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Cardiac Repolarisation and Drug Regulation

Assessing Cardiac Safety 10 Years after the CPMP Guidance

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Abstract

December 2007 marks the 10-year anniversary of the first regulatory guidance for evaluation of drug-induced QT interval prolongation. A decade on, it seems surprising that this document, which was released by the Committee on Proprietary Medicinal Products, caused such acrimony in the industry. Sponsors now routinely evaluate their new drugs for an effect on cardiac electrophysiology in preclinical studies, in addition to obtaining ECGs in all phases of drug development and conducting a formal thorough QT study in humans.

However, concurrently, new concerns have also emerged on broader issues related to the cardiovascular safety of drugs because of their potential to shorten the QT interval as well as to induce proischaemic, profibrotic or prothrombotic effects. Drugs may also have an indirect effect by adversely affecting one or more of the cardiovascular risk factors (e.g. through fluid retention or induction of dyslipidaemia).

In addition to peroxisome proliferator-activated receptor agonists and cyclooxygenase 2 selective inhibitors, three other drugs, darbepoetin alfa, pergolide and tegaserod, provide a more contemporary regulatory stance on tolerance of cardiovascular risk of drugs and their benefit-risk assessment. This recent, more assertive, risk-averse stance has significant implications for future drug development. These include the routine evaluation of cardiovascular safety for certain classes of drugs. Drugs that are intended for long-term use will almost certainly require long-term clinical evaluation in studies that enrol populations that most closely resemble the ultimate target population. Novel mechanisms of action and biomarkers by themselves are no guarantee of improved safety or benefits. Even some traditional biomarkers have come to be viewed with scepticism. Requirements for more extensive and earlier postmarketing assessment of clinical benefits and rare, but serious risks associated with new medicinal products should create a new standard of evidence for industry and regulators and almost certainly result in better assessment of benefit/risk, more effective and balanced regulatory actions and better care for patients.

In December 1997, the Committee on Proprietary Medicinal Products (CPMP), the EU scientific advisory body for human medicines, became the first regulatory body to publicly express concerns regarding the adverse effects of drugs on cardiac repolarisation when it adopted its 'Points to Consider'

document, entitled *The Assessment of the Potential for QT Interval Prolongation by Non-Cardiovascular Medicinal Products*.[1]

In marking the 10th anniversary of this first strategic regulatory guidance document on drug-induced QT interval prolongation, this review briefly summarises some of the important milestones leading to this document and ultimately culminating in mid-2005 in the International Conference on Harmonisation (ICH) E14 guidance entitled *The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs*.[2] This review also explores other areas of cardiac safety that are beginning to attract regulatory and clinical interest and are likely to be critical in the future development and approval of new drugs.

1. First Recognition of Drug-Induced QT Prolongation

Quinidine was first introduced as an antiarrhythmic drug in 1918.[3] Its antiarrhythmic efficacy was attributed to its ability to prolong cardiac repolarisation duration, as long ago as 1926.[4] However, its use was soon followed by reports of syncopal attacks and unexpected fatalities, and these adverse effects were attributed to respiratory paralysis or ventricular irritability.[3,5,6] The earliest well documented accounts of an association between the use of quinidine and QT interval prolongation were published in 1943;[7,8] indeed, it was considered that QT interval prolongation was an early significant indication of the onset of its activity.

In one of the first analyses of a large series of cases (n = 168) of QT interval prolongation reported in 1951, the only drug to appear in the list of causes was quinidine (in eight patients).[9] In six patients, the cause was unknown and the authors concluded, "Future studies may make it possible to place them in their proper categories".

The association between quinidine and various forms of ventricular tachyarrhythmias was appreciated as early as 1921,[10] and in 1956, Thomson[11] reviewed in detail quinidine as a cause of sudden death and ventricular tachyarrhythmias. Although cardiac failure as a risk factor was recognised in this review, it is not surprising that no connection was made between quinidine-induced QT interval prolongation and these tachyarrhythmias. The probable aetiology of prolonged QT interval in the six patients with no known cause reported by Bellet and Finkelstein[9] and the connection between QT interval prolongation and ventricular arrhythmias[11] had to await the first descriptions of congenital forms of long QT syndromes in 1957–64.[12-15]

In 1964 it was demonstrated that the syncopal attacks associated with quinidine were due to cardiac rhythm disturbances, described at that time as paroxysmal ventricular fibrillation, which had the ECG features of 'torsade de pointes' (TdP),[16] although the term itself was not coined until 1966.[17] By 1991, it was fairly well established that quinidine had an adverse effect on mortality compared with other class I antiarrhythmic agents and that its use required individualised assessment of patients for potential benefit and harm.[18]

In 1958, thioridazine was introduced to the market for the treatment of schizophrenia. The observations that apparently well tested non-cardiac drugs could also have unintended adverse cardiac effects were made as long ago as 1963, if not earlier, when the use of thioridazine was associated with two fatalities with quinidine-like electrocardiographic abnormalities.[19,20] Following further reports, this effect was later shown to be caused by electrophysiological changes that reflect on the surface ECG as QT interval prolongation.[21-28] Concern later extended to other drugs of its chemical class (phenothiazines).[29-35]

