The Current Regulatory Landscape for Cardiac & Cardiovascular Safety Assessments: Part I

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Cardiac and cardiovascular safety concerns continue to be leading reasons for drug failures during development and marketing, and have led to product withdrawals. Several high-profile marketing withdrawals involved drugs for non-life-threatening diseases. For example, in 1998, terfenadine (Seldane), an antihistamine used for allergies, was removed from the US market following deaths from a form of polymorphic ventricular tachycardia called *Torsades de Pointes* (TdP)—a French term, which literally translated, means "twisting of the points." In 2000, cisapride (Propulsid), a very effective and successful gastroprokinetic agent marketed by Janssen/Ortho for gastroesophageal reflux disease (GERD), to speed gastric emptying while increasing esophageal sphincter tone, was withdrawn from the market after a warning from the US Food and Drug Administration (FDA) to prescribers regarding the product's propensity to prolong cardiac repolarization. Regulatory concern over drug-induced TdP led to preclinical and clinical draft guidance documents in 2002, which were finalized in 2005 with the publication of the cornerstone International Conference on Harmonisation (ICH) guidelines "S7B"[1] and"E14,"[2] respectively. E14 is discussed later.

A third example is rofecoxib (Vioxx), a selective cyclooxygenase-2 (COX-2) inhibitor used as an anti-inflammatory agent. Rofecoxib was voluntarily removed from the worldwide market in 2004 following an interim analysis in a clinical trial that found an increased risk of cardiovascular events in the rofecoxib treatment arm compared with the placebo arm. Although allergies, GERD and arthritis have major impacts on quality of life, the risk/benefit assessment for the drugs cited became unfavorable.

Another high-profile drug safety case study that is currently ongoing involves the marketed agent rosiglitazone (Avandia), a thiazolidinedione used in the treatment of Type 2 diabetes mellitus (T2DM). Although the risk/benefit assessment announced by FDA in September 2010 is in favor of keeping rosiglitazone on the market with considerable restrictions, conflicting cardiac data continue to be reported and are discussed in this article.

These cardiac-related cases have led to heightened drug safety awareness. This review of current regulatory landscapes for cardiac and cardiovascular safety assessments—split into two parts—provides an overview of the circumstances leading to the release of five key guidance documents by the ICH, FDA, and European Medicines Agency (EMA) that address clinical cardiovascular safety concerns (see **Table 1**) and their global ramifications.

Part I provides an overview of the history of formalized cardiac safety assessment, a brief discussion of the dedicated study used to investigate a drug's propensity to increase the length of the QT interval and a review of the regulatory history of formalized cardiovascular safety assessment for antidiabetic drugs for T2DM.

Part II, to be published in the February issue of *Regulatory Focus*, will discuss key aspects of FDA's guidance for industry on cardiovascular safety assessment published in December 2008 and the continuing discussion in the literature regarding the cardiovascular safety of Avandia and Actos, provide insight into the FDA's July 2010 Advisory Committee meeting on Avandia, briefly discuss the EMA's January 2010 draft guidance, and end with a discussion of potential ramifications for the future global development of antidiabetic drugs for T2DM.

QT Prolongation as a Cardiac Safety Biomarker

Each segment of the surface electrocardiogram (ECG) can be assigned a length in the time domain. The QT interval represents the total time of cardiac muscle cell depolarization (contraction) and repolarization (returning to the relaxed state such that contraction can occur again). It is defined as the length in the time domain from the onset of the Q-wave to the off-set of the T-wave, measured in milliseconds (msec). Precise categorization of the normal QT interval for a given individual is impractical since it changes with every heartbeat. However, consideration of the typical ranges observed in groups of individuals following a supine period is useful.[3] Since the QT interval is impacted by heart rate, tending

Table 1: ICH, FDA, and EMA Cardiac & Cardiovascular Safety Guidance, 2005–10

Date	Title (see *References* for associated web sites)
May 2005	**ICH Guideline** *Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs E14*[2]
November 2006	**Health Canada: Health Canada Question and Answer Document Regarding the ICH S7B and E14 Guidances**[6]
June 2008	**ICH E14 Implementation Group: Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs: Questions and Answers**[7]
December 2008	**FDA** *Guidance for Industry: Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*[14]
January 2010	**EMA:** *Guideline on Clinical Investigation of Medicinal Products in the Treatment of Diabetes Mellitus [Draft]*[15]

to be shorter as heart rate increases, it is typically corrected for heart rate by one or more of several mathematical formulae, resulting in QTc data. In this context, the normal distribution of QTc intervals for healthy adult males suggests a range from around 350–460 milliseconds (msec). For healthy adult females, the distribution is similar but falls around a somewhat higher mean, suggesting a range from around 360–470 msec.[4]

While imperfectly related to the occurrence of TdP, QT prolongation has become a cardiac safety biomarker for a drug's potential to lead to TdP.

