

## ***ICH E14 Step 2: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential For Non-Antiarrhythmic Drugs***

**EMA Explanatory Notes:** The EMA explanatory notes released as part of the Step 2 draft guidance succinctly summarizes the most pressing issues facing the clinical evaluation QT. The notes invite scientific input supported by current experimental or published evidence if possible, on six different aspects of the guidance:

1. The extent to which negative non-clinical studies (see ICH S7B guidance) can exclude a clinical risk beyond a reasonable doubt.
2. Categories for drugs for which there would be no need for a clinical ‘thorough QT/QTc study’
3. Categorization of clinical risk for drugs that prolong the mean QT/QTc interval by around 5 msec or less, 6 to 10 msec, 11 to 15 msec, 16 to 20 msec and those that prolong the mean QT/QTc interval by more than 21 msec.
4. Definition of a negative ‘thorough QT/QTc study’ as one where the largest time-matched mean difference between the drug and placebo (baseline subtracted) for the QTc interval is a round 5 msec or less, with a one-sided confidence interval that excludes an effect >8.0 msec, this upper bound was chosen to reflect the uncertainty related to the variability of repeated measurements.
5. Relative emphasis on population mean values versus individual outlier analysis in determining the outcome of the ‘thorough QT/QTc study’ as either positive or negative.
6. The extent to which results of a negative clinical ‘thorough QT/QTc study’ can be extrapolated to exclude a risk in patients, especially in the context of patients with increased risk (e.g., extending the indication of an antihypertensive drug to include subsequently those with chronic heart failure).

It is our understanding that ICH is planning a public meeting for the spring of 2005 to discuss both the E14 and S7B Step 2 guidance documents. The EMA explanatory notes constitute a ready-made agenda for this public meeting. Pfizer fully supports the proposed public meeting, and offers our active participation at the meeting.

### **General Comments:**

With E14 now at Step 2, FDA needs to consider developing internal guidance on the assessment of the effect of drugs on cardiac repolarization. Looking at recent examples of labeling and approval packages, review Divisions are often working to different standards when considering QT issues. Guidance in the form of a MaPP would serve to clarify assessment standards for both review Divisions and Sponsors, especially

regarding points where ICH regional differences in the evaluation of QT prolongation are now emerging.

## **1.2 Objectives**

The document comments that the “assessment of the effects of drugs on cardiac repolarization is the subject of active investigation. When additional data (non-clinical and clinical) are accumulated in the future, this document may be re-evaluated and revised”. The questions posed in the EMEA explanatory notes need to be pursued cooperatively by Regulatory Agencies and the Pharmaceutical Industry as a process for updating the guidance.

In cases where drugs are in development for the treatment of serious and life threatening conditions (e.g., oncology products), it may not be feasible or appropriate to perform a ‘thorough QT’ study in a healthy volunteer patient population. The guidance should consider expanding on cases where a ‘thorough QT’ study might not be appropriate and provide some discussion on what types of QT analysis could be performed on the clinical trials data (comparing patient ECG data from baseline and while on treatment; broader use of categorical analysis for looking at QT data).

## **2.1 Design Consideration**

As noted in the Step 1 ICH E14 Clinical QT guidance, the QT/QTc interval is subject to significant intrinsic variability resulting from many factors (e.g. activity level, postural changes, circadian patterns, and food ingestion). These factors all relate to autonomic tone and there is extensive literature demonstrating that changes in autonomic tone affect QT/QTc. This is consistent with the observation that vasodilators such as alfuzosin and vardenafil can prolong QTc by 5-10 msec despite no known effect on ion channels. It is becoming clear that when designing future “thorough QT” studies both drug and non-drugs related effects on autonomic tone must be considered.

Under what circumstances would additional information from the collection of ECGs be "necessary" as opposed to "allowed" from the regulatory perspective? Would particular "special populations" be required as part of this "collection"? What would constitute satisfactory data if this "collection" were "allowed?"

### **2.1.1. Subject Enrollment, Safety Monitoring, and Discontinuation Criteria**

The section avoids mention of large populations known to be at risk. What is the regulatory perspective on reasonable criteria for discontinuation of patients with history of MI? Non-ischemic heart failure? Heart failure with preserved systolic function? Left ventricular hypertrophy? Bundle branch block? Taking concomitant medications that prolong QT/QTc?