By the early 1970s, this concern had extended to the entire therapeutic class of antipsychotic agents, regardless of their chemical structure.[36-38] Thus, during the period of 1960–70, it was already well recognised that psychoactive drugs could prolong the QT interval and produce these rapid cardiac arrhythmias, often with a fatal outcome. Indeed, some of these agents were sufficiently potent in their QT-prolonging (class III antiarrhythmic) activity, and such was the faith in QT interval prolongation as an efficient antiarrhythmic mechanism, that at one

time, melperone (a butyrophenone antipsychotic) was being investigated for its use as an antiarrhythmic agent.[39,40]

Studies in patients with overdoses of tricyclic antidepressant drugs during the 1970s further highlighted a causal association between non-cardiac drugs and QT interval prolongation; thus implicating another therapeutic class.[41-45]

At about the same time in the early 1970s, the antianginal drug prenylamine, which was first introduced to the market in the 1960s, also came to be associated with reports of QT interval prolongation and TdP.[46-49] It is interesting to note that amiodarone was also first introduced in 1962 as a coronary vasodilator antianginal agent. Bepridil and lidoflazine were other antianginal agents that were associated with QT interval prolongation and TdP.[50-57] Indeed, with bepridil and lidoflazine, the frequency of TdP was sufficiently high that this adverse effect was reported in small clinical trials.[56,58,59] Lidoflazine, although approved in a number of countries, was never marketed and ultimately it was shown to affect the current that is responsible for cardiac repolarisation.[60] Thus, by the late 1970s, it was fairly well recognised that a variety of non-cardiac drug classes and antianginal drugs could prolong the QT interval and induce TdP.

In terms of antiarrhythmic agents other than quinidine, concerns regarding QT interval prolongation also extended subsequently to other (then recently introduced) drugs that were actually intended to be safer and more effective in treating cardiac arrhythmias, such as mexiletine (class IB),[61] disopyramide and procainamide (both class IA).[62-64] The proarrhythmic effects of antiarrhythmic agents as a class of drugs began to attract serious attention in the early 1980s.[65,66] At about this time, the term 'proarrhythmia' first made its appearance to alert the prescribing community that antiarrhythmic drugs may aggravate arrhythmia.[67] In one report, quinidine significantly prolonged the QT interval, whereas mexiletine did not.[68] However, proarrhythmic reactions were recorded in 18 of 221 (8%) patients taking quinidine and 10 of 217 (5%) patients taking mexiletine.[68]

Although a few established drugs were known to prolong the QT interval (such as bretylium, betanidine, amiodarone and sotalol), one notable example of a new drug was lorcainide, a class IC antiarrhythmic drug. Lorcainide was found to prolong not only the refractory period of isolated Purkinje and ventricular muscle preparations[69] but also QT interval in humans[70] and was reported to be arrhythmogenic in canine ventricular preparations.[71] Lorcainide was interesting because, like the N-acetyl metabolite of procainamide, both lorcainide and its metabolite norlorcainide caused concentration-dependent prolongation of the QT interval.[72] Thus, even metabolites were beginning to attract attention for their potential QT liability.[73]

Although not consistently reported to prolong the QT interval,[74] a structurally related antiarrhythmic drug, encainide, was already known to induce malignant ventricular arrhythmias in a substantial number of patients.[75] In 1989, the CAST (Cardiac Arrhythmia Suppression Trial) study was abruptly terminated following the finding that, compared with placebo, class IC antiarrhythmic drugs (flecainide and encainide, and subsequently moracizine) were associated with an increased risk of mortality, presumed to be due to cardiac arrhythmias.[76] These proarrhythmic effects of antiarrhythmic drugs led to severe prescribing restrictions on their use and regulatory authorities were now concerned with the safety of antiarrhythmic drugs generally.

Regulatory concerns about the potential of drugs to increase the duration of the QT interval gathered momentum during the 3-year period from 1988 to 1991, when three drugs were withdrawn from the market because of their propensity to induce this cardiotoxic effect, including TdP. The drugs concerned were prenylamine (withdrawn from the market in 1988), lidoflazine (withdrawn 1989) and terodiline (withdrawn 1991). Terodiline is particularly interesting because it was first introduced for clinical use as an antianginal drug in Scandinavia in 1965. However, its potent anticholinergic activity resulted in frequent and severe urinary retention. Therefore, in the early 1980s, it was redeveloped for

use in urinary incontinence and first marketed in the UK in 1986 for this new indication.

In addition to prenylamine, lidoflazine and terodiline, three other drugs also began to attract significant regulatory and clinical attention for the same reasons during this period. These were pimozide (an antipsychotic drug), terfenadine and astemizole (both non-sedating antihistamine agents). There was ample evidence by now that the effect on cardiac repolarisation was concentration dependent (type A pharmacological reaction) and, in some cases, might also be stereoselective.[77]

These regulatory and clinical concerns intensified further during the period 1991–6 as a result of further reports of TdP (some fatal) associated with pimozide, terfenadine and astemizole and two new drugs belonging to completely new therapeutic classes, halofantrine (an antimalarial drug) and cisapride (a gastric prokinetic drug).[78-80] The role of drug interactions, resulting from inhibition of the metabolic elimination of the culprit drugs, was also becoming much clearer.[81]

Reports of QT interval prolongation and TdP associated with these non-antiarrhythmic drugs, primarily terfenadine, led to what was probably the first ever meeting on this important subject. Academic investigators, physicians from the US FDA and clinical scientists from the pharmaceutical industry gathered at the Annual Meeting of the Symposium on New Drugs and Devices in Philadelphia to review and discuss the implications for patient safety and drug development of a prolonged corrected QT (QTc) interval. The main theme of the meeting was to consider whether prolongation of QTc interval was beneficial or harmful. The proceedings of this symposium, although lacking any regulatory status, were published in August 1993[82] and stimulated further interest in this area of drug safety.