Regulatory History of Formalized Cardiac Safety Assessment

Between the late 1980s and the early 2000s, a series of high-profile drug marketing withdrawals for cardiac reasons focused regulatory attention on cardiac safety assessments. Many of the withdrawals involved TdP. Although TdP is a rare repolarization disruption, it can result in death. Several hundred deaths from widely-prescribed drugs for relatively benign conditions indicated that the risk/benefit balance was clinically unacceptable. The first section of **Table 2** provides a sample list of drugs withdrawn from the market for proarrhythmic cardiac safety reasons in the US and the UK from the late 1980s to the mid-2000s. The second section lists drugs removed from the market in the US and the EU for generalized cardiac/cardiovascular safety reasons.

The first regulatory publication issued as a result of ICH collaboration, entitled, *Safety Pharmacology Studies for Assessing the Potential for Delayed Repolarization (QT Interval Prolongation by Human Pharmaceuticals)*, focused on nonclinical signals and *in vivo* and *in vitro* models for determining whether QT prolongation could be associated with the use of a drug under consideration. The document was released for Step 2 comment of the ICH process in the first quarter of 2002 by the ICH Steering Committee, and is also commonly referred to in the pharmaceutical industry as the "S7B Step 2" document.

The main objective of the guidance was to protect clinical trial participants and patients receiving marketed products from "delayed repolarization-associated ventricular tachycardia, TdP, and lethal arrhythmia resulting from administration of pharmaceuticals." It provided a nonclinical testing strategy in the form of an algorithm to assess risk, and influenced the future course of drug development as a result of either positive or negative cardiac signals from ionic current assays (such as I_{Kr}), isolated cardiac muscle cell preparations, and results from *in vivo/in vitro* QT assessments. For the first time, US sponsors of pharmaceutical drugs had objective guidelines that provided insight into FDA's thinking regarding the nature of early studies and the timing of repolarization studies in relation to clinical development.

In response to the five drugs removed from the market for QT prolongation issues between 1998 and 2000, FDA, in conjunction with the Pharmaceutical Research and Manufacturers of America (PhRMA), formed a working group to address biomarkers, like the QT interval, to assess cardiac safety prior to registration and approval. In light of Health Canada's publication of draft guidance in the first quarter of 2001, this became a combined (US and Canadian) ICH effort (ICH E14).

The working group released a draft document, also known as the "Preliminary Concept Paper (PCP)", in the fourth quarter of 2002, which was the second formal guideline issued by FDA to address safety concerns associated with QT interval prolongation. The Drug Information Association/FDA/Canada Health Authorities' meeting in 2003 allowed industry to discuss the paper, officially titled, "The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhymic Drugs," with FDA in an open forum. Participants included the highly respected experts Douglas Throckmorton and Robert Temple, of FDA's CardioRenal Division.

This was the second paper to address formally the clinical and regulatory issues surrounding QT interval prolongation. The purpose of the PCP was to further describe proper nonclinical QT work-up and to establish the sensitivity and specificity of various nonclinical

studies (e.g., HERG assay, action potential duration, whole animal QT), using existing and newly developed data.

Later in 2003, another DIA/FDA meeting, entitled, "ECGs in Clinical Trials: The New Regulatory Realities," was held as a follow-up to the first. Although consensus was limited, a few important ideas emerged from this meeting:

- If QT signals are found, a "thorough study" must be submitted to the agency. (FDA's Douglas Throckmorton, MD)
- All ECG data for the "thorough study" must be submitted to the agency in a digital format. (FDA's Norman Stockbridge, MD, PhD)

Regulatory discussions that started in the EU and then involved Canada and the US eventually led to the publication of the cornerstone ICH guideline (2005), which has been in force in those countries for several years, and, more recently, adopted by Japan.[5] In 2006, Heath Canada released a document containing four questions and answers that provided insight into its interpretation of the requirements of ICH E14,[6] and an ICH E14 questions and answers document was released in 2008.[7] The ICH E14 document now governs cardiac safety assessment in all ICH regions.

