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Drugs, QTc Interval Prolongation and Final ICH E14 Guideline

An Important Milestone with Challenges Ahead

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Abstract

Regulatory concerns on the ability of an ever-increasing number of non-antiarrhythmic drugs to delay ventricular repolarisation, prolong the corrected QT (QTc) interval and induce potentially fatal ventricular tachyarrhythmias have culminated in the adoption of two, internationally harmonised, regulatory guidelines. On 12 May 2005, the International Conference on Harmonisation (ICH) reached an important milestone when it adopted the final texts for clinical (ICH topic E14) and non-clinical (ICH topic S7B) strategies by which drugs should be investigated for their potential to induce these effects during their development.

ICH E14 provides recommendations to sponsors concerning the design, conduct, analysis and interpretation of clinical studies to assess the potential of a drug to delay cardiac repolarisation. Specifically, it calls for a clinical 'thorough QT/QTc study' (typically conducted in healthy volunteers), which is intended to determine whether a drug has a threshold pharmacological effect on cardiac repolarisation, as detected by QT/QTc interval prolongation. The E14 recommendations are generally applicable not only to new drugs that have systemic bioavailability but also to approved drugs when a new dose, route of administra-

tion or target population that may result in an increased risk is explored. The guideline provides for exceptions when this study may not be required.

Recognising the fractious relationship between ICH E14 and ICH S7B, and the persistence of a number of issues that may require clarity and/or the emergence of other new scientific issues in the future, the ICH Steering Committee has formed an Implementation Working Group that is charged with providing clarity on aspects of the guideline that are ambiguous and responding to issues on which the sponsors are uncertain. This paper provides a commentary on some of the challenges that are likely to be faced by the sponsors of drugs during the next few years of application of these two guidelines. The adoption of these guidelines has left a number of questions unanswered and raised some new ones. When in doubt, the sponsor should seek formal regulatory clarity before making key decisions that may impact further development, assessment and approval of a new chemical entity. Although the goal of developing drugs with much lower torsadogenic potential and without inappropriate restriction in the use (or even rejection) of potentially beneficial drugs is within sight, it is questionable whether the risk of drug-induced proarrhythmia will be eliminated completely.

Although small increases in the duration of corrected QT (QTc) interval on the surface ECG can be antiarrhythmic, drug-induced prolongation of the QTc interval, when excessive in the right setting, can be proarrhythmic and degenerate into torsade de pointes, a unique form of polymorphic ventricular tachycardia. Consequently, this effect is a matter of concern when it is associated with non-antiarrhythmic drugs. The number of non-antiarrhythmic drugs that carry what has been termed the 'QT-liability' continues to increase almost daily.[1,2] Given the potentially fatal consequences of this mechanism-based, concentration-dependent adverse drug reaction, it is not surprising that more than any other drug-induced adverse reaction, it has been responsible in recent times for the withdrawal of a wide range of non-antiarrhythmic drugs from the market. A list of these agents has been published elsewhere.[3]

Regulatory authorities have reacted to this apparently recent 'pharmaco-epidemic' by denying or delaying the approval of a number of new drugs and placing severe restrictions on the use of many old and some new drugs because of concerns arising from their potential to prolong the QTc interval. Regulatory and clinical expectations of a better preapproval characterisation of new chemical entities (NCEs) for this potential risk have had a very profound influence on their development, assessment and approval. For sponsors of new drugs, although the EU had promulgated locally applicable points to consider when developing non-cardiovascular drugs for their potential to prolong the QT interval,[4] there was an urgent need for an internationally harmonised guideline on what the regulatory authorities elsewhere, especially the US FDA and Japanese Pharmaceutical and Medical Devices Agency (PMDA, a part of the Ministry of Health, Labour and Welfare), expected in terms of preapproval characterisation of a new drug for this potential risk.

1. Regulatory Implementation of ICH E14 and ICH S7B

On 12 May 2005, an important milestone in drug safety was reached when the International Conference on Harmonisation (ICH) adopted two guidelines for regulatory implementation in the three regions concerned – one dealing with non-clinical strategy (ICH topic S7B) and the other dealing with clinical strategy (ICH topic E14) by which to evaluate an NCE for its proarrhythmic effects during drug development.

Entitled "The non-clinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals",[5] ICH S7B describes a non-clinical testing strategy by which to identify the potential of a test substance and its metabolites to delay ventricular repolarisation and to relate the extent of delayed ventricular repolarisation to the concentrations of a test substance and its metabolites. Although four levels of non-clinical approaches are referred to in the text, the core testing systems recommended are *in vitro* assay of the rapid component of the delayed rectifier potassium current (I_{Kr}) and *in vivo* study in dog or other laboratory animals such as monkey, swine, rabbit, ferret and guinea pig. I_{Kr} is the major repolarising current in the ventricles and is the target of the vast majority of the QT-prolonging drugs. The guideline proposes a concept of integrated risk assessment that can contribute to the design of clinical investigations and interpretation of their results. It also requires that *in vitro* I_{Kr} and *in vivo* QT assays, when performed for regulatory submission, should be conducted in compliance with good laboratory practice.

Entitled "The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs",[6] ICH E14 provides recommendations to sponsors concerning the design, conduct, analysis and interpretation of clinical studies to assess the potential of a drug to prolong the QT interval. In particular, it calls for a specifically dedicated clinical 'thorough QT/QTc study' (typically in healthy volunteers) that is intended to determine whether a drug has a threshold pharmacological effect on cardiac repolarisation, as detected by QT/QTc interval prolongation. Since this study is also expected to evaluate the effect of the drug on all ECG parameters such as the heart rate, other cardiac intervals and T-wave morphology, and not just the QTc interval, it is better termed 'thorough ECG trial' with an acronym TET, as first popularised by Morganroth.[7] The recommendations contained in ICH E14 are generally applicable not only to new drugs that have systemic bioavailability but also to approved drugs when a new dose or route of administration (that results in an increased exposure to the drug) or target population (that may be more susceptible to torsade de pointes) are explored. The guideline may not apply to products with highly localised distribution and those administered topically and not absorbed.

When adopting these two new guidelines, the ICH Steering Committee recognised that with the rapid pace of scientific advancements in this field, additional issues will no doubt emerge in the future and that due to the fractious relationship between ICH E14 and ICH S7B, there were several unresolved scientific as well as regional issues that may need further clarity. Therefore, the Committee recommended the formation of an Implementation Working Group (IWG) with a remit to provide clarity on aspects of the guideline that are ambiguous, respond to issues on which the sponsors are uncertain and/or track issues that may emerge following scientific advances after these guidelines have been adopted. In order to ultimately align the two guidelines more closely, the IWG includes E14 as well as an S7B members from each of the three regulatory authorities. The IWG is now operational and the sponsors can address their queries to it via the ICH website (e-mail address: e14@ich.org). It is expected that IWG will report regularly to the ICH Steering Committee and will recommend whether a revision to the guidelines is warranted.

At the time of writing this commentary, the EU Committee for Medicinal Products for Human Use (CHMP) had adopted these guidelines (E14 as CHMP/ICH/2/04 and S7B as CHMP/ICH/423/02) during their meeting in May 2005 (Step 5) with an operational implementation date of November 2005. Both the US FDA and the Japanese PMDA will notify later the dates for implementation of these guidelines within their jurisdiction.

Both ICH S7B and ICH E14 are expected to have significant impact on drug innovation and development as well as public safety. An earlier commentary had discussed some major E14-related scientific issues that needed to be addressed and resolved carefully before the adoption of E14 and S7B if these two guidelines were to evolve into worthy

documents.[3] Although most of the issues that were raised appear to have been resolved in the recently adopted versions, a number of questions have still been left unanswered and some new ones have been raised. Therefore, despite the adoption of these guidelines, the sponsors will be confronted with several uncertainties and challenges. These are discussed in the following sections, together with the author's perspective on how some of these issues might be approached. This perspective, of course, does not constitute an official regulatory view and the sponsor should always seek formal regulatory guidance from either the IWG or the regional authority whenever a significant issue emerges during the drug development process. The fractious relationship between ICH E14 and ICH S7B, as they stand today, has now further burdened the sponsors with not only having to undertake non-clinical studies that are in full compliance of good laboratory practice but also having to conduct a TET if they are to meet the expectations of all the three major regulatory authorities in a single universally acceptable Common Technical Document.