From a regulatory perspective, three important points made were that (i) insufficient evidence existed to suggest that prolongation of the QT interval corrected for heart rate (QTc) was necessarily beneficial; (ii) except in life-threatening situations, drug-induced QTc interval prolongation must be considered a risk;[83] and (iii) QT interval prolongation was not a good indicator of whether or not a class III antiarrhythmic will suppress a target arrhythmia; however, exaggerated QT prolongation was a predictor of TdP.[84]

Regulators at the meeting expressed the view that it was a wonder that quinidine was still on the market. Lipicky[83] and Botstein[85] from the FDA emphasised the importance of proper pharmacological study design and the significance of dose-QTc response relationship. Such studies should pay careful attention to the metabolic profile of the drug in order to identify subpopulations at risk of QTc interval prolongation, especially when resulting from drug interactions.

In November 1994, the SWORD (Survival With Oral d-Sotalol) study, which evaluated d-sotalol, a drug that acts exclusively by prolonging the QT interval, was also terminated prematurely because of increased mortality associated with its use compared with placebo.[86] This study served to remove any lingering misconceptions about drug-induced QT interval prolongation being predominantly a therapeutic or beneficial effect. As a result, the focus on drug-induced QT interval prolongation changed, and it is now regarded as a toxic effect that could have a beneficial effect in some circumstances. The balance between the therapeutic antiarrhythmic versus the potentially fatal proarrhythmic prolongations of the QT interval was recognised by all accounts as being a very delicate one, and this balance depended on the presence of many readily identifiable risk factors.[87]

Regulatory authorities were particularly troubled by the fact that, for the majority of these drugs, there was no evidence of their QT or arrhythmogenic liability during clinical trials, and the potentially fatal risk had not become evident until long after the drugs had been approved for routine clinical use. The number of torsadogenic drugs appeared to be clearly on the increase, and although the risk of TdP is sufficiently low that it could not be detected during clinical trials, it was recognised that there were mechanism-based, concentration-related, surrogate markers, the action potential duration (APD)

in vitro and the QT interval *in vivo*, by which a new drug could be studied during the pre-approval period.

2. The Committee on Proprietary Medicinal Products Document

During 1995–6, the UK drug regulatory authority also approved two new drugs that were associated with QT interval prolongation. In clinical trials, both sertindole (an atypical antipsychotic) and mizolastine (another non-sedating antihistamine) induced QT interval prolongation in a small number of patients.[88-90] Whereas the QT interval prolongation caused by sertindole was quite marked, the effect of mizolastine was very modest. Although neither drug was reported to have induced TdP in clinical trials, there was considerable difference in the benefit-risk evaluation of these drugs between the various Member States of the EU. A number of Member States (Germany, Greece, Spain, The Netherlands and Sweden) raised major objections regarding the QT liability of mizolastine. Since no consensus could be achieved, in May 1996 the Swedish authority referred the application to the CPMP for arbitration – in itself a relatively rare event in those days.

The arbitration process, which concluded in December 1996, resulted in a number of contraindications and warnings being included in the Summary of Product Characteristics for mizolastine.[89] In order to facilitate the arbitration process and avoid similar differences in future, the CPMP had already decided in May 1996 to convene an *ad hoc* group of experts on the QT interval to advise on appropriate preclinical and clinical testing of compounds to identify new drugs with QT liability and the documentation necessary to provide reassurance concerning the safe clinical usage of such products. The aim was to harmonise an EU-wide approach to evaluation of this effect on the benefit-risk profile of drugs. The CPMP experts proposed a preclinical and clinical strategy, now popularly referred to as 'the CPMP document', by which non-cardiovascular medicinal products should be evaluated during their development, and this was adopted by the CPMP during their meeting on 17 December 1997.[1] At the same meeting, the CPMP also adopted the first regulatory guidance on the investigation of drug interaction potential of a drug, entitled *Note for Guidance on the Investigation of Drug Interactions*.[91]

The CPMP document[1] cautioned that the potential of non-cardiac medicinal products to prolong the QT interval and induce TdP had significant implications for their future development. It was recognised that the strategies proposed would need to be revised to keep pace with ongoing development in science. Certain medicinal products might be considered exempt if justified (e.g. monoclonal antibodies, blood products etc.).

Within the framework of *in vivo* preclinical studies, usually carried out over a range of escalating doses, the recommendation was to include robust monitoring of the following:

- basic haemodynamics;
- ECG (with a focus on QT interval, and T and U wave morphologies);
- occurrence of any arrhythmias;
- correlation of these changes with pharmacokinetic profile of the drug.

Importantly, the recommendations included conduct of suitable and adequate *in vitro* electrophysiological studies prior to the first use of new drugs in humans.[1] The focus was on careful exploration of the reverse rate dependency of an effect on APD and appearance of early after-depolarisations at concentrations that should exceed the anticipated maximal therapeutic plasma concentrations, taking into consideration factors such as drug interactions. Evidence of QT interval prolongation or change in T-wave morphology in *in vivo* studies mandated additional animal studies and/or *in vitro* electrophysiological studies to identify the subtype of the ionic channel(s) involved and effects at other cardiac receptors. It was also recommended that comparison should be made to marketed compounds known to affect the APD and QT interval, using (where possible) compounds having structural similarities to the new drug and/or having similar therapeutic indications. It was cautioned that, in some cases, further development of the drug might not be justified.