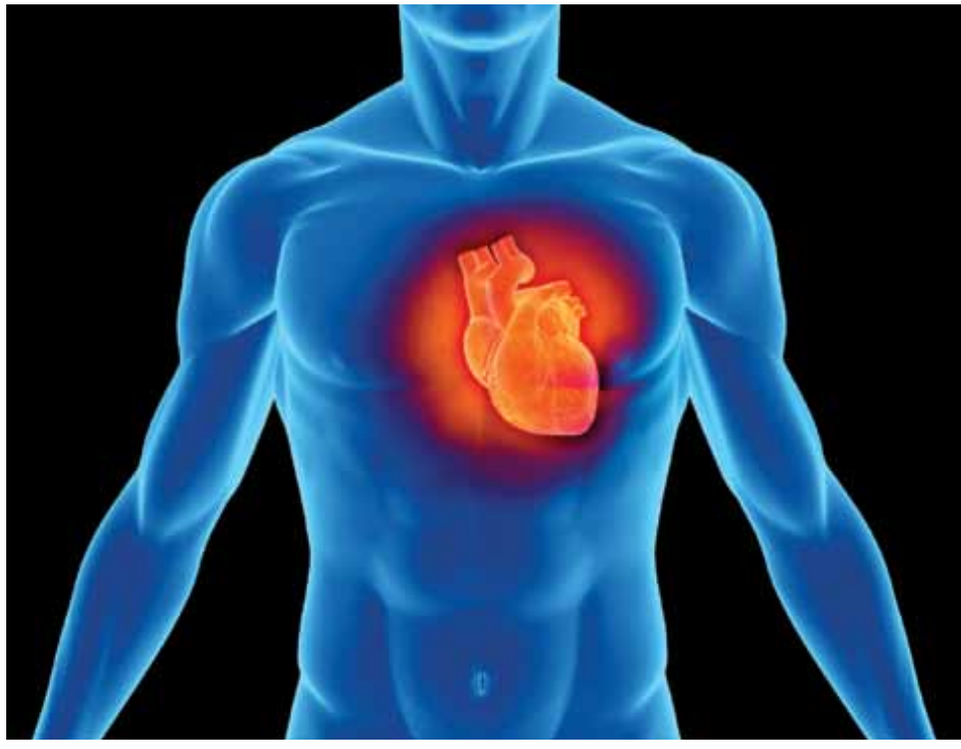
The Thorough QT/QT Study

ICH E14 discusses the assessment of an investigational drug's propensity to increase the length of the QT interval as seen on the ECG. Discussions of the fundamentals regarding the QT interval and QT interval prolongation were presented in *Regulatory Focus* in the articles entitled, "The Clinical and Regulatory Implications of QT Interval Prolongation"[8] and "An Update on the Implications of QT Interval Prolongation"[9] in the May 2004 and 2005 issues, respectively.

The clinical trial described is called the Thorough QT/QTc (TQT) Study, and is a rigorous examination of a drug's QT/QTc prolongation liability. QT/QTc is considered a cardiac safety biomarker for the potential occurrence of drug-induced TdP, and hence of the drug's "torsadogenic" liability. Torsadogenic liability is one factor considered by regulators when making decisions concerning marketing approval and marketing withdrawal. (For more detailed discussion see the bibliography at the end of this article.)

Regulatory History of Formalized Cardiovascular Safety Assessment for Antidiabetic Drugs for T2DM

Nissen and Wolski published a meta-analysis in the *New England Journal of Medicine* purporting to show a greater incidence of myocardial infarction in the pooled rosiglitazone group compared with the pooled control group.[10] The odds ratio from the meta-analysis was 1.43 (95% CI: 1.03-1.98, p=0.03), which attained statistical significance. While many scientists questioned the validity of the statistical methodology employed in the analysis, the publication of these finding provoked considerable media attention, resulting in a joint meeting of FDA's Endocrinologic and Metabolic Drugs Advisory Committee and its Drug Safety and Risk Management Advisory Committee on 30 July 2007. This meeting focused on the cardiovascular ischemic and thrombotic risks of the thiazolidinediones (the other marketed drug in this class being pioglitazone, Actos) with a particular focus on rosiglitazone.



