

The role of Thorough QT testing in managing drug development

With few exceptions, all compounds being submitted to the Food and Drug Administration (FDA) for approval in the United States will require an assessment of QT prolongation, either by a standard Thorough QT/QTc study, or a similar study modified to fit the safety profile of the compound and indicated patient population. How and when this assessment is performed is a critical business decision. Several scientific factors come in to play, including the patient population, indication, safety profile, metabolites and metabolism. These factors also have impact upon the business implications, including drug portfolio management, licensing, labelling and marketing.

Torsade de Pointes (TdP), or twisting of the points, is a specific, potentially fatal arrhythmia associated with prolongation of the QT interval on the ECG. It is a form of irregular ventricular tachycardia that is often self-limiting with a varied clinical presentation. The arrhythmia at any one time may present with no symptoms, or with palpitations, dizziness, syncope or sudden death. Because of this complex relationship, the association of a drug with the syndrome may not be obvious.

The ability to demonstrate a relationship between a drug and the syndrome is further complicated by several factors. Most compounds that cause TdP do so, not after the first administration of the drug, but after patients have been on the medication for a significant period of time, thereby obscuring the relationship to the drug.

This delayed response is often due to a 'perfect storm' scenario – a summation of effects, which individually may not have produced an event. The concomitant administration of medications with a QT prolonging effect can result in incremental QT prolongation. Drug-drug interactions may result

in high drug concentrations and further QT prolongation. Some drugs, such as ketoconazole, can do both. Medications that cause electrolyte abnormalities such as hypokalemia and hypomagnesemia can also precipitate events. These effects may occur either by direct effects, such as with diuretics, or through adverse events such as vomiting and diarrhoea.

There are several subsets of patients that are at higher risk due to underlying heart disease, liver or renal disease, genetic defects or gender. Approximately 75% of all drug-induced TdP occurs in women.

The low incidence of fatal events has made it very difficult in the past to demonstrate a relationship between a specific medication and TdP when it occurs in a background of co-morbid conditions and concomitant medications. The incidence of fatal TdP in torsadogenic non-antiarrhythmic medications is in the range of one in the tens, to hundreds of thousands of patients treated with the compound.

This is the crux of the problem for drug developers and regulators alike. The standard

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submission dossier lacks the number and complexity of patients necessary to demonstrate such a relationship. Hence the decade-long odyssey by regulatory agencies to demonstrate such a risk before millions of patients are exposed to a potentially fatal compound.

Understanding the physiology: the I_{Kr} channel

Some understanding of the physiology of the cardiac action potential and its perturbation by torsadogenic compounds is necessary to put the current regulatory climate in perspective and understand how it might change in the future.

Contraction of the myocardium is coupled to rapid changes in the myocardial cell membrane called depolarisation. During depolarisation, the internal resting negative membrane becomes rapidly positive. The sum total of all the ventricular myocardial cell action potentials is represented by the QRS on the surface electrocardiogram. The action potential is coupled to calcium release and cardiac contraction. The process whereby the membrane is returned to a negative state by an outflow of positive current is termed repolarisation, and roughly corresponds to the T wave on the ECG. A significant component of this repolarisation current flow is related to release from the cell of positive charged potassium ions through special, selective ion channels that are dependent upon the voltage changes within the cell.

In the 1950s, congenital syndromes of syncope and sudden death were described. Subsequently, several types of Congenital Long QT Syndrome (LQTS) were identified. Intense research into the genetics of these syndromes revealed that each syndrome affected a different ion channel. Drug-induced QT prolongation and TdP is almost always associated with inhibition of the so-called

hERG or I_{Kr} ion channel, the channel that is abnormal in Type II LQTS.

The name hERG channel refers to the gene first identified in the fruit fly that codes for the I_{Kr} channel. It was demonstrated that exposure of fruit flies to ether with a mutation in this gene produced rapid jerky movements much like a Go-Go dancer. Hence the name, human Ether Related a go-go Gene (hERG). This ion channel is pharmacologically promiscuous and has multiple reactive sites on its intracellular aspect that interact with a wide variety of chemical structures. The propensity to interact with multiple chemical structures and other, indirect mechanisms involving the channel make it difficult to predict which compounds will have difficulties.

QT prolongation is necessary, but not sufficient, to cause TdP. Several compounds cause QT prolongation, but because of activity at other ion channels, may actually decrease the risk of arrhythmias. Amiodarone is the classic example. Although amiodarone does cause TdP, the extent of the QT prolongation is markedly out of proportion to the low incidence of TdP. Ranolazine, a recently approved anti-anginal agent, causes a dose-related increase in QT interval, but appears in clinical trials to decrease the incidence of arrhythmias. There is currently intense investigation into other biomarkers on the ECG and its derivatives that may be better indicators of TdP risk.

Regulatory

A number of compounds were removed from the market in the US due to the risk of TdP (see Table 1). The resultant regulatory response to the withdrawal of these medications has taken over a decade to mature and was finally codified by the International Committee on Harmonization (ICH) in the 7SB for non-clinical development, and E14, related to clinical development. Despite this long incubation period, there are still many unanswered questions about assessing the risk of TdP. Coincident with this regulatory evolution has been a scientific evolution that promises to extend beyond the confines of ICH E14.