2. Scope of ICH E14

Although ICH E14 calls for a clinical 'thorough QT/QTc study' (hereafter referred to as 'Thorough ECG Trial' or TET) for new drugs with systemic bioavailability, its scope has been better defined in the final version. It would usually not be the first study, as it is important to have basic clinical data for its design and conduct, including tolerability, pharmacokinetics and the activity of the metabolites. The guideline may not apply to products with highly localised distribution and those administered topically and not absorbed. This seems to be a very prudent approach since drugs such as terfenadine, even though administered orally, have hardly any systemic bioavailability and similarly, a number of drugs are actually administered topically with the expectation that they will be systemically absorbed. Thus, there is frequently no correlation between the route of administration and systemic bioavailability. Recent concerns following reports of death and other serious adverse effects from overdoses of fentanyl in patients using fentanyl transdermal patches for pain control are a vivid reminder that occasionally topical products may have erratic absorption and that the extent of bioavailability of the drug concerned is more important than its route of administration.[8]

Although the parenteral use of small peptides and biologics (such as oxytocin, vasopressin, octreotide and gonadotropin-releasing hormone agonists and antagonists) has been associated with QTc interval prolongation and torsade de pointes,[9-12] these reports are of highly questionable causal link and are confounded by the presence of other risk factors and cardiovascular or endocrine changes. Not only are these reports very rare but also the underlying mechanism of the effect is unknown. Therefore, uncertainty still remains with regard to the application of ICH E14 to blood or plasma products, small peptides, biologics, hormones, infusions of amino acids or crystalloids, vaccines and many biotechnology products, as well as orphan medicinal products such as enzyme replacement therapy.

The final version of ICH E14 has reiterated that while the document is concerned primarily with the development of novel agents, the recommendations might also be applicable to approved drugs when a new dose or route of administration is being developed. While this regulatory expectation is perfectly legitimate, especially when another drug in the same chemical or pharmacological class has been associated with an effect on ventricular repolarisation, uncertainties remain with regard to developing drugs for a variety of different indications over the life of a drug when a TET has already been conducted with the drug concerned prior to its original indication.

The phosphodiesterase V inhibitors (sildenafil, vardenafil and tadalafil), approved for erectile dysfunction in males, provide a particularly pertinent example. There are drug development efforts under way with the aim of extending their indications for use in pulmonary hypertension. This class of drugs raises interesting issues because in *in vivo* studies in dogs, none of these drugs had an effect on the QT interval and these drugs have already been tested in

TETs conducted exclusively in the healthy male population. Their effects on QTc interval (individually corrected and at peak concentration [C_{max}]) were 2.8ms for tadalafil, 5ms for sildenafil and 6ms for vardenafil at supratherapeutic doses.[13,14] However, their new indication in pulmonary hypertension will result in a continuous use on a daily basis (as opposed to intermittent use in erectile dysfunction) in an additional target population (females in addition to males) that has a greater susceptibility to I_{Kr} blockade. Will a new TET be required for any of them, given their extensive postmarketing use and lack of any documented reports of proarrhythmias? Clearly, the decision in such circumstances will have to be guided by the doses investigated and their effects observed in previous TETs and the likely difference in exposure, the clinical pattern of use and the proarrhythmic susceptibility of the new target population.

Issues will also emerge when developing combination products. Will a fixed combination of two active agents, whether or not already previously approved, require one TET with the combination or two studies with each individual component? Will a TET be required in children if a drug, already approved for use in adults, is required to be developed for paediatric use, as is now frequently required in almost all jurisdictions? How will the drugs intended exclusively for paediatric populations be investigated for their potential to prolong the QT interval in the setting of a TET? These difficult issues will also present challenges in the future.

Since robust ECG monitoring during early clinical pharmacology studies is now generally routine (regardless of non-clinical signals),[15] a question arises whether a TET is necessary if these early clinical pharmacology studies yield unequivocal evidence of an effect on QTc interval.

Although it is emphasised that sponsors should seek formal regulatory guidance from the IWG or the regional authorities when there are doubts or uncertainties on key issues, it seems reasonable that:

- Blood or plasma products, small peptides, hormones, infusions of amino acids or crystalloids, vaccines, biotechnology products as well as orphan medicinal products should, by default, be exempt from a TET unless the non-clinical data are indicative of a risk. Decision on the need for such a study should be made on a case-by-case consideration, depending on any previous experience and data on the product.
- When a drug is further developed for additional indications, the decision on whether a TET is required prior to approving the new indication should be made on an integrated assessment of change in systemic exposure to the drug, potential susceptibility of the target population, non-clinical data, postmarketing experience with the previous use of the drug and whether other drugs in that class are associated with an effect on ventricular repolarisation. The need for another TET may also be reduced provided that an adequate supratherapeutic dose/concentration was investigated in the previous TET.
- For fixed combination products, the same consideration should apply as long as there is no drug-drug interaction between the two components and all components have been previously approved. Any new component should be investigated separately for its effects just as any NCE would be and the possibility of an interaction (both pharmacokinetic and pharmacodynamic) should be carefully investigated and excluded. If an interaction is present or suspected, the actual combination should be the subject of a TET. In this context, it is helpful to remember that an interaction may not be immediately apparent. For example, a fixed combination product of sotalol with a thiazide diuretic (Sotazide®)[1] that was indicated for hypertension had proved to be highly proarrhythmic (because of the contribution of hypokalaemia induced by the thiazide component).[16]
- As far as the development of a new drug exclusively for use in the paediatric population is concerned, greater reliance may have to be placed on non-clinical data. If necessary, a TET should be conducted in adults but, more crucial-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

ly, ECG monitoring should be robust in all paediatric trials. For other drugs, data on the potential of a drug to alter ventricular repolarisation may have to be extrapolated, if already available, from a TET and postmarketing experience with the use of the drug in adults.

- If early clinical pharmacology studies show a clear drug effect on the QTc interval, a more constructive approach might be to circumvent a TET and continue robust ECG monitoring in all clinical pharmacology studies such as studies addressing special populations, drug interactions, food effect and bioequivalence and in subsequent dose-ranging and pivotal studies. This strategy would depend on whether the investigational drug warrants comparison to other drugs in the same class.

3. Value of Non-Clinical Data

The EU and Japan on one hand and the FDA on the other have very divergent views on the predictive value of non-clinical data. The final version of ICH E14 (Step 4) has accommodated these differences by acknowledging that factors that could reduce the need for a TET include the inability to conduct the study in healthy volunteers or patients, how the drug is studied and used (e.g. administered under continuous monitoring), as well as non-clinical data.

This laudable revision, accepted by the E14 Expert Working Group members representing the industry, has placed a dual burden on the sponsors of the new drugs. First of all, the EU and the Japanese authorities will require non-clinical studies since they acknowledge the predictive value of non-clinical assays and do not regard a TET in healthy volunteers as an infallible tool by which to exclude the risk in patient populations. Second, to enable the FDA to decide whether a TET, which can cost several million US dollars, is necessary for a particular drug, the sponsors will need to submit non-clinical studies that are fully compliant with good laboratory practice if they wish to claim an exemption. Finally, the phrase '*could reduce*' is subject to variable interpretations. For a further discussion on safety margins and designating non-clinical data as positive or negative, see section 8.

The current resolute stance of the FDA on non-clinical data suggests that they would require a TET for almost all new drugs regardless of the non-clinical data. This approach of the FDA seems to be based on their analysis of 19 recently evaluated drugs for which both sets of data (clinical and non-clinical), gathered from recently conducted studies, were available. This analysis apparently identified two drugs that were negative in non-clinical assays but prolonged the QTc interval in healthy volunteers. However, it is worth noting the changes in QTc intervals associated with both these drugs had just exceeded 5ms and corrections to the QT interval were made by Fridericia correction and not the more accurate individual correction formula. These data were presented at a public discussion meeting (on Step 2 of ICH E14) in Bethesda, MD, USA in April 2005. Cavero and Crumb[17] have reported on the proceedings of this meeting at which there was an extensive discussion on the predictability of non-clinical data and believe the two drugs to be vardenafil and alfuzosin. Neither has been associated with reports of torsade de pointes despite extensive clinical use. The overwhelming and almost unanimous view at this meeting was that the need for a TET should be driven by the non-clinical data. Furthermore, studies over the previous 18 months strongly support the conclusion, shared by a vast majority of experts in this field, that an ICH S7B-compliant package of non-clinical studies, when interpreted with a careful attention to safety margins and problems related to human ether-a-go-go (hERG) trafficking, appears capable of excluding a clinical risk[18-22] and therefore, informing the clinical development programme. Currently available data would require any claims to the contrary to be substantiated by robust scientific evidence. Wible et al.[23] have recently reported a novel comprehensive high-throughput screen using a system called hERG-Lite®. This system correctly predicted hERG risk for all the 100 compounds tested with no false positives or negatives. All 50 hERG blockers were detected as drugs with hERG risk in the hERG-

Lite® assay, and fell into two classes: B (for blocker) and C (for complex; block and trafficking inhibition). There seems to be little doubt that non-clinical data should guide not only the safety monitoring during early human tolerance studies but also the need for a TET. If the objective is to identify torsadogenic drugs, then it is worth bearing in mind that at present, we do not know of any drug that was found to be negative in non-clinical studies that was later found to induce torsade de pointes in humans. Furthermore, when drugs known to be torsadogenic in humans were later tested in non-clinical systems, they invariably declared their torsadogenic potential. No doubt, a rare drug with discordant non-clinical and clinical data may well emerge in the future but it seems rather imprudent to formulate a major policy with significant impact on drug development on the basis of a potential rarity.