The clinical strategy[1] provided guidance on ECG documentation and the number of subjects required to adequately test the drug. This included techniques for recording ECGs, manual evaluation of these ECGs by cardiologists experienced in such evaluations, appropriate correction of measured QT interval for changes in heart rate and correlating ECG changes with plasma concentrations of the drug and/or the most significant metabolites as appropriate. The significance of stereoselectivity in cardiac toxicity was recognised in this guidance.[1]

The CPMP document[1] also suggested a set of categorical responses as a general guide for consideration as 'signal' values of QT interval changes from baseline that might represent a drug-induced effect as opposed to changes due to spontaneous variability.[92-94] These included individual changes in QTc interval from baseline (<30ms is unlikely to raise concern, 30–60ms is likely to represent a drug effect and raise concern about the potential risk and >60ms would raise clear concerns about the potential risk). In addition, a newly emergent absolute QTc interval in excess of 500ms, regardless of the magnitude of change from baseline, would raise clear concerns about the potential of a new drug to induce arrhythmias including TdP.

In order to address the clinical relevance of drugs with and without preclinical findings indicating QT interval prolongation, two separate strategies were proposed. When appropriate, special attention was required to ensure that phase II/III studies included the likely at-risk groups, including patients with cardiovascular disease (with and without diuretic treatment), if careful ethical and scientific considerations justified such a decision.

The document[1] then concluded with a regulatory evaluation of the benefit-risk profile of the drug. The principal contributors to this document were Denmark, France, Germany, Sweden and the UK.

The document[1] included no reference to the rapidly activating delayed rectifier potassium (IKr) current or the human ether-a-go-go related gene (hERG) channel. Preclinical studies with the former were relatively few and the hERG channel had just been discovered. The draft document released for consultation in March 1997 required correction of the measured QT interval by Bazett as well as Fridericia corrections. However, the industry rejected the use of the Fridericia correction as being novel with little or no clinical experience with its use. Therefore, references to the Fridericia correction were removed from the document that was finally adopted on 17 December 1997.[1]

Nevertheless, the document generated considerable acrimony. As far as the author is able to recall, this was, and remains to this day, the only guidance document that has resulted in a large number of meetings organised, beginning in June 1998, by academia, industry and other commercial organisations on both sides of the Atlantic.

3. Academic Concerns

Against the background of rancour from the industry that followed the adoption of the CPMP document,[1] support from three academic sources greatly contributed to a wider recognition of the fact that drug-induced changes in cardiac repolarisation were a significant public health concern.

In 1998, the *Journal of Cardiovascular Electrophysiology* published an editorial that expressed the wider clinical concerns and recommended that the exclusion of potassium channel antagonist properties might be considered in the future as a requirement before new molecules are approved for marketing, and stricter warnings in the package insert of drugs with known repolarisation prolonging activity could be enforced.[95]

In June 1999, the European Society of Cardiology convened a policy conference in Nice, France, attended by a number of experts.[96] The meeting endorsed public health concerns arising from drug-induced QT interval prolongation and TdP, and the conclusions were published in a policy document.[96] The conference concluded that it was imperative to investigate any new chemical entity for its effect on cardiac repolarisation before its first use in humans but also recognised the dilemma this raised. This policy document[96] described an example of a flow chart of various preclinical studies for decision-making during drug development.

In April 2000, the European Society of Cardiology organised a follow-up meeting to discuss the way forward. The meeting was an education and training course for industry and was entitled "The Potential for QT Prolongation and Proarrhythmia by Non-Antiarrhythmic Drugs: Pathophysiology, Clinical Presentation, Drug Development and Regulatory Issues".

In August 2000, the Duke Clinical Research Institute together with the *American Heart Journal* convened an expert meeting on repolarisation changes in Rockville, Maryland, USA.[97] This meeting identified current knowledge, critical gaps and new approaches to drug development and patient management.[97] Principal topics included the cellular electrophysiology and screening tools for drug development. In addition, the participants agreed that it is imperative that clinicians be educated about medications that prolong the QT interval.

It was reiterated that not all drugs that significantly prolong the QT interval were associated with proarrhythmia and that screening drugs solely on the basis of a single parameter was undesirable.[97] Nevertheless, the participants expressed a general agreement that a QT interval of >500ms conferred a significant risk of proarrhythmia.

Hammond et al.[98] conducted a survey of the then current practice in the pharmaceutical industry for assessing the potential for QT interval prolongation by non-cardiovascular medicinal products. Although the survey provided only a snapshot, it was evident that the practice of testing drugs for an effect on cardiac repolarisation was highly heterogeneous and not necessarily the best practice.

4. Health Canada/US FDA Document

The Canadian regulatory authority, Health Canada, followed up the CPMP initiative in March 2001, when their guidance document entitled *Assessment of the QT Prolongation Potential of Non-Antiarrhythmic Drugs* was released for consultation.[99] This guidance also recommended a strategy of preclinical *in vitro* studies and clinical studies in order to better characterise the risk.