ICH S7B outlines some preliminary requirements to ensure patient safety in early clinical trials. Non-clinical assessment of TdP risk is an area of intense research. Although there are certainly parameters that will ultimately be demonstrated to be highly predictive, at this time the FDA has stated it will not accept non-clinical models as a substitute for a careful clinical assessment.

The FDA has presented data demonstrating there is an approximately 10% false negative rate

Table 1: Drugs withdrawn from the US market due to TdP 1998-2000

DRUG	APPROVAL	WITHDRAWN
cisapride	1993	2000
astemizole	1988	1999
grepafloxacin	1997	1999
mibefradil*	1997	1998
terfenadine	1985	1998

* Drug-drug interactions could cause accumulation of QT prolonging drugs

of non-clinical development packages for compounds that ultimately have a clinically demonstrated QT effect. European regulatory agencies seem much more comfortable with non-clinical model predictability, but if a compound is to be approved in the US, it will almost certainly require a clinical QT assessment of some kind.

Because clinical results trump non-clinical data, it is essential to look at clinical development in relation to TdP risk and drug development strategy.

For more than a decade, regulatory agencies around the world have struggled with the problem of assessing TdP risk prior to extensive patient exposure to potentially dangerous medications (Table 2). The process culminated in the Guidance for Industry: E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs, released in 2005. It was implemented in that year in Europe and the US, the following year in Canada, but has of yet has not been implemented in Japan.

ICH E14 advocates a study dedicated to the assessment of QT for all compounds coming to approval – the ‘Thorough QT/QTc’ Study (TQTS). The TQTS is sometimes called a Definitive QT or Definitive ECG Study. The rationale is that a small prolongation of the QT interval detected in healthy volunteers could indicate a much larger QT prolongation in the target population. This small prolongation might be a predictor of TdP risk. It is becoming clear that this ‘one size fits all’ approach is not useful for all compounds.

The recommended study is a randomised, double-blind, placebo-controlled study in healthy volunteers. The drug is given in both a therapeutic dose and a supra-therapeutic dose. The latter dose level is designed to look at what might happen in the ‘perfect storm’ scenario, when drug exposure may be very high due to overdose or metabolic impairment/inhibitors. In addition, there is an active control providing a known QT prolonging effect to ensure that the study is sufficiently sensitive to demonstrate a QT prolonging effect of regulatory interest if present in the study compound.

These are relatively large and expensive studies. Optimal drug development requires that they be done to the highest standards. Repeating a TQTS would result in significant time and cost delays. Careful communication with the FDA about all study design issues is critical, especially if there are factors that make a classic TQTS impossible. Equally important is the careful selection of a Phase 1 vendor and ECG core laboratory.

The study may be cross-over or parallel in

Figure 2: Regulatory Evolution

YEAR	EVENT
1997	EMA issues Points to Consider document
1998	Terfenadine withdrawn by FDA
1999	European Society of Cardiology holds Policy Conference
1999	FDA Working Group assembled
2001	HealthCanada issues Concept Paper
2003	HealthCanada and FDA issue Joint Concept Paper
2005	ICH issues S7B and E14 Step 5
2005	FDA and EMA Implemented E14
2006	HealthCanada Implemented E14

design, depending upon the half-life of the drug and metabolites, and whether there is accumulation requiring multiple dosing. Cross-over is preferred because it requires fewer subjects and allows for determination of individual heart rate correction factors. As demonstrated by terfenadine, metabolites are very important and not just active metabolites. After all, QT prolongation is a side effect, not a therapeutic effect, for non-cardiovascular compounds.

A positive study is defined as when the mean, time-matched mean difference QTc prolongation 95% upper boundary of exceed 10ms. The significance of a positive study is it compels the drug developer to perform a more comprehensive search for QT prolongation and risk of TdP in later stage drug development, potentially involving much larger and more complex studies for approval. A positive study would likely result in labelling restrictions. In addition, extensive post-marketing commitments could be dictated based upon the positive results. The FDA’s future mandate will require more diligent prosecution of post-marketing commitments.

A negative study, on the other hand, would allow the compound to be developed in a more traditional, and less expensive and risky, manner.

What has become very apparent since the adoption of ICH E14 is that there are many exceptions to the model proposed for the TQTS. Many compounds, especially oncology compounds and

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neuroleptics, are too toxic to be given to healthy volunteers, even in therapeutic doses. In addition, there are ethical issues exposing end-stage oncology patients to placebo for even a short cross-over study. Subjects with weeks to live cannot be expected to be admitted to a Phase 1 Unit for a multi-arm crossover study with baseline days. The FDA is sensitive to these issues and is working with the Cardiac Safety Research Consortium (www.cardiac-safety.org) to provide some clarity on QT liability assessment for such compounds. Several study design modifications for such considerations have been advocated. What is clear is that the FDA will require some kind of QT assessment plan for all compounds. The inability to perform a standard TQTS is not a plan.