4. Study Population and Achieving Supratherapeutic Concentrations

Recognising that the number of pharmacotherapeutic classes of drugs that may not lend themselves to testing at supratherapeutic concentrations, especially in healthy volunteers, may be substantial; the final version of ICH E14 now recommends that when a TET cannot be conducted in healthy volunteers due to safety or tolerability concerns, it can often be conducted in patient populations. When even this is not possible, the importance of detecting the proarrhythmic risk means that other ways of detecting effects of a drug on the QT/QTc interval need to be developed. These might include the collection of ECGs at multiple timepoints under tightly controlled settings that target a broad range of doses in early clinical development. Indeed, it is recognised that a TET might not be possible and the guideline acknowledges that alternative methodologies to TET are under active investigation. Examples include evaluating the relationship between concentration and QT/QTc effects based on data collected during early phase clinical studies or more intensively evaluating ECGs during, for example, dose-ranging studies. It must be appreciated that given the normal variability in QTc interval, these early-phase clinical studies may have serious limitations in terms of sample size exposed to various doses and duration of exposure.

The use of metabolic inhibitors alters the relative concentrations of the parent drug and its metabolites at a given dose and provides little or no information on the activity of these metabolites. The final version has clarified the use of inhibitors to achieve supratherapeutic concentrations. In terms of investigating the effects of supratherapeutic concentrations, the guideline reiterates that these effects could be studied under conditions of maximum inhibition (of metabolism) but since the effects could be mediated by the metabolite(s), it now clarifies that this approach calls for a full understanding of the pharmacokinetic and pharmacodynamic properties of the parent drug and significant human metabolites.

If, in the spirit of ICH E5 guidance, data are to be extrapolated confidently from a TET in one population to another, the term supratherapeutic concentration may raise some issues. It is frequently the case that compared with the EU, doses in Japan are generally lower while those in the US are higher. Cisapride (withdrawn in 2000 because of its torsadogenic potential) was a good example. Clearly, the inability to test supratherapeutic concentrations limits the predictive value of a TET conducted in healthy volunteers or in patients. One alternative that merits consideration is the study of subjects who are neither the healthy volunteers selected at random nor the patients. First-degree relatives of patients with acquired long QT syndrome have been shown in a recent study to experience a greater (intravenous) quinidine-induced prolongation of terminal repolarisation compared with control relatives.[24] This super-sensitivity of first-degree relatives is likely related to a genetic predisposition to acquired long QT syndrome. Although these subjects are difficult to find and recruit, they may offer one way out in those situations when supratherapeutic concentrations cannot be attained because of other dose-limiting toxicity.

There is little doubt that metabolic inhibitors have a role only when characterising the effect of

parent drugs such as terfenadine that are subject to such avid metabolism and very low systemic bioavailability that it becomes difficult to achieve supratherapeutic concentrations normally. However, for a variety of reasons the use of inhibitors to achieve supratherapeutic concentrations should be seen as a second-line option. First of all, it is possible that the inhibitor itself has an effect on the QT interval (e.g. quinidine, ketoconazole etc.). Apart from providing no information on the effects of active metabolites, this approach also overlooks any potential interactions – pharmacokinetic as well as pharmacodynamic – between the parent drug and its metabolites. Drug-metabolite interactions have been reported and are increasingly recognised to be important. An alternative approach adopted by Pfizer when investigating the effects of six antipsychotic drugs on QTc interval in study 054 involved dosing to steady state, first without and then with the metabolic inhibitors of the drugs concerned.[25]

The final ICH E14 has speculated that although data are limited, it is not expected that the results of the TET would be affected by ethnic factors. However, it is still non-committal on the issue of the sex of the TET population. This has led to a view that a study population consisting exclusively of males would be adequate. This restriction of the study population to male volunteers is highly undesirable since females have a greater susceptibility to QT interval prolongation and their enrolment may disclose subtle effects not otherwise evident.[26-30] There are not only these pharmacodynamic differences but also significant pharmacokinetic differences between the sexes. Therefore, as long as there are no other contraindications, every effort should be made to ensure that females are also enrolled into a TET.

With regard to global drug development, considerations of the ethnicity of the study population are important. This is an area that requires active investigation. Ethnic variations have been demonstrated in the activities of drug metabolising enzymes such as cytochrome P450 (CYP) 2C9, 2C19 and 2D6. Although there appear to be no ethnic differences in QTc interval duration,[31] the possibility of an interethnic variation in response to a standard challenge with QT-prolonging drug cannot be ruled out. Evidence is beginning to emerge of significant interethnic variations in the frequency of pathogenic potassium and sodium channel variants in apparently healthy individuals.[32,33] White Caucasians may be more susceptible to QT interval prolongation by hERG blockers than the Asians.

5. Recording, Measuring and Correcting the QT Interval

Methods of recording, measuring and correcting the QT interval have given rise to confusion. This is a pity since the guideline is, and always has been, quite explicit. With regard to recording ECGs, the guideline states that the clinical ECG database is typically derived from the collection of 12-lead surface ECGs, although ambulatory ECG techniques show promise. Continuous 12-lead ECG (Holter) recordings have been used extensively in TETs performed by at least one leading ECG core laboratory. This technology has been chosen for about 75% of the approximately four-dozen studies contracted to this laboratory.[7] These platforms enable continuous 12-lead ECG collection throughout an entire 24-hour period. ECG waveforms are collected and stored on solid-state memory cards that are forwarded to the ECG core laboratory. Continuous 12-lead ECG platforms enhance precision, as the core laboratory can extract multiple ECGs at specific timepoints, even retrospectively. In one study, Holter-derived and standard ECGs produced nearly identical sotalol-induced QT/QTc and RR changes from baseline, as did the manual digipad and on-screen caliper measurements.[34] Digital 12-lead Holter technology has many advantages and it is rapidly gaining widespread regulatory acceptance as evidenced by the approval of drugs, the development of which used this technology.

With regard to measuring ECG intervals in clinical trials, the final version of the guideline states that:

- Several methods for measuring ECG intervals have been used in clinical trials, and for a given trial, the sponsor should describe the accuracy

and precision of QT/QTc interval measurements using the selected system. The method chosen will depend on the level of precision appropriate for a given trial.

- For example, the 'thorough QT/QTc study' would warrant particularly careful attention to interval measurement. At present, this would usually involve the measurement by a few skilled readers (whether or not assisted by computer) operating from a centralised ECG laboratory.
- If well characterised data validating the use of fully automated technologies become available, the recommendations in the guidance for the measurement of ECG intervals could be modified.
- In the absence of a concern in the early clinical trial(s), ECG reading by machine has a role in the rapid assessment of ECGs for safety when the recordings are otherwise inaccessible.

It is clear that '*measurement by a few skilled readers*' is the primary modus operandi and the computers may provide only the '*assistance*'.

It is the author's understanding of the intentions of the E14 Expert Working Group that skilled readers will analyse the ECGs (paper or digital records) manually. By this is meant that these skilled readers will place the markers manually on the ECGs, which are expected to be free from any computer-placed markers. It has been argued that a combination of automated and manual approaches may be optimal, in which trained professional readers operating from a central laboratory review the machine-read ECGs and re-compute any intervals for which the automated placement of the fiduciary points is considered to be inappropriate (the so-called 'computer-assisted' or 'semi-automated' measurement). Although the (few) protagonists of computer-placed markers with manual over-read claim that this approach is highly reproducible, it is uncertain if it has the required accuracy, given the very limited experience with it.[35,36] This approach appears to be not only subjective and highly *ad hoc* but also tedious and therefore, unreliable – reproducibility not being synonymous with accuracy. Any sponsor intending to substitute fully manual measurements by any form of automated or semi-automated measurements for providing the pivotal QT-safety data would do well to consult regulatory authorities beforehand.