### **2.1.2. The ‘Thorough QT/QTc Study’: Dose-Effect and Time Course Relationships**

The guidance states the “drug should be tested at substantial multiples of the anticipated maximum therapeutic exposure”. What is a practical required upper limit for “substantial multiples of the anticipated maximum therapeutic dose?” In some instances regulators (FDA) have requested nearly 10X the anticipated therapeutic dose (Foradil Aerolizer and Clarinex), and this in instances where interactions involving metabolizing enzymes were not a factor. In other cases, drugs have been tested at 4-5 fold the clinical dose (Levitra, Cialis, Uroxatral) to approach the circulating levels produced by metabolic inhibitors

E14 currently states: “Alternately, if concentrations of a drug can be increased by drug-drug or drug-food interactions involving metabolizing enzymes (e.g., CYP3A4, CYP2D6) or transporters (e.g., P-glycoprotein), these (T-QT) studies can be performed under conditions of maximal inhibition.” This point was touched upon at a recent FDA Advisory Committee meeting (Clinical Pharmacology Subcommittee of the Advisory Committee for Pharmaceutical Science, November 3, 2004). The Advisory Committee posed the following question to their expert panel: “Is it acceptable to recommend that under certain conditions (e.g., to estimate QT effects) it is important to determine the maximum exposure of a NME that a patient may experience by increasing the exposure to the NME in the presence of either a) a single inhibitor, b) multiple inhibitors (when there are more than one pathway responsible for its metabolic clearance) or c) under multiple-impaired conditions (e.g., renal impairment and co-administration of a metabolic inhibitor)?”. The panel voted 12 to 0 (with 1 abstention) against using metabolic inhibitors to increase exposure. We disagree with the panel on this recommendation. There are instances where metabolic inhibition is the more suitable approach (evaluating the effect of a metabolite on QT prolongation, intolerance of suprathreshold doses given without inhibitors e.g. due to GI upset) and request that this option be retained in the guidance.

The guidance is still very conservative in its definition of the threshold for concern (5 msec). At public meetings, various regulators have made comment that the level of concerns is around 10 msec prolongation of QTc. Again the evidence, to support a recommendation of 5msec for the threshold of concern has not been disclosed, and should be considered tentative until academic experts and industry have had the opportunity to review the supportive data. This should be a key point for discussion at the spring ICH public meeting. As recommended by PhRMA QT SET, a non-inferiority limit of 10 msec for the largest mean difference from placebo (baseline-subtracted) would allow the true mean difference from placebo to be about 4 msec or less at any time point, maintain alpha at 0.05 or less (conservative, for patient safety), maintain overall power for 5 - 8 time points when ECGs are recorded (in favor of study drug) and require a sample size of 48 - 54 subjects for a crossover study.

Another important point for discussion at the public meeting are examples (or examples of classes) of drugs considered to be “well-characterized and consistently produce...QT/QTc interval that is currently viewed as clinically not important”

"Equipotence" with a drug of the same class may be difficult to establish." It would be more clinically practical to utilize a drug that is "well characterized and consistently produce...QT/QTc interval that is currently viewed as clinically not important", and more clinically meaningful for a post-hoc comparison to be made between the dose-ranges used to treat the indicated disease.

### 2.1.3 Clinical Trial Evaluation After the 'Thorough QT/QTc Study'

The guidance states that "even if the 'thorough /QTc' study is negative, if other evidence of an effect in a patient population from subsequent studies...were to emerge, then additional investigation would be needed". What specific types of "additional investigation" should be considered?

## 2.2 Collection, Assessment, and Submission of ECG Data

### 2.2.2 Assessment of Standard 12-Lead ECGs

Should the "skilled readers" of the "core laboratory" be instructed to measure QT or QU interval? What is the minimally acceptable methodology that will be allowed by the Agency [lead 2 only; frontal leads only; precordial lead(s)]? What will be the regulatory gold standard should different methodologies used to assess the same drug yield discordant results in the measurement of QT/QTc? This comment also pertains to the analysis of ECGs from Clinical trials

## 3.1 QT Interval Correction Formulae

The guidance states: "In early trials evaluating the effects of a new drug on the QT/QTc interval in healthy volunteers, designed to detect relatively small effects (e.g., 5 msec), it is important to apply the most accurate correction available (e.g., methods using individually-derived relationships between RR and QT intervals)". Please describe the rationale and evidence supporting the statement that "individually-derived" methods are more accurate than other correction formulae.

## 3.2 Analysis of QT/QTc Interval Data

### 3.2.2 Categorical Analysis

Please change the categories for maximum post dose QTc to  $\geq 450$ ,  $\geq 480$  and  $\geq 500$  for accuracy and practical reasons. Standard statistical methodology is to make these types of tables left-continuous, and they would thus be more conservative. QTc intervals are rounded to the nearest msec. Under the current criteria, a subject with a QTc of 500.4 msec would be rounded to 500 and not included in the table.

As the categories for absolute values and changes from baseline are arbitrary why not consider a graphical approach where the percentage of subjects falling in the category is

plotted against different criteria for categories. Changes in the curves that are generated would indicate a differentiation in treatments and the information being tabulated would be available from the plot.