues below.

Sponsors would no doubt welcome the guidance provided in the updated Q & A document regarding the criteria for and the extent (routine vs. intensive) of ECG monitoring in late phase clinical trials when there is preceding evidence of QT prolongation by the investigational drug. While intensive ECG monitoring is the norm when a TQT study is positive, the IWG explicitly recognizes now that in some cases in which there is a large margin of safety between therapeutic exposures with no ECG interval changes and the exposures that result in significant changes, an intensive ECG follow-up strategy might not be warranted. Alternatively, if the exposure to QT-prolonging supratherapeutic concentration is anticipated at the clinical dose (low safety margin), intensive monitoring could be carried out only in the subset of patients at risk if such a subset can be easily identified. Otherwise intensive monitoring is appropriate for the entire late phase clinical trial population. We appreciate that in a document such as the Q & A document, it may not be feasible to include the details of what constitutes routine or intensive ECG monitoring in different clinical settings. Although the level of monitoring will depend on the properties of the drug, its indication and the duration of clinical trials, we propose in

Tables 1 and 2 a framework of ECG monitoring which can be adapted to an individual development programme.

The updated Q & A document explains that given the limitations of collecting ECGs in late stage trials, the focus of the analysis is on outliers, not on central tendency, and goes on to state that this monitoring is intended to be performed locally, without the involvement of a central core laboratory. Whilst we appreciate the sentiments, this intention requires some discussion. It is difficult to understand how local monitoring can compromise analysis of central tendency but not of outlier analysis and if there are limitations in collecting ECGs in late stage trials, the limitations must be even greater reading them reliably at the local level. One important issue that bears heavily on this debate on central vs. local reading of ECGs in late stage trials is their precise utility. If it is to serve any evidence-based purpose at all in influencing regulatory decisions, the readings must be standardized and reliable. If they have no influence on regulatory decisions, one must question whether there is any point at all in monitoring and submitting data from ECGs in late phase clinical trials when the TQT is negative.

Measuring the QT_c interval correctly is a challenging task for ECG readers from all backgrounds [21, 22]. Overestimation of the QT_c intervals of healthy patients is common and the extent varies with the background of the reader [21]. Not surprisingly, therefore, the quality and interpretation of locally read ECGs varies markedly from site to site and as discussed above, automatic algorithms are particularly inaccurate on ECGs with repolarization changes, e.g. non-specific ST-T waves [19, 20]. ECG monitoring in late phase clinical trials is also intended to protect the patients

Table 1

Early evidence of QT effect, safety margins and ECG monitoring in late phase clinical trials

Concentration with QT _c effect	Clinical safety margin	95% upper bound of mean effect		
		<10	10–20	>20
Therapeutic	1	Routine	Intensive	Intensive
Supratherapeutic*	2–3	Routine	Intensive	Intensive
	4–6	Routine	Routine	Intensive
	7+	Routine	Routine	Routine

*Safety margins are a guide only, based on typical increases in C_{max} following full metabolic inhibition.

Table 2

Scheme of ECG monitoring in late phase clinical trials

Level of ECG monitoring	Scheme of ECG monitoring (depending on study duration)	ECGs to be analyzed
Routine	Single ECGs in all patients at baseline, usually at steady-state and periodically thereafter when clinically indicated	Locally (assuming high quality ECG readings can be guaranteed)
Intensive	Triplicate ECGs in all patients at baseline, usually at steady-state and at least three time points thereafter (could be more in long-term studies)	Centrally

enrolled in these trials. Therefore, for drugs with a likelihood of a positive QT effect in late phase clinical trials, local reading of these ECGs should be acceptable as long as accurate high quality ECG data can be guaranteed. ICH E14 guidance requires that machine calibration records and performance data should be maintained on file and that in the case of multicentre trials, training sessions are encouraged to ensure consistency of operator technique (e.g. skin preparation, lead placement, patient position) and data acquisition practices. It is at present uncertain whether the data on QT safety of a drug in healthy volunteers can be extrapolated readily to the patient population with a variety of co-morbidities and co-medications. Therefore, there is a case for suggesting that even when a TQT is negative, the presence of co-morbidities that give rise to ECG abnormalities calls for high quality ECG readings even during routine ECG monitoring.

Correction formula used to compute QT_c interval

In order to derive a heart rate-corrected QT_c interval, ICH E14 makes references to a number of approaches, including generic population-derived correction formulae such as the Fridericia's correction (QT_{cF}) and the Bazett's correction (QT_{cB}) or correction formulae derived from the entire study population (QT_{cS}) or calculated in each individual in the study (QT_{cI}).

The updated Q & A document clarifies that presentation of data using the Fridericia correction is likely to be appropriate in most situations but other methods could be more appropriate. It confirms that there is no single recommended alternative but emphasizes factors that deserve considerations in this regard:

- It is important that the method(s) of correction, criteria for the selection of the method of correction, and rationale for the components of the method of correction be specified prior to analysis to limit bias.
- Corrections that are individualized to a subject's unique heart rate QT dynamic are not likely to work well when the data are sparse or when the baseline data upon which the correction is based do not cover at least the heart rate range observed on study drug.