The guideline also requires that readers of ECGs should be blinded to time, treatment and subject identifier, and one reader should examine all the ECG recordings from a given subject and that the degree of inter- and intra-reader variability should be established by having the assessors reread a subset of the data (both normal and abnormal) under blinded conditions. In practical terms, blinding may be a problem if one reader is to read all ECGs from the same subject. Therefore, blinding should only apply to time and treatment. Furthermore, intra-reader variability may well exceed inter-reader variability. Therefore, when quality control and assurance procedures have established low inter-reader variability in terms of QT interval measurement, more than one reader should be able to read ECGs from the same subject. It also follows that even when read by a single reader, evidence of low intra-reader variability should be required. From a safety standpoint, the cardiologist doing the morphology interpretation should not be blinded to patient or visit (but still blinded to drug/placebo, dose, etc.) as the ability to view ECG morphology from consecutive visits allows the reader to better identify subtle changes in T waves and other morphological changes that could prove to be significant.

It had been a matter of some unease that one could obtain very different summary statistics from the same dataset simply by using alternative heart rate corrections or baseline computations. The final guideline has gone some way in removing any ambiguity. In early trials evaluating the effects of a new drug on the QT/QTc interval in healthy volunteers, designed to detect relatively small effects such as a QTc interval prolongation of 5ms, it is important to apply the most accurate correction available. Because the best correction approach is a subject of controversy, uncorrected QT and RR interval data, heart rate data, as well as QT interval data corrected using Bazett's and Fridericia's corrections should be submitted in all applications, in addition to QT

interval data corrected using any other formulae. A concurrent positive control group is strongly encouraged to support the use of newer correction approaches (e.g. individual subject correction) in order to demonstrate the ability of the correction method to allow detection of relevant effects on the QT/QTc interval.

ICH E14 recommends that corrections for heart rate using individual subject data are the most suitable for the TET. These individual correction formulae should be derived from QT/RR relationship, at baseline or during placebo administration, with heart rates that span a wide range of heart rates. Therefore, it is important to have a sufficient number of baseline (or placebo) ECGs to reliably estimate the individual correction formulae. Furthermore, hysteresis of the QT interval (lag between changes in heart rate and QTc interval) has been shown to occur with the normal QT/RR relationship when autonomic tone changes. Marked hysteresis present during autonomically mediated fluctuations in heart rate makes it impossible for a single correction formula to accurately predict QT intervals in an individual, let alone in populations.[37] For instance, although the 'individual correction factor' is perhaps the most accurate correction method described to date,[38,39] analysis using this method requires RR interval changes >5ms within a 10s recording to be eliminated from the dataset to derive the correction curve, thus diminishing the possibility of studying hysteresis. Dynamic assessment of the beat-to-beat QT/RR interval relationship provides a means to differentiate QT interval prolongation effects induced by a hERG-blocking drug from changes in the QT interval incurred through autonomic-mediated reflexes.[37,40]

6. Computing the Mean Drug Effect on QTc Interval

Another area in draft ICH E14 that required clarification was the computation of changes in central tendency. Sponsors as well as many regulators seemed to vary in their understanding of what was meant by "*largest time-matched mean difference between the drug and placebo (baseline-subtracted) over the collection period*", "*time-averaged QT/QTc intervals*" and "*analysis of changes occurring at the C_{max} for each individual*".

The final version of the guideline implies that the effect of an investigational drug on the QT/QTc interval should be primarily analysed using the "*largest time-matched mean difference between the drug and placebo (baseline-adjusted) over the collection period*". Additional approaches to the assessment of central tendency could include analysis of changes occurring around the C_{max} for each individual. This last analysis, it is pointed out, would be especially important if the drug has large between-subject variability in the rate of absorption or metabolism. The recommendations also require that intrinsic variability of the QTc interval be addressed in the conduct of a TET. This can be accomplished by standardising recording conditions that are controlled for factors that affect the QTc interval and by collecting multiple ECGs at baseline and during the study at the same timepoints especially since the primary analysis is to be 'time-matched'. However, the document is silent on what constitutes an acceptable *baseline* value and how the "*largest time-matched mean difference between the drug and placebo (baseline-adjusted)*" should be calculated.

The final ICH E14 guideline sets the threshold level of regulatory concern at a mean effect on QTc value of around 5ms as evidenced by a 95% upper confidence bound of 10ms. The statistical aspects of evaluating drug-induced prolongation of the QTc interval are complex, given the wide intra-individual and inter-individual variability of this parameter. The Pharmaceutical Research and Manufacturers of America QT Statistics Expert Working Team has recently reported on the key statistical issues that arise in the evaluation of drug-induced QT/QTc prolongation in a TET and issues that surround the design, choice of endpoints and analysis of a TET.[41] Many questions are at present unanswered. One of the issues is the designation of TET as positive or negative when there is a disparity between the mean effect and its 95% upper confidence bound (e.g. mean effect of 4ms and an upper bound of 11ms or a mean effect of 6ms and an upper bound

of 9ms). Intuitively, the upper bound will be the key parameter, although no such limits are set for the positive control. The mean effects of moxifloxacin, the most widely used positive control, vary widely among studies.

6.1 Baseline QTc Interval

As far as the determination of baseline value is concerned, there are three potential approaches. In what follows, a 'single ECG' is defined as an average of triplicate ECGs obtained over 2–4 minutes. For each subject, one approach is to obtain a mean baseline QTc interval value derived by averaging single ECGs, recorded every 15 minutes at four timepoints during the hour preceding administration of a treatment (active drug or placebo). A better approach is to derive a timepoint-specific single ECG value at each predefined timepoint, during the 24-hour period preceding the administration of a treatment, that correspond to the intended timepoints for on-therapy recordings during an entire day. This latter approach has the advantage of compensating for circadian changes. The third approach is to average all the timepoint-specific single ECGs obtained during the entire 24-hour period to derive a single statistic. In a TET of tadalafil, Beasley et al.[13] recorded baseline ECGs at 0, 3, 4, 6, 9, 12 and 24 hours for 2 days before placebo or tadalafil dosing, and at 3, 4, 6 and 24 hours after the dose of tadalafil or placebo. For each timepoint, the QT interval was calculated as the mean of ten ECGs.

It is of course recognised that the use of this 24-hour time-matched baseline profile will only be beneficial if the potential circadian variability is stable over the whole period of the trial within each subject and if it cannot be attributed to the circadian variability of heart rate. In reality, circadian variability is hardly ever consistent or stable. It is also worth emphasising that in crossover studies, baseline values should be established immediately preceding *each* treatment period, by using a baseline day and defining the ECG values for the same timepoints that will be defined during treatment, thereby allowing for a time-matched analysis. Using a single baseline before all treatment arms in a crossover trial will usually lead to period effects since there is a high QTc variability over time within an individual. Calculating the placebo effect (change from baseline) also permits determination of how well the trial was conducted to reduce background spontaneous variability. The positive control group should be treated exactly like the other groups and the temptation to use the positive control only first or last for all subjects should be resisted. The argument that the positive control must be used either first or last does not overweigh the importance that the positive control arm should be conducted in the same manner as all other treatments. Therefore, whenever feasible, the positive control arm should be blinded. This approach on one hand ensures that all treatment periods are handled in the same manner and quality while, on the other hand, it excludes the bias arising from any potential expectations of the volunteers with regard to the effects of a drug.

6.2 Largest Time-Matched Mean Difference Between the Drug and Placebo

The ICH E14 Statistical Group, a team of regulatory and industry statisticians with expertise in QT studies, provided assistance to the ICH E14 Expert Working Group with regard to determining the largest time-matched mean difference. Both the groups discussed the following three definitions of the endpoint.