Rosiglitazone's sponsor and FDA both presented data before the joint committee. The members voted on a predetermined set of questions. They voted 20-3 that rosiglitazone increased the cardiac risk in patients with T2DM, although, as Krall[11] noted, "many members of the committee made statements accompanying their votes that drew a distinction between the risk as compared with placebo and the risk as compared with other antidiabetic drugs." Still, the committee's members voted 22-1 that rosiglitazone should not be removed from the market. Advisory committee votes are not binding on FDA, but the agency generally follows the recommendations. On this occasion, FDA followed its advisory committees' recommendations—meaning that rosiglitazone was not removed from the market. In November 2007, to address the potential for increased cardiac risk, the sponsor agreed to add new warning language concerning potential increased risk for heart attacks to the drug's label. The label cited four meta-analyses with differing results and

Table 2. Drug Withdrawals for Proarrhythmic and Generalized Cardiac & Cardiovascular Safety Concerns

Proarrhythmic Cardiac Safety Concerns (UK, US)			
Drug	**Indication**	**Year Withdrawn**	**Major Safety Concern**
Terodiline	Urinary incontinence	1991 (UK, US)	QTc prolongation, TdP
Sparfloxacin	Antibiotic	1996 (US)	QTc prolongation
Sertindole	Antipsychotic	1998 (UK)	QTc prolongation, TdP, sudden death
Terfenadine	Antihistamine	1998 (US)	QTc prolongation, TdP
Astemizole	Antihistamine	1999 (US)	QTc prolongation, TdP
Grepafloxacin	Antibiotic	1999 (UK, US)	QTc prolongation, cardiac arrhythmias
Cisapride	Gastroesophageal reflux	2000 (UK, US)	QTc prolongation, cardiac arrhythmias
Droperidol	Schizophrenia	2001 (UK, US)	QTc prolongation, TdP
Levacetylmethadol	Opiate addiction	2003 (UK)	QTc prolongation, TdP, cardiac arrest
Generalized Cardiac Safety Concerns (EU, US)			
Drug	**Indication**	**Year Withdrawn**	**Major Safety Concern**
Fenfluramine	Appetite suppressant	1997 (EU, US)	Valvular heart disease
Dexafenfluramine	Appetite suppressant	1997 (EU, US)	Valvular heart disease
Amfepramone	Obesity	2000 (EU)	Primary pulmonary arterial hypertension
Phenylpropanolamine	Appetite suppressant	2000 (US)	Cerebral hemorrhage
Rofecoxib	Arthritis	2004 (EU, US)	Increased cardiovascular event risk

included the statement, "In their entirety, the available data on the risk of myocardial ischemia are inconclusive."[12]

Despite rosiglitazone's remaining on the market, in July 2008, a meeting of FDA's Endocrinologic and Metabolic Drugs Advisory Committee addressed potential overarching new regulatory guidance concerning cardiovascular assessments, both pre- and postapproval, for drugs and biologics for treatment of T2DM. The committee voted 14-2 that, even for drugs and biologics that do not display a concerning cardiovascular safety signal during Phase 2 and Phase 3 development, there should be a requirement to conduct a long-term cardiovascular trial, or to "provide other equivalent evidence to rule out an unacceptable cardiovascular risk."[13] The *Guidance for Industry Diabetes Mellitus—Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*,[14] issued in December 2008, very rapidly following the committee's meeting, addressed this issue. This issue has also been addressed by EMA. In January 2010, it released a draft document entitled, *Guidance on clinical investigations of medical products in the treatment of diabetes mellitus*, that covered many aspects of such investigation, including cardiovascular safety.[15] Further discussions are provided in Part II of this review.

Summary

- Cardiac safety remains a key concern for all key ICH geographies, including the US, the EU and Japan.
- Cardiac safety assessments of potential QT/QTc interval prolongation must be addressed during drug development.
- Non-QT interval prolongation cardiovascular issues are emerging and have led to promulgation of FDA guidance for the treatment of T2DM.

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