The preclinical strategy[99] proposed was more detailed than, but broadly similar to, that advocated in the CPMP document.[1] The document recognised that, while the IKr current tended to be the most usual site of action of QT prolonging drugs, prolongation of repolarisation through actions on other ion currents was theoretically possible. It also acknowledged that drug effect on IKr current could also be studied using suitable heterologous systems expressing the cloned human IKr channel.

In terms of clinical strategy, the Health Canada document[99] provided detailed guidance on the design and conduct of studies, exclusion and inclusion criteria, measurement of QT interval, more robust approaches to its correction for heart rate, discontinuation of subjects and subset analysis. It expanded on the strengths and the limitations of QT-related endpoints and recognised the limitations of analysis by central tendency using only the time-averaged variable and retained outlier analysis very much in line with the CPMP document.

The regulatory concerns and implications were stated in uncompromising terms. It emphasised that, "QT prolongation, with or without documented arrhythmia may be the basis for non-approval of a drug or discontinuation of its clinical development", and that "failure to perform an adequate non-clinical and clinical assessment … may likewise be adequate justification to delay or deny marketing authorisation".[99] The concept of benefit/risk was also clearly spelt out. Drugs that prolong the QT interval at recommended therapeutic doses should not be candidates for clinical development or licence approval unless they provide benefits for serious diseases or diseases not amenable to treatment with safer drugs, or have demonstrated efficacy in patients refractory or intolerant to the alternative drugs.

Finally, the Health Canada document[99] recommended that prior to the launch of a QT prolonging drug, a letter should be issued to healthcare professionals advising them of the cardiotoxic risks associated with the new agent and appropriate risk management strategies.

Although the FDA had not released any official guidance, even for consultation, the scientific staff

at the FDA had composed a draft document entitled *Development of Drugs that Alter Ventricular Repolarization*.[100] The detailed draft document dated 2 September 1999 outlined various methodological approaches to evaluation of the QT liability of a drug, including a range of preclinical studies.

In November 2002, the FDA and Health Canada issued a jointly agreed *Proposed Concept Paper* on investigating drugs for their effect on cardiac repolarisation. This paper was extensively discussed in a consultation workshop held at The University of Maryland at Shady Grove, Rockville, Maryland, USA, in January 2003. As a result of this workshop, this concept paper was revised and entered into the ICH process for harmonisation across the three ICH regions.[101]

5. International Conference on Harmonisation Guidelines

In May 2001, the ICH S7B Expert Working Group began development of a guideline on the nonclinical evaluation of drugs for their potential to delay ventricular repolarisation. Initial discussions on potential harmonisation of a guideline for the clinical assessment of drugs for their QT liability started with the ICH E14 Expert Working Group meeting in Tokyo during February 2003. Such was the regulatory concern on drug-induced QT interval prolongation and subsequent proarrhythmias that there was a general desire and unanimity to 'fast track' the topic.

Both of these ICH guidelines were signed off in May 2005: ICH S7B[102] dealing with preclinical strategy and ICH E14[2] dealing with clinical strategy. The two documents were endorsed by the ICH Steering Committee at Step 4 of the ICH process and the final versions dated 12 May 2005 were recommended for adoption to the regulatory bodies of the EU, Japan and the US. These two are the only ICH guidance notes that deal with a specific drug toxicity. The ICH Steering Committee also set up the ICH E14 Implementation Working Group in order to respond to any questions or uncertainties and, if necessary, update the guidance with advances in the science.

ICH S7B promotes a concept of integrated risk assessment[102] based on the chemical and pharmacological class of the drug together with data from two core tests: *in vitro* IKr assay and *in vivo* studies in a suitable species. The integrated risk assessment also takes into account follow-up studies specially investigating the electrophysiology of the drug (APD assay and various proarrhythmia models), as well as other data from studies investigating toxicology, pharmacodynamics, pharmacokinetics, tissue distribution and accumulation and drug interactions.

The focus of ICH E14 is a specific thorough QT study, typically conducted in healthy volunteers, as the primary method for evaluating the potential effect of non-cardiac agents on cardiac repolarisation during drug development.[2]

The reader is referred to the final version of ICH E14[2] for details, but the main features of the guideline include:

- applicability of ICH E14;
- populations to be studied;
- use of a supratherapeutic dose of the investigational drug;
- use of a positive control to establish assay sensitivity;
- robust methods for measuring QT interval and its correction for heart rate;
- statistical approaches to analysis;
- emphasis on analysis by change in central tendency as computed by mean time-matched, placebo-corrected change from baseline;
- a threshold level of change in central tendency that will raise regulatory concern (set at around 5ms as evidenced by an upper bound of the 95% confidence interval around the mean effect on QTc interval of 10ms);
- presentation of data for regulatory evaluation;
- monitoring of ECGs in phase III studies, depending on preclinical data and the outcome of the thorough QT study;
- exploration of pharmacogenetic factors.

ICH E14 also elaborates on regulatory implications in terms of labelling and benefit-risk and postmarketing risk management strategies.

The FDA and the EU have implemented both the ICH guidelines[2,102] effective from October 2005 and November 2005, respectively. The Japanese authority, the Pharmaceutical and Medical Devices Agency, has not yet officially implemented either of these two ICH guidelines. Health Canada adopted the two ICH guidelines in April 2006 but also developed two key regional guidance documents to support the interpretation and implementation of these ICH guidelines: one on analysis and review of QT/QTc interval data[103] and another on product monograph content,[104] effective from November 2006. At the same time, they issued a question and answer document[105] that is intended to clarify their regional regulatory expectations with regard to the ICH S7B and E14 guidelines.