1. Maximum over time of the (maximum mean increase from baseline for study drug) minus (the maximum mean increase from baseline for placebo), regardless of the timepoints (which could be different for the drug and the placebo) at which these increases occurred on either the drug or the placebo (figure 1). The primary determinants in this case are the maximum increases on study drug as well as on the placebo. A high placebo response minimises the drug effect and diurnal effects could confound the conclusions.
2. Maximum over time of the (maximum mean increase from baseline for study drug minus the mean change from baseline for placebo at the corresponding timepoint) [figure 2]. The primary determinant in this case is the maximum increase on

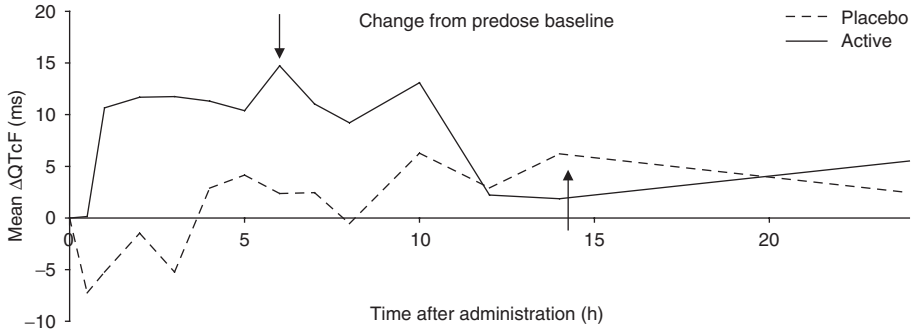

Fig. 1. Maximum increase in mean Fridericia corrected QT (QTcF) interval on drug is +15ms and, regardless of the timepoint, the maximum increase in mean QTcF on placebo is +6ms. Therefore, the largest time-matched mean difference between the drug and placebo is +9ms.

study drug. A marked diurnal effect could mask the drug effect. The diurnal effect is removed in this analysis and the difference from placebo is driven by the response to the drug.

3. Maximum over time of the (mean change from baseline on study drug minus the mean change from baseline on placebo at the corresponding timepoint) [figure 3]. The primary determinants in this case are the ΔΔQTc values at each timepoint. This computation is driven by the largest response to the drug and the smallest response to the placebo. This analysis requires plotting ΔQTc on drug and ΔQTc on placebo at each timepoint and then computing ΔΔQTc at each timepoint (the difference between the two ΔQTc – the first delta being the change from baseline and the second delta being the change from placebo). It will be apparent that the effect size (maximum ΔΔQTc) at a given timepoint is the same whether the difference at that timepoint is calculated (i) following computation of drug-placebo differences for individual subjects first and then deriving a mean value of these individual differences or (ii) following computation of the mean on-drug value and mean on-placebo value first and then deriving the drug-placebo difference.

The Expert Working Group agreed that the most appropriate endpoint of regulatory interest corresponded with definition 3 (the maximum ΔΔQTc with its corresponding timepoint). The author's understanding of how definition 3 should be applied to calculate the "*largest time-matched mean difference between the drug and placebo (baseline-adjusted)*" is outlined in sections 6.3–6.4.

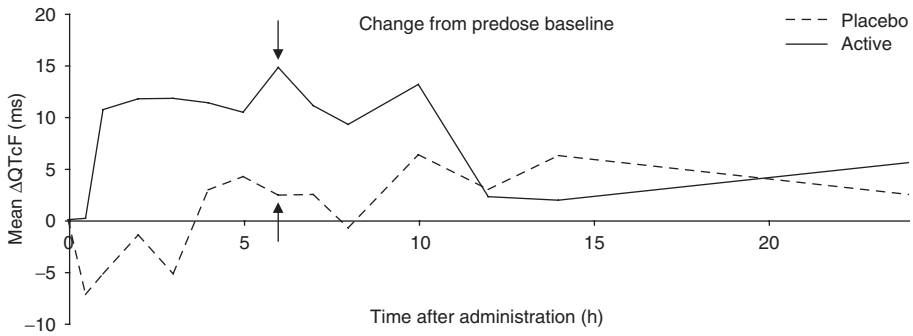

Fig. 2. Maximum increase in mean Fridericia corrected QT (QTcF) interval on drug is +15ms at 6 hours and, at the corresponding timepoint, the mean change in QTcF on placebo is +2.5ms. Therefore, the largest time-matched mean difference between the drug and placebo is +12.5ms.

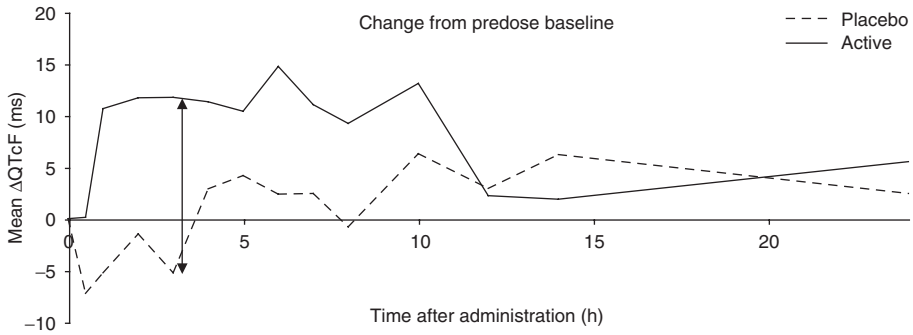

Fig. 3. At 3 hours' postadministration, the difference between Fridericia corrected mean changes in QT intervals (QTcF) on the drug and the placebo (ΔΔQTc) is the largest with a value of 17ms (computed from a ΔQTc of +12ms on drug and a ΔQTc of −5ms on placebo). At all other timepoints, the value of ΔΔQTc value is <17ms.

6.3 Parallel Studies

If D is the drug group and P is the placebo group, the baseline values for QTcD and QTcP should be computed for the two parallel groups by first considering all the drug-free baseline ECGs obtained prior to administration of the drug or the placebo. Then, $\Delta QTcD_0$, $\Delta QTcD_{0.5}$, $\Delta QTcD_{1.0}$, $\Delta QTcD_{1.5}$, $\Delta QTcD_{2.0}$, $\Delta QTcD_{2.5}$, $\Delta QTcD_{3.0}$ and so on should be calculated for each subject in the drug group and $\Delta QTcP_0$, $\Delta QTcP_{0.5}$, $\Delta QTcP_{1.0}$, $\Delta QTcP_{1.5}$, $\Delta QTcP_{2.0}$, $\Delta QTcP_{2.5}$, $\Delta QTcP_{3.0}$ and so on should be calculated for each subject in the placebo group. All these individual ΔQTc values at each timepoint should be averaged and a mean ΔQTc calculated at each timepoint for the drug as well as for the placebo groups. This will allow computation of the difference (ΔΔQTc) between mean ΔQTc on drug and mean ΔQTc on placebo at each timepoint. It is evident that ΔQTcD will be 0, ΔQTcP will be 0 and ΔΔQTc will also be 0 at timepoint 0 hour (baseline). Having done this for each timepoint, the timepoint at which the mean (+ standard error) ΔΔQTc is largest is identified. This mean ΔΔQTc value, with its 95% upper confidence bound, is used to define the effect of the drug on QTc interval. It is the parameter of regulatory interest – it is the largest ΔΔQTc value at one single timepoint and this timepoint is the same for both the active drug and the placebo.

6.4 Crossover Studies

A similar method can be employed for crossover studies; however, in the crossover design, if, instead of calculating the mean largest ΔΔQTc by averaging all the ΔΔQTc values of all the subjects at each timepoint, the mean largest ΔΔQTc were to be calculated by averaging only the largest ΔΔQTc value for each subject regardless of the timepoint at which it occurred, the parameter will have a larger value. Application of this method of computing mean largest ΔΔQTc compensates for inter-individual variability in peak effect since the largest ΔΔQTc value for different subjects may occur at different timepoints. These two forms of analyses are shown in table I and table II. There is also a risk that this parameter will tend to be larger as one increases the number of timepoints at which QTc intervals are measured. Since the largest time-matched difference at any timepoint will detect the QTc duration at its longest duration irrespective of the C_{max}, the C_{max} analysis will then not provide any more sensitivity in detecting the cardiac repolarisation changes due to the test drug.

Pharmacokinetic/pharmacodynamic modelling should be regarded as an additional form of analysis that is valuable only when a TET is not possible. It is not surprising that the final guideline points out that establishing the relationship of drug concentrations to changes in QT/QTc interval may provide addi-

Table I. Calculating the "largest time-matched mean difference between the drug and placebo (baseline adjusted)"

Time (h)	Subject 1 (ms)		Subject 2 (ms)		Subject 3 (ms)		Subject 4 (ms)	
	drug	placebo	drug	placebo	drug	placebo	drug	placebo
Raw QTc data[a]								
0	417	416	420	421	419	415	415	414
1	425	418	427	421	440	423	417	416
2	430	419	441	423	468	419	423	418
3	435	417	438	422	495	422	420	418
4	425	421	424	418	462	420	431	420
5	420	416	421	416	431	418	406	406
ΔQTc data[a]								
0	0	0	0	0	0	0	0	0
1	8	2	7	0	21	8	2	2
2	13	3	21	2	49	4	8	4
3	18	1	18	1	76[b]	7	5	4
4	8	5	4	−3	43	5	16	6
5	3	0	1	−5	12	3	−9	−8

a QTc interval data from a 'thorough QT/QTc study' in four subjects with six timepoints (0h values are average values from multiple drug-free ECGs).

b Data indicate that subject 3 exhibits a categorical response (ΔQTc interval) of 76ms and not 69ms.