Strategic implications

Many companies are performing studies to assess QT liability very early in development in single ascending dose (SAD) and multiple ascending dose

(MAD) studies. These studies involve many of the intense technical attributes of a TQTS, but lack an active control and adequate sample sizes to exclude a 95% upper CI of 10ms QT prolongation. They provide a point estimate of the effect and may provide the highest exposure to the compound in the drug development process. Though not generally a regulatory substitute for a TQTS, they do allow a general estimate of QT liability very early in development, which is critical for planning. As opposed to the TQTS, these early studies are often called QT Intensive or Robust QT studies, but there is no definitive description of their attributes.

Robust QT studies may assume greater significance in development plans for agents that cannot be subjected to a TQTS due to toxicity or patient populations, as the practicalities of developing such compounds are weighed against each component of the TQTS. For example, the inability of administering suprathreshold doses of a cytotoxic agent or delay of treatment for placebo or baseline days in a terminal patient should be considered in the design of such a study.

Popular antihistamine pulled from market after causing 350 deaths

Seldane® (terfenadine) can be considered the poster child for the drugs removed from the US market due to drug-induced TdP. Terfenadine was a long-acting antihistamine not associated with sedation and was viewed as a great advancement in the treatment of the widespread and annoying, but non-serious condition, allergic rhinitis.

The drug was approved in 1984. The first death seen with therapeutic doses was in 1990, although prior to that, there were several deaths associated with overdoses. By 1992 the sponsor had collected 15 deaths and 83 cases of TdP. The compound received Black Box labelling. Terfenadine was the 10th most prescribed drug in the US at the time.

It was not until 1997 that the FDA finally recommended withdrawal of the compound from the market. Inexplicably, the agency approved a generic formulation the same year. It was another year before that compound was actually withdrawn from the market. By this time, the medication had caused approximately 350 documented deaths. The actual toll was probably much higher due to the low reporting rates in post-marketing surveillance (approximately 1 in 10) and the difficulties in determining attribution. It has been estimated the drug was prescribed approximately 100 million times before its withdrawal.

The delay in withdrawal was attributed to waiting for the approval of an alternative drug. Ironically, the follow-on compound was the active metabolite of terfenadine, fenofexadine. This underscores the importance of investigating the QT effects of both the compound of interest and its metabolites.

Drug development implications

QT risk assessment can be divided into four parts. The first is obviously the non-clinical studies that are done prior to First-in-Human studies, followed by the supplement Robust or Intensive QT study early in development. Once more is known about the compound's metabolism and metabolites, the TQTS can be performed. Finally, later development and post-marketing commitments can be grouped together, as they follow and are determined by the TQTS results.

A strong non-clinical repolarisation signal should not necessarily halt development of a compound, but should provoke careful assessment of alternative leads and assessment of actual importance of the compound and its implication. A compound with a novel mechanism applicable to several types of cancer would have a much different analysis than an antihypertensive, even if novel in mechanism.

In my experience, the two most common uses for the results of a Robust QT study is for portfolio management and value enhancement. For larger companies with a family of compounds around a drug target and some concern about QT liability, such a study can provide an indication of the extent of that liability. Data obtained early in development can be used to push forward an alternative compound before significant time and effort has gone into a compound with a QT liability.

Smaller companies planning to out-license a

compound often look at a Robust QT study as a way to provide reassurance about QT liability for their development partner. Using a Robust QT model, this can be achieved earlier and cheaper than waiting for TQTS results and increase value by demonstrating decreased QT risk.

A well-designed and executed Robust or Intensive QT study can provide useful follow-up information to a non-clinical signal. A strong Robust QT signal following a non-clinical signal would probably eliminate all but the most promising drugs for serious indications without adequate alternative therapies. While a negative Robust QT signal would give some reassurance. Similarly, a strong Robust QT signal in the absence of a non-clinical signal would also be a red flag.

As stated above, the TQTS should be late enough in development so the proof of concept, therapeutic dose, PK of the drug and its metabolites are understood. But it should also be performed early enough to minimise exposure to large numbers of patients before the risk is known. Although it is often called a Phase 1 study because it is usually done in healthy volunteers, the TQTS is usually done in Phase 2 for these reasons. Occasionally it is done concurrently with Phase 3. However, if the results are positive, that approach could jeopardise the Phase 3 plan. This late-study execution is a relatively common scenario for compounds whose development plan was being formulated at the time the exact recommendations of ICH E14 were being determined, and should decrease in new compounds for which development planning began after ICH E14 implementation.

In summary, most compounds will likely require a TQTS regardless of the non-clinical assessment, whether similar compounds have been approved without such assessment or similar compounds have a long clinical use history without a QT or TdP signal. The FDA has accepted alternative study designs for certain subsets of compounds and in certain indications. The inability to perform a TQTS does not exempt the compound from a plan to assess QT prolongation risk.

Many companies are trying to get a jump on TQTS results by assessing QT liability in very early clinical trials. These types of studies make it possible to adjust drug portfolios and add value. **DDW**

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