The FDA is also to be commended highly for having set up a QT Interdisciplinary Review Team to review the protocols and study reports of all thorough QT studies and also studies intended to substitute for a thorough QT study. The objective is to ensure that sponsors always receive the best available, consistent advice on the conduct of and the need for a thorough QT study.

Since 2003, approximately 90 thorough QT studies have been completed on new drugs across a whole range of therapeutic classes. A detailed analysis of these studies, including the effect sizes found, and correlating the results with raw data from preclinical studies on each corresponding drug would greatly improve our understanding of the way forward on this complex safety issue.

6. Short QT Interval

As a result of the studies conducted in compliance of regulatory requirements, a number of compounds are now increasingly found to shorten action potential duration and, therefore, the QT interval. Although the significance of a short QT interval has hitherto remained elusive, recent description of congenital forms of short QT syndromes, and the arrhythmias associated with these syndromes, has begun to unravel an uncanny parallel with drug-induced prolongation of QT interval and its consequences.

Our understanding of and concerns regarding drug-induced prolongation of the QT interval have evolved slowly, beginning with the clinical manifestation of congenital long QT syndrome. The molecular basis of a parallel between congenital forms of long QT and short QT syndromes is immediately apparent as shown in table I. Early evidence suggests that, just as prolongation of QT interval can be proarrhythmic, shortening of QT interval may also prove to be proarrhythmic.[106-108] As new compounds that shorten QT interval progress further into clinical development and reach regulatory authorities for approval, questions will inevitably arise on the significance of drug-induced QT shortening. Therefore, it is not surprising that drug-induced shortening of the QT interval is emerging as another issue of potential clinical and regulatory concern.[109]

Gussak et al.[110] first described idiopathic short QT interval as a new clinical syndrome. Subsequent studies have identified a number of variants of short QT interval caused by mutations in at least three

Table I. Parallel between congenital long QT (LQT) syndromes and short QT (SQT) syndromes

Channel involved	LQT syndrome type	SQT syndrome type
Potassium	Loss of function mutation in: *KCNH2* leads to LQT2 *KCNQ1* leads to LQT1 *KCNJ2* leads to LQT7	Gain of function mutation in: *KCNH2* leads to SQT1 *KCNQ1* leads to SQT2 *KCNJ2* leads to SQT3
Sodium	Gain of function mutation in: *SCN5A* leads to LQT3	Loss of function mutation in: *SCN5A* leads to Brugada syndrome
Calcium	Gain of function mutation in: *CACNA1C* leads to LQT8	Loss of function mutation in: *CACNA1C* leads to SQT4[a] *CACNB2b* leads to SQT5[a]

a Not formally designated as SQT4 and SQT5 at the time of writing.

potassium channel genes, namely *KCNH2*,[111] *KCNQ1*[112] and *KCNJ2*,[113] that result in gain of function and/or early deactivation of the current mediated by the channels encoded by these genes. The QTc interval in these individuals is generally <320ms. More recently, Antzelevitch et al.[114] have described loss-of-function missense mutations in *CACNA1C* and *CACNB2* genes encoding the α_1 and β_{2b} subunits of the L-type calcium channel, giving rise to shorter than normal QTc interval. In this study, QTc interval ranged from 330 to 370ms among probands and clinically affected family members.

Although the variants of short QT syndrome have been styled as SQT1, SQT2 and SQT3, the genotype-phenotype correlations of each variant short QT syndrome are not at present as well characterised as they are for the long QT syndrome. Short QT syndrome is associated with syncope, sudden death (possibly caused by malignant ventricular tachyarrhythmias) or atrial fibrillation. Epidemiological data suggests that a shorter than normal QT interval (≤360ms) is associated with idiopathic ventricular fibrillation.[115,116] Some studies have sought to emphasise the rarity of subjects with a short QT interval in general hospital or ambulatory healthy populations.[117-119] However, one study identified the presence of a *hERG* mutation with current accelerating properties in a significant proportion of the population.[120] However, the rarity and prognosis of congenital short QTc interval in an apparently healthy population does not necessarily imply that the same will be true for drug-induced shortening of the QTc interval.

Drugs activating adenosine triphosphate-dependent potassium channels have been known for a long time.[121] Among the better known are pinacidil, lemakalim (BRL 38227, the optical isomer of cromakalim) and nicorandil. There is evidence that pinacidil and lemakalim induce shortening of APD and have profibrillatory effects in preclinical studies.[122-126] With regard to humans, DeSilvey and Moss[127] reported shortening of the QT interval following treatment with primidone in three patients with congenital QT interval prolongation. Nicorandil has frequently been used in the treatment of patients with long QT syndrome.[128] It has complex electrophysiological actions and shortens the QT interval, but these are not potent enough to induce any proarrhythmic effect in angina patients with normal QT interval.[129]

Experimental drugs that activate the slow component of the delayed rectifier current (IKs) in cardiac cell channels in a concentration-dependent manner have been reported.[130] Recently, some new compounds at early experimental stage have been found to accelerate IKr current through an effect on hERG channels.[131,132] Whether or not, following a normal QT interval at baseline, a proarrhythmic shortening of the QT interval can be induced by drugs acting at IKr or other ion channels remains to be seen. Nevertheless, if the cardiac safety of drugs is a matter of concern, the arrhythmias associated with congenital short QT syndrome and the discovery of potassium channel activators have important implications for the sole use of QTc interval prolongation as a surrogate marker of drug-induced proarrhythmias.