QTc = corrected QT.

tional information to assist the planning and interpretation of studies assessing cardiac repolarisation.

7. Computing the QTc Interval Categorical Responses

With respect to categorical analysis, the final guideline, as its predecessor, notes that there is no consensus concerning the choice of upper threshold values for absolute QT/QTc interval and changes from baseline. While lower thresholds increase the false-positive rate, higher thresholds increase the risk of failing to detect a signal of concern. In clinical trials, a prolongation of QTc interval of >500ms during therapy has been a threshold of particular concern. The guideline suggests that multiple analyses using different thresholds are a reasonable approach to this uncertainty, including: (i) absolute QTc interval prolongation of >450ms, >480ms and >500ms; and (ii) QTc interval increases from baseline of >30ms and >60ms.

It has been suggested by some investigators that when computing change from baseline (with regard to categorical responses of increase in QTc interval of 30–60ms and >60ms), it should be placebo

Table II. Computation of individual and mean difference in corrected QT interval (ΔΔQTc) values from data in table I[a]

Time (h)	Subject 1 (ms)	Subject 2 (ms)	Subject 3 (ms)	Subject 4 (ms)	Mean of 4 subjects (ms)
0	0	0	0	0	0
1	6	7	13	0	6.50
2	10	19	45	4	19.50
3	17	17	69	1	26.00[b]
4	3	7	38	10	14.50
5	3	6	9	−1	4.25

a QTc interval data from a 'thorough QT/QTc study' in four subjects with six timepoints (0h values are average values from multiple drug-free ECGs).

b The largest time-matched mean difference between the drug and placebo (baseline adjusted) is 26ms at 3 hours. However, it can also be 28.75ms if only the largest ΔΔQTc interval values for the four subjects (regardless of the timepoint at which the change occurred) are used for computation (17ms for subject 1, 19ms for subject 2, 69ms for subject 3 and 10ms for subject 4).

adjusted to allow for circadian variability. Thus, a subject experiencing ΔQTc of 45ms from baseline on drug at a particular timepoint and experiencing ΔQTc of −20ms from baseline on placebo at that timepoint would qualify as one who has a categorical response of 65ms. The difficulty with this approach is that it is only possible in crossover studies and circadian variability is hardly ever that stable even within a subject. Data analyses also indicate that individual ΔΔQTc thus derived is statistically slightly more variable, even when no drug effect exists.

Experience with >20 TETs over the last 3 years suggests that as far as categorical analysis is concerned, there is little to be gained by analysing QTc interval data by thresholds for absolute QTc interval prolongations of >450ms and >480ms. Evaluation of the drug effect will likely be complicated by these multiple analyses and difficult to interpret if only one or two 'cuts' of the data show an effect. Therefore, analysis that includes only new absolute QTc interval of >500ms and change from baseline in QTc interval of 30–60ms and >60ms should be adequate. When evaluated collectively, these two forms of categorical responses also address the complications arising from tendency of the QTc interval to regress to mean.

8. Impact of the 'Thorough QT/QTc Study' on Subsequent Drug Development

One very important clarification introduced in the final version of ICH E14 relates to the significance of a TET for subsequent development of the drug. As stated in the previous draft, it appeared that a positive study would automatically result in the drug being considered proarrhythmic and might attract all the prescribing restrictions. In contrast, the revised version clarifies that the TET is intended to determine whether the drug has a threshold pharmacological effect on cardiac repolarisation, as detected by QT/QTc prolongation, to enable a decision to be made on whether robust ECG monitoring is warranted during the later stages of drug development. A positive study does not identify the drug as being necessarily proarrhythmic. This goes a long way to addressing concerns raised in the earlier commentary[3] that a low threshold will result in a large number of (false positive) new drugs attracting unwarranted restrictive labelling and that there are three possible outcomes from the analysis of clinical QTc-related data. These are: no effect, a clinically insignificant effect or a clinically significant effect.

Whereas previously a negative TET 'trumped' positive non-clinical data of concern, Step 4 of ICH E14 has now given greater recognition to non-clinical data even when the TET is negative. The revised text acknowledges that there could be very unusual cases in which the TET is negative but the available non-clinical data are strongly positive (e.g. hERG positive at low concentrations and *in vivo* animal model results that are strongly positive). If this discrepancy cannot be explained by other data, and the drug is in a class of pharmacological concern, the guideline recommends that expanded ECG safety evaluation during the later stages of drug development might be appropriate

It is worth noting that there is no universal definition on what constitutes 'strongly positive' non-clinical data, with all its consequences for a negative TET and subsequent drug development. It is widely accepted that any characterisation of potency of an effect must embrace the concept of a safety margin. ICH S7B does not include this concept and, therefore, this raises an additional regulatory concern with regard to the definition of what constitutes 'strongly positive' non-clinical data.

Redfern et al.[18] have determined the relative value of non-clinical cardiac electrophysiological data (*in vitro* and *in vivo*) for predicting risk of torsade de pointes in clinical use. In addition to cardiac action potential duration (APD) *in vitro* and QT prolongation *in vivo* in dogs, they used published data on hERG (or I_{Kr}) activity, as the basis for comparison against QT effects and reports of torsade de pointes in humans for 100 drugs. Their data on hERG or I_{Kr} IC_{50} (the concentration of the drug required to produce 50% inhibition of the channel) suggest that a 30-fold margin between hERG IC_{50} and peak free therapeutic plasma concentrations

may be adequate to confidently exclude a clinical effect on cardiac repolarisation. This safety margin is also supported by data reviewed by Webster et al.[42] However, for the sake of greater certainty, Redfern et al.[18] recommend a higher safety margin in the future but correctly emphasise that the acceptable safety margin should depend on the lethality of the disease to be treated – ranging from 10-fold for a lethal disease to >100-fold for (symptomatic treatment of) a benign condition. Thus, if a safety margin is generally <30-fold, non-clinical data could be considered positive and require robust monitoring in later phase clinical development regardless of a negative TET. When calculating this safety margin, there are three possible variations. It can be the ratio of *in vitro* hERG IC_{50} to: (i) EC_{50} (drug concentration required to elicit 50% response at the intended pharmacological target); (ii) effective free plasma concentrations; or (iii) effective myocardial concentration that is so dependent on lipophilicity of the drug. The point is illustrated by terfenadine that is about 260 times more lipophilic than cetirizine. Depending on the method of calculation, the three corresponding cardiac safety index values are 0.5, >104 and 0.4, respectively, for terfenadine and >3, 28 and >56, respectively, for cetirizine.[43] Similar considerations also apply when designating the *in vivo* study in dogs as 'strongly positive'.

Thus, only when the non-clinical data and the TET are *both* negative, will some regulatory authorities allow collection of on-therapy ECGs in accordance with the current practices in each therapeutic area to constitute sufficient evaluation during subsequent stages of drug development. Some have interpreted this to mean that in such circumstances QT interval data need not be collected routinely during phase II and III studies. This is not the understanding of the regulatory authorities. The guideline directly or indirectly addresses this issue. It provides recommendations and requires data on patients that have discontinued use of the study drug due to prespecified categorical changes in QTc interval as well as the effect of the drug in a patient population studied following even a negative TET. It also requires data on dosage reductions prompted by QT/QTc interval prolongation. It is difficult to see how this information can be gathered if the QT intervals of patients in phases II and III are not monitored. In summary, if the sponsors are intending not to routinely measure QT intervals, they would be well advised to confirm with regulatory authorities their planned schedules and details of what ECG parameters they actually intend to monitor in phases II and III studies.