Bouvy *et al.* have reported that TQT studies are highly cost-ineffective in terms of clinical outcomes, given the less than satisfactory correlation between QT interval duration and QT-related pro-arrhythmias and their rarity [23]. The main reason for the high costs associated with TQT studies is the highly technical methods applied to the analysis of a large number of ECG recordings. Because the use of an inappropriate formula can give false results in the presence of substantial drug-related changes in heart rate, sponsors often seek advice on which is the most cost-

effective correction to apply. We believe that the universal or routine use of QT_{cI} represents a less cost-effective approach since centralized ECG laboratories often advocate adding a separate baseline day in crossover TQT studies with the derivation of QT_{cI} as the only justification. For drugs that cause an increase in heart rate, the use of QT_{cI} is of course well justified.

Specifically as it concerns the use of correction formula, we would like to share our experience. We have analyzed 75 TQT studies (26 parallel design and 49 crossover design), either published and/or as described in the FDA reviews of recently approved drugs. Of these 75 studies, 32 used QT_{cF}, 31 used QT_{cI} and 12 used QT_{cS} (also referred to as QT_{cP}) corrections for the primary endpoint. Twenty-three studies used only one correction (19 QT_{cF} and four QT_{cI} corrections). A further 39 studies used one additional correction (30 QT_{cF}, seven QT_{cI} and two QT_{cS} corrections). Of the 32 studies that used QT_{cF} for primary endpoint, 10 (31%) used QT_{cI} for secondary endpoint whereas, strikingly, as many as 27 (87%) of the 31 studies that used QT_{cI} for primary endpoint also chose to include QT_{cF} for secondary endpoint. These findings are summarized in Table 3.

With regard to the results, 46 (88.5%) of the 52 studies that used more than one corrections reported similar results with different corrections used in the studies. In one of these 46 studies, the FDA had concluded that although the results were similar following QT_{cI} and QT_{cF} corrections, QT_{cI} correction should be rejected because of lack of enough baseline data to compute the QT_{cI} correction accurately.

Of the remaining six studies:

- In two studies that used QT_{cI} correction as the primary correction, the FDA review concluded that QT_{cF} correction was superior to QT_{cI} correction.
- In one study each, QT_{cF} and QT_{cS} corrections gave slightly higher values for the increase in QT_c interval.
- In only two studies there were differences between QT_{cF} and QT_{cI} corrected values for the change in QT_c interval. One of these drugs was associated with marked drug-induced changes in heart rate and the other with drug-induced glucose-lowering effect.

Table 3

Corrections used in 75 TQT studies

Primary	QT _{cI}	QT _{cF}	QT _{cS}	None other	Other
QT _{cI}	31	27	6	4 of 31	1 + novel
QT _{cF}	10	32	4	19 of 32	7
QT _{cS}	2	12	12	0 of 12	0
Total	43	71	22	23 of 75	9

Bold-type indicates number of studies with corresponding primary correction formula.

All in all, this analysis supports the IWG view that the QT_cF correction is likely to be appropriate in most situations.

Conclusions

The update to the previous ICH E14 Q & A document is to be welcomed as it clarifies further a few additional areas of previous uncertainty. It clarifies that sponsors are recommended to include both genders in TQT studies and undertake analyses of the concentration–response relationship by gender in cases when there is a reasonable basis to study this. The problem is how does one determine *a priori* that such a reason exists. Therefore, it is particularly helpful to have clarified that regardless of any gender-related differences, the primary analysis of a thorough QT study, and as a corollary the evaluation of the QT liability of a drug, should be conducted on the pooled population and the study powered accordingly. It also provides valuable guidance on the heart rate correction formula and the extent of ECG monitoring in late phase clinical trials.

From the sponsor perspective, it seems prudent not to disregard gender-related differences which are much greater than differences arising from application of different correction formula. Therefore, we recommend that unless the preclinical toxicology of the drug or its indication dictates otherwise, the TQT population should be well balanced in terms of gender and that subgroup analysis by gender should be performed, paying special attention to E–R slopes and outliers with categorical responses. When there is evidence of clinically relevant QT_c prolongation at or close to therapeutic dose, ECGs should be read blindly and centrally by a core laboratory. For ECGs obtained during routine ECG monitoring in late phase clinical trials, locally read data should be acceptable as long as accurate high quality ECG data can be guaranteed. Furthermore, the measured QT interval should be corrected by Fridericia correction which can be set as the default formula for most trials. QT_c correction may be a secondary primary endpoint if the pharmacology of the drug justifies it, such as increase heart rate or autonomic tone. Even then, care should be exercised to gather sufficient drug free baseline data to be able to compute these confidently.

We note that the updated Q & A document does not address issues related to age and ethnicity. Since these demographic factors could also influence QT response following exposure to a drug, we hope future updates will address these issues.

Competing Interests

The authors have completed the Unified Competing Interest Form. This is available on request from the corresponding author. Both the authors declare no support from any

organization for the submitted work. RRS is the Director of a consultancy company which provides fee-earning advice to pharmaceutical companies on the design, conduct, analysis and interpretation of thorough QT studies but has no other financial relationships with any organizations that might have an interest in the submitted work in the previous 5 years. Since 3 July 2012, JM is the Chief Cardiac Consultant of eResearch Technology Inc (ERT), Philadelphia, PA, USA, a company that provides centralized cardiac safety services to the pharmaceutical industry. As a public company from 1997 to 2012, the ECG revenue of ERT, as well as the compensation JM receives from ERT, is publicly disclosed.

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