7. Cardiac Safety in Broader Context

Over the last 10 years or so, concerns about the cardiac safety of drugs have extended beyond their proarrhythmic potential. It is now evident that a number of drugs also have significant proischaemic, profibrotic or prothrombotic potential.

Soon after the introduction of oral contraceptive agents in the mid-1960s, it became evident that oral contraceptive pills containing high doses of estrogens were associated with an increased risk of thromboembolism.[133] Subsequently, there were similar concerns regarding other formulations of contraceptive pills and hormone replacement therapy.

Other drugs that attracted much attention in the late 1980s and early 1990s were a number of inotropic agents indicated for the treatment of chronic heart failure. Despite improvement in exercise tolerance tests, drugs such as xamoterol, flosequinan, vesnarinone and ibopamine were found to increase mortality, presumed to be due to proarrhythmias. Oral formulations of drugs such as milrinone and

enoxamine were removed from the market. This led the CPMP to revise its guideline on investigation of drugs for cardiac failure, by emphasising clinical symptoms, cardiovascular morbidity and all-cause mortality, rather than an improvement in exercise tolerance test, as the primary endpoints for regulatory approval of such drugs.[134]

The epidemic of primary pulmonary hypertension that followed the introduction of aminorex to the market in Austria, Germany and Switzerland in 1965, and its subsequent disappearance when the drug was withdrawn in 1972, is all too well known.[135,136] This complication has since been reported with a number of other oral anorectic agents such as fenfluramine in 1981[137] and dexfenfluramine in 1992.[138] The valvular effects of drugs such as ergotamine and methysergide have been known for a long time but in 1997, dexfenfluramine was removed from the market because of a high risk of serious valvulopathy.[139-141] Ioannides-Demos et al.[142] have reviewed the cardiovascular effects of a number of anorectic agents in detail.

Since 2003, two drugs, rofecoxib and muraglitazar, both with novel mechanisms of action, appear to have provided a renewed stimulus to the regulatory and clinical concerns on cardiovascular safety of new drugs.[143,144] As a result, many new drugs have failed at each major point in their life cycles: termination from further development, failure to secure regulatory approval and withdrawal from the market. Others have attracted significant prescribing restrictions.

The proischaemic effects of NSAIDs were first documented in a landmark study with the cyclooxygenase (COX)-2 selective inhibitor rofecoxib,[143] resulting in its withdrawal from the market in September 2004. Two studies[145,146] with the use of parecoxib/valdecoxib in coronary artery bypass graft surgery also showed a higher rate of serious cardiovascular thromboembolic events (e.g. myocardial infarction, cerebrovascular accident) compared with placebo. This risk was not observed in a general surgery setting.[147] As a result of an extended review covering other COX-2 selective and non-selective inhibitors, all NSAIDs had prescribing restrictions placed on their use.[148] This particular group of drugs has attracted considerable attention since they are used very widely and are intended for long-term use by the elderly population, which is already at high risk of myocardial ischaemia.

A number of other non-cardiac drugs have unexpectedly been reported to induce fluid retention, precipitate cardiac failure and other potentially fatal cardiovascular events. A particularly striking example is the peroxisome proliferator-activated receptor (PPAR) α/γ dual agonist muraglitazar, which never made it to the market. In clinical trials, oedema and cardiac failure were dose dependent and an analysis of data revealed that muraglitazar had clinically and statistically significant adverse effects on cardiovascular outcomes.[144] These data led to the regulatory rejection of muraglitazar, but the drug does illustrate how the industry has now engaged itself in addressing the cardiac safety of drugs under development. A commendable example of this engagement by the industry was the prompt termination of clinical trials with torcetrapib, a cholesteryl ester transfer protein inhibitor, despite its activity in raising high-density lipoprotein-cholesterol levels, as soon as it became evident that the drug was associated with increased mortality.[149] Similarly, a number of PPAR α/γ dual agonists have been terminated from further development because direct cardiotoxic effects were observed during preclinical studies. These effects are usually seen in long-term preclinical safety studies. For example, with muraglitazar, cardiac hypertrophy, left ventricular dysfunction and oedema were observed in studies up to 12 months in duration.[150]

Individuals with diabetes mellitus have an increased risk of developing heart failure, usually as a consequence of coronary artery disease, although a specific diabetic cardiomyopathy, secondary to a microangiopathy, may also exist. The thiazolidinediones, which are PPAR-γ agonists, are a relatively new class of insulin-sensitising agents that are used in the management of type 2 diabetes. The first agent of this class, troglitazone, was withdrawn because of hepatotoxicity, but two other agents, rosiglitazone and pioglitazone, are currently in wide clin-

ical use. There is no evidence that PPAR-γ agonists are directly cardiotoxic, and their adverse cardiac effects appear to be mediated indirectly through fluid retention.[151] PPAR-γ is selectively expressed in the medullary collecting duct and pelvic urothelium, suggesting that PPAR-γ may have effects on the reabsorption of water and electrolytes in the distal nephron and also that fluid retention is most likely a class effect of all PPARs with γ activity.[152] Pioglitazone has been shown to reduce coronary and stroke events compared with placebo in a population with diabetes and cardiovascular disease.[153] However, this benefit was counterbalanced by an increase in congestive heart failure as well as symptomatic oedema.[154] Most recently, a controversy has been provoked by the alleged cardiovascular safety of rosiglitazone.[155]