A positive TET (defined as one in which the 95% upper confidence bound for the largest time-matched mean effect of the drug on the QTc interval includes 10ms) or 'strongly positive' non-clinical data (as discussed previously) will almost always call for an expanded ECG safety evaluation during later stages of drug development. One objective of this evaluation should be to fully describe the effect of the drug on the QT/QTc interval in the target patient population with particular attention to dose- and concentration-related effects. It is important to include in these analyses patients exposed to the full range of potential doses and patients with additional risk factors for torsade de pointes. These analyses would ordinarily focus on outliers as well as on changes in mean QT/QTc interval. Depending on the size of the effect seen in the TET, more intense monitoring of patients with additional risk factors for torsade de pointes might be needed. Ideally, the major clinical studies should include an adequate representation of female and elderly patients, as well as patients with co-morbidities and concomitant medications typical of the expected target population. Analyses of the ECG and adverse event data from certain patient subgroups are of particular interest, such as:

- patients with electrolyte abnormalities (e.g. hypokalaemia);
- patients with congestive heart failure;
- patients with impaired drug metabolising capacity or clearance (e.g. renal or hepatic impairment, drug interactions);
- female patients;
- patients aged <16 and >65 years.

A possibility that cannot be excluded is that the positive control in an occasional TET will not exhib-

it the effect it is expected to. In such a case, the validity of the TET is in doubt. If the conclusion from such a TET is to suggest that the new drug is 'negative', clearly a new TET is required before this conclusion can be accepted. However, if the TET is 'positive', the true potential (less or even more potent) of the new drug to prolong the QTc interval, and by inference its benefit-risk profile, remains in doubt. Although its potency may be discerned from non-clinical and early-phase clinical data, the sponsor in this instance is committed to robust ECG monitoring during later phase clinical trials. Alternatively, depending on an integrated assessment of all available data, the potential benefits of the drug and alternative therapies available, a strong case can be made for repeating the TET.

9. Future of ICH E14 and ICH S7B and Way Forward

No other area of drug safety has attracted as much interest from regulators, sponsors of new drugs, academic scientists and prescribing physicians as has drug-induced QT interval prolongation. This is not surprising given the wide range of drugs found to produce this effect and, arising from a potentially fatal outcome therefrom, the significant impact it has on benefit-risk assessment of a drug.

One major problem with ICH E14 and S7B guidelines is the excessive focus on QT interval as a surrogate of proarrhythmic risk. While data are required in terms of the number and percentage of subjects in each treatment group in TET developing changes from baseline that represent the appearance or worsening of the morphological abnormality of repolarisation waveforms, there is no clue on how these data will impact on the designation of a TET as either positive or negative. With the advances in technology, it seems that it may be possible to derive other relatively less complex ECG-derived parameters for risk assessment such as transmural dispersion in repolarisation that is thought to be represented by the interval from the peak to the end of T wave. Another disappointing feature of ICH E14 and S7B is the focus on *prolongation* of the QT interval without adequate recognition of the ancillary pharmacology of the drug that modulates the clinical risk or shortening of QTc interval. It is now becoming increasingly evident that shortening of QTc interval, generally below 300ms, can also be proarrhythmic.[44,45] Whether or not there are drugs that shorten a normal QT interval at baseline to a proarrhythmic level remains to be seen. Mexiletine uniformly shortens ventricular repolarisation and APD. Despite normal QTc interval, mexiletine induces torsade de pointes and, in approximately 5% of patients, proarrhythmic reactions.[46] Furthermore, there are recent reports of at least two new drugs that shorten QT interval.[47,48] It has already been noted previously that a regulatory assessment, based solely on the potential of a drug to *prolong* the QTc interval, may result in either restriction in the use (or even rejection) of a potentially beneficial drug or approval of an otherwise hazardous drug without the restrictions required to promote its safe use.

There is an immense research effort aimed at evaluating the best techniques for recording, measuring, correcting and interpreting drug-induced QT interval prolongation. Concurrently, recognising the imperfect nature of the QT interval as a surrogate for torsade de pointes, efforts searching for biomarkers of greater predictive value are also under way.[49,50]

The result of implementing ICH E14 and S7B across the globe will generate exciting data over the next 5 years. These data will provide a better perspective on the correlation between non-clinical data, the TET and the clinical risk. The strength of this correlation will be critical to the future reappraisal of the need for either the TET or the S7B-compliant non-clinical studies. Even if there were a few sporadic compounds for which the non-clinical data might not predict the clinical risk, the TET may still need to be examined in terms of its own predictive value as well as its cost effectiveness. In a recent report from the FDA that deals with innovation and stagnation in the pharmaceutical industry, an area of opportunity identified is an urgent need to develop tools to accurately assess the risk of new drugs causing heart rhythm abnormalities.[51]

The ICH Note for Guidance on Planning Pharmacovigilance Activities (ICH E2E) is highly relevant to drug-induced proarrhythmias. This guideline has been adopted by the CHMP (CPMP/ICH/5716/03) and came into operation in June 2005. All new drugs seeking approval will require a 'safety specification' that should specifically discuss: (i) limitations of the safety database; (ii) safety in populations not studied; (iii) actual and potential risks requiring further evaluation; (iv) drug-drug and drug-food interactions; (v) epidemiology of the indication(s); and (vi) pharmacological class effects. Since clinical trials are conducted in a highly select population of 3000–4000 patients, the ICH E14 guideline points out that in evaluating the safety database of a new drug, consideration should be given to the extent to which the inclusion and exclusion criteria for patient eligibility might have influenced the study population with respect to the risk of QT/QTc interval prolongation and associated adverse events (e.g. exclusion of patients with cardiac co-morbidities or renal/hepatic impairment, or prohibition of diuretics as concomitant medications). There is now a pressing need for a guideline on postmarketing surveillance of drugs for their proarrhythmic risk.

10. Conclusions

No battery of non-clinical studies or clinical trials, however robust, will *always* identify *all* the drugs with extremely low risk of torsade de pointes. Complete elimination of the risk of torsade de pointes is an unrealistic expectation since torsade de pointes is said to be a '*moving target*'.[2] As stated earlier, benefit-risk analysis in drug development and the regulatory approval process includes the seriousness of the condition under treatment and alternatives already available. Depending on the benefits offered by the new drug, an incidence of a potentially fatal event at the rate of 1 in 3000 may be unacceptable whereas an incidence of 1 in 500 000 may be considered acceptable, with a whole range of benefit-risk in between. In the final analysis, as with other potentially fatal adverse drug reactions, such as myelotoxicity, gastrointestinal haemorrhage, hepatotoxicity or rhabdomyolysis, a level of proarrhythmic risk may have to be tolerated.

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References

1. Shah RR. The significance of QT interval in drug development. Br J Clin Pharmacol 2002; 54: 188-202
2. Priori SG. Exploring the hidden danger of noncardiac drugs. J Cardiovasc Electrophysiol 1998; 9: 1114-6
3. Shah RR. Drugs, QT interval prolongation and ICH E14: the need to get it right. Drug Saf 2005; 28: 115-25
4. Committee for Proprietary Medicinal Products. 'Points to consider: the assessment of the potential for QT interval prolongation by non-cardiovascular medicinal products' (CPMP/986/96) [online]. European Medicines Evaluation Agency; 1997 Dec 17; London, UK. Available from URL: http://www.emea.eu.int/pdfs/human/swp/09896en.pdf [Accessed 2005 Aug 8]
5. International Conference on Harmonisation. The non-clinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals [online]. Available from URL: http://www.ich.org/MediaServer.jser?@_ID=2192&@_MODE=GLB [Accessed 2005 Sep 14]
6. International Conference on Harmonisation. The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs [online]. Available from URL: http://www.ich.org/MediaServer.jser?@_ID=1476&@_MODE=GLB [Accessed 2005 Sep 14]
7. Grisanti S, Morganroth J, Shah RR. A practical approach to cardiac safety. Appl Clin Trial. In press
8. Food and Drug Administration. Safety warnings regarding use of fentanyl transdermal (skin) patches [online]. Public Health Advisory, 2005, July 15. Available from URL: http://www.fda.gov/cder/drug/advisory/fentanyl.htm [Accessed 2005 Aug 8]