Although there have always been concerns about the cardiac safety of a number of drug classes,[156,157] there is further evidence that gives rise to renewed concern. For example, there are now concerns on the potential of imatinib to induce severe cardiac failure,[158] reports of sudden death in patients with underlying serious heart problems or defects, and reports of stroke and heart attack in adults with certain risk factors in association with usual doses of products used for the treatment of attention deficit hyperactivity disorder[159] and a higher death rate associated with the use of darbepoetin alfa to treat anaemia in cancer patients not receiving chemotherapy.[160] This use of darbepoetin alfa is not an approved use, and the finding may apply to other erythropoiesis-stimulating agents.

Two drugs withdrawn from the market recently further illustrate the extent of regulatory concern. Pergolide is an ergot alkaloid-derived medication, which was approved nearly two decades ago for the treatment of Parkinson's disease. Although pergolide-induced profibrotic reactions in the peritoneum have been known for a long time,[161,162] results of two new studies showed that some patients treated with pergolide had serious damage to their heart valves when compared with patients who did not receive the drug.[163,164] These two studies not only confirmed earlier sporadic case reports of this risk, they emphasised its potential scale. Therefore, this drug was withdrawn from the market in March 2007.[165]

The latest casualty of concerns surrounding the cardiovascular safety of drugs is tegaserod, indicated for the treatment of irritable bowel syndrome.[166] Tegaserod was approved in the US in July 2002 for short-term treatment of women with constipation-dominant irritable bowel syndrome. Its approved use was subsequently extended in August 2004 for treatment of chronic constipation for men and women under the age of 65 years. Although approved and marketed in 55 countries, it was denied approval in the EU in December 2005. This drug was also removed from the market in March 2007 following finding of an increased risk of serious cardiovascular adverse events (e.g. angina, heart attacks and strokes) associated with its use. Thirteen of the 11 600 tegaserod-treated patients (0.1%) had confirmed cardiovascular ischaemic events compared with only 1 of >7000 placebo-treated patients (0.01%).[166]

The drugs discussed in this section illustrate the more contemporary regulatory stance on tolerance of cardiovascular risk of drugs and their benefit-risk assessment. This recent, more assertive, risk-averse position has significant implications for approval of a number of novel drugs and future drug development. These include routine evaluation of drugs of certain drug classes for their cardiovascular safety. Drugs that are intended for long-term use will almost certainly require long-term clinical evaluation in a substantial number of patients in studies that have a duration well beyond the 12 months that seems routine at present. In addition, studies will require enrolment of populations that more closely resemble the ultimate target population. It may no longer be acceptable to exclude patients with cardiovascular diseases or the elderly unless there are compelling reasons to do so. All these studies will have to focus on at least excluding a cardiovascular risk (the spotlight being on safety) and, if possible, on demonstrating clinical outcomes that really matter, namely improved mortality, morbidity and quality of life (the spotlight being on efficacy). Careful

evaluation of robust ECG data from large phase III trials for silent coronary events (myocardial infarction, ischaemic ST segment and T wave changes, etc.) may provide better predictive data for these type of cardiac outcomes, just as QT interval does for TdP.

8. Conclusions

Concerns about the cardiovascular safety of new drugs immediately raise some fundamental issues for the current paradigms of drug development and regulatory approval. On one hand, novel drugs must show efficacy and should be made available expediently if the objective is to promote public health. Therefore, pre-approval clinical trials are necessarily efficacy orientated and of relatively short duration in relatively small populations. On the other hand, these trials are unlikely to uncover small increases in relative risks. Since cardiovascular risk factors and diseases are common, any increase in cardiovascular risk associated with non-cardiovascular drugs is unacceptable because even a small (adverse) effect size in this setting can have profound public health implications. It follows, therefore, that new drugs must be shown to be free from such hazards. This disconnect between the desire to promote public health and protect public safety needs an urgent resolution.

Advances in science and genomic technology have enabled us to identify novel pharmacological targets, develop drugs with novel mechanisms of action and novel biomarkers. However, this success has proved to be too seductive, leading some stakeholders to believe that the end result will be safer and more effective medicinal products. And yet, there is little evidence of direct clinical benefits. Novel mechanisms of action and biomarkers by themselves are no guarantee of improved safety or benefits. Even some traditional biomarkers have come to be viewed with scepticism.

One approach, proposed as a solution to this dilemma, is to perform post-approval clinical trials that have been termed ‘large simple safety study’, a study focusing on a small number of specified outcomes, generally with reduced routine data collection.[167,168] Such studies, when adequately designed and targeted, together with full implementation of ICH initiatives on pharmacovigilance planning[169] and risk management and minimisation strategies,[170,171] might eliminate a delay in withdrawal of a drug because of a rare but serious, and relatively latent, adverse safety profile. Requirements for more extensive and earlier postmarketing assessment of clinical benefits and rare but serious risks associated with new medicinal products are here to stay, and these have created a new standard of evidence for industry and regulators and will almost certainly result in better assessment of benefit/risk, more effective and balanced regulatory actions and better care for patients.[172]

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