9. Mauro VF, Bingle JF, Ginn SM, et al. Torsade de pointes in a patient receiving intravenous vasopressin. Crit Care Med 1988; 16: 200-1
10. Charbit B, Funck-Brentano C, Samain E, et al. QT interval prolongation after oxytocin bolus during surgical induced abortion. Clin Pharmacol Ther 2004; 76: 359-64
11. Marfella R, Nappo F, De Angelis L, et al. The effect of acute hyperglycaemia on QTc duration in healthy man. Diabetologia 2000; 43: 571-5
12. Liou SC, Chen C, Wong SY, et al. Ventricular tachycardia after oxytocin injection in patients with prolonged Q-T interval syndrome: report of two cases. Acta Anaesthesiol Sin 1998; 36: 49-52
13. Beasley CM, Mitchell MI, Dmitrienko AA, et al. The combined use of ibutilide as an active control with intensive electrocardiographic sampling and signal averaging as a sensitive method to assess the effects of tadalafil on the human QT interval. J Am Coll Cardiol 2005; 46: 678-87
14. Food and Drug Administration. FDA Cardiovascular and Renal Advisory Committee (29 May 2003). Levitra briefing document [online]. Available from URL: http://www.fda.gov/ohrms/dockets/ac/03/briefing/3956B1_05_Bayer-Levitra.pdf [Accessed 2005 Aug 8]
15. Bass AS, Tomaselli G, Bullingham R, et al. Drugs effects on ventricular repolarization: a critical evaluation of the strengths and weaknesses of current methodologies and regulatory practices. J Pharmacol Toxicol Methods 2005; 52: 12-21
16. McKibbin JK, Pocock WA, Barlow JB, et al. Sotalol, hypokalaemia, syncope, and torsade de pointes. Br Heart J 1984; 2: 157-62
17. Cavero I, Crumb W. The use of electrocardiograms in clinical trials: a public discussion of the proposed ICH E14 regulatory guidance. Expert Opin Drug Saf 2005; 4: 795-9
18. Redfern WS, Carlsson L, Davis AS, et al. Relationships between preclinical cardiac electrophysiology, clinical QT interval prolongation and torsade de pointes for a broad range of drugs: evidence for a provisional safety margin in drug development. Cardiovasc Res 2003; 58: 32-45
19. Shryock JC, Song Y, Wu L, et al. A mechanistic approach to assess the proarrhythmic risk of QT-prolonging drugs in preclinical pharmacologic studies. J Electrocardiol 2004; 37 Suppl.: 34-9
20. Joshi A, Dimino T, Vohra Y, et al. Preclinical strategies to assess QT liability and torsadogenic potential of new drugs: the role of experimental models. J Electrocardiol 2004; 37 Suppl.: 7-14
21. Ficker E, Kuryshev YA, Dennis AT, et al. Mechanisms of arsenic-induced prolongation of cardiac repolarization. Mol Pharmacol 2004; 66: 33-44
22. Kuryshev YA, Ficker E, Wang L, et al. Pentamidine-induced long QT syndrome and block of hERG trafficking. J Pharmacol Exp Ther 2005; 312: 316-23
23. Wible BA, Hawryluk P, Ficker E, et al. HERG-Lite: a novel comprehensive high-throughput screen for drug-induced hERG risk. J Pharmacol Toxicol Methods 2005; 52: 136-45
24. Kannankeril PJ, Roden DM, Norris KJ, et al. Genetic susceptibility to acquired long QT syndrome: pharmacologic challenge in first-degree relatives. Heart Rhythm 2005; 2: 134-40
25. Pfizer Inc. Briefing document for Zeldox capsules. Psychopharmacological Advisory Committee [online]. Rockville (MD): Food and Drug Administration, 2000 Jul 19. Available from URL: http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3619b1a.pdf [Accessed 2005 Sep 2]
26. Rodriguez I, Kilborn MJ, Liu XK, et al. Drug-induced QT prolongation in women during the menstrual cycle. JAMA 2001; 285: 1322-6
27. Benton RE, Sale M, Flockhart D, et al. Greater quinidine-induced QTc interval prolongation in women. Clin Pharmacol Ther 2000; 67: 413-8
28. Abi-Gerges N, Philp K, Pollard C, et al. Sex differences in ventricular repolarization: from cardiac electrophysiology to torsades de pointes. Fundam Clin Pharmacol 2004; 18: 139-51
29. James AF, Cho SC, Hancox JC. Recent advances in understanding sex differences in cardiac repolarization. Prog Biophys Mol Biol 2005 Jun 24, [Epub ahead of print]
30. Nakagawa M, Ooie T, Ou B, et al. Gender differences in autonomic modulation of ventricular repolarization in humans. J Cardiovasc Electrophysiol 2005; 16: 278-84
31. Mansi IA, Nash IS. Ethnic differences in electrocardiographic intervals and axes. J Electrocardiol 2001; 34: 303-7
32. Ackerman MJ, Tester DJ, Jones GS, et al. Ethnic differences in cardiac potassium channel variants: implications for genetic susceptibility to sudden cardiac death and genetic testing for congenital long QT syndrome. Mayo Clin Proc 2003; 78: 1479-87
33. Ackerman MJ, Splawski I, Makielski JC, et al. Spectrum and prevalence of cardiac sodium channel variants among black, white, Asian, and Hispanic individuals: implications for arrhythmogenic susceptibility and Brugada/long QT syndrome genetic testing. Heart Rhythm 2004; 1: 600-7
34. Sarapa N, Morganroth J, Couderc JP, et al. Electrocardiographic identification of drug-induced QT prolongation: assessment by different recording and measurement methods. Ann Noninvasive Electrocardiol 2004; 9: 48-57
35. Savelieva I, Yi G, Guo X, et al. Agreement and reproducibility of automatic versus manual measurement of QT interval and QT dispersion. Am J Cardiol 1998; 81: 471-7
36. Azie NE, Adam G, Darpo B, et al. Comparing methods of measurement for detecting drug-induced changes in the QT interval: implications for thoroughly conducted ECG studies. Ann Noninvasive Electrocardiol 2004; 9: 166-74
37. Malik M. The imprecision in heart rate correction may lead to artificial observations of drug induced QT interval changes. PACE 2002; 25: 209-16
38. Malik M, Farbom P, Batchvarov V, et al. Relation between QT and RR intervals is highly individual among healthy subjects: implications for heart rate correction of the QT interval. Heart 2002; 87: 220-8
39. Batchvarov VN, Ghuran A, Smetana P, et al. QT-RR relationship in healthy subjects exhibits substantial intersubject variability and high intrasubject stability. Am J Physiol 2002; 282: H2356-63
40. Fossa AA, Wisialowski T, Magnano A, et al. Dynamic beat-to-beat modeling of the QT-RR interval relationship: analysis of QT prolongation during alterations of autonomic state versus human ether a-go-go-related gene inhibition. J Pharmacol Exp Ther 2005; 312: 1-11
41. Patterson SD, on behalf of Pharmaceutical Research and Manufacturers of America QT Statistics Expert Team. Investigating drug-induced QT and QTc prolongation in the clinic: a review of statistical design and analysis considerations. Drug Inf J 2005; 39: 243-66
42. Webster R, Leishman D, Walker D. Towards a drug concentration effect relationship for QT prolongation and torsades de pointes. Curr Opin Drug Discov Devel 2002; 5: 116-26

43. Cavero I, Crumb W. Native and cloned ion channels from human heart: laboratory models for evaluating the cardiac safety of new drugs. Eur Heart J 2001; 3 Suppl. K: K53-63
44. Wolpert C, Schimpf R, Veltmann C, et al. Clinical characteristics and treatment of short QT syndrome. Expert Rev Cardiovasc Ther 2005; 3: 611-7
45. Antzelevitch C. Cardiac repolarization: the long and short of it. Europace 2005; 7 Suppl. 2: 3-9
46. Morganroth J. Comparative efficacy and safety of oral mexiletine and quinidine in benign or potentially lethal ventricular arrhythmias. Am J Cardiol 1987; 60: 1276-81
47. Kang J, Chen X-L, Wang H, et al. Discovery of a small molecule activator of the human ether-ago-go-related gene (hERG) cardiac K+ channel. Mol Pharmacol 2005; 67: 827-36
48. Zhou J, Augelli-Szafran CE, Bradley JA, et al. Novel potent human ether-a-go-go-related gene (hERG) potassium channel enhancers and their in vitro antiarrhythmic activity. Mol Pharmacol 2005; 68: 876-84
49. Kinter LB, Siegl PKS, Bass AS. New preclinical guidelines on drug effects on ventricular repolarization: safety pharmacology comes of age. J Pharmacol Toxicol Methods 2005; 52: 153-8
50. Lawrence CL, Pollard BE, Hammond TG, et al. Nonclinical proarrhythmia models: predicting torsades de pointes. J Pharmacol Toxicol Methods 2005; 52: 46-59
51. US FDA. Report on 'Stagnation and innovation: challenge and opportunity on the critical path to new medical products'. Rockville (MD): Food and Drug Administration, 2004 Mar. Available from URL: http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.pdf [Accessed 2005 Jul 23]

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