A SPECIAL REPORT

CARDIAC SAFETY

ASSESSMENT UPDATE

WHAT DO RECENT REGULATORY CHANGES MEAN TO **PHARMA** AND **BIOTECH SPONSORS?**

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Update: TQT Cardiac Studies

Lisa Henderson

With the ICH adopting an alternative path to the traditional assessments for QTc interval prolongation in E14, the FDA also will offer waivers to these high-cost studies in favor of the lower-cost alternative. In this article, *Applied Clinical Trials* updates cardiac safety assessments and the FDA's view.

In December 2015, the ICH updated its E14 Guideline Q&A to define an alternative path for identifying the cardiac safety issue of QT prolongation in non-cardiac drugs. This is the most fundamental revision to the Q&A of "The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs" since its implementation in 2005 and is based on a study conducted with the Cardiac Safety Research Consortium (CSRC). The adopted alternative describes how data from ECGs collected during Phase I or other early clinical trials can be used to demonstrate a drug's QT effect. What it represents for sponsors is earlier collection of QT data, which could represent a savings of over 80% as compared to the currently sanctioned Thorough QT (TQT) studies which hover in the $2M to $4M range.

Cardiologists and clinical trialists had long been discussing ways to address cost challenges surrounding TQT studies when they started to emerge, soon after the Guideline was issued in May 2005. The guideline basically states that drugs in clinical trials for non-cardiovascular (CV) conditions should undergo TQT studies to ensure that the drugs did not cause clinically relevant QTc interval prolongation. These longer intervals predispose a patient to Torsade de Pointes, a life threatening arrhythmia. Sponsors quickly adopted TQT studies, and approximately 500 have been conducted over the past 10 years.

Now the ICH has adopted one alternative path—call it 'concentration effect modeling'— which relies on intensive, high quality ECG analysis and the use of exposure response modeling to determine the extent of QTc prolongation. Further proof of the method's validation is that the FDA accepted this approach in lieu of a TQT study earlier in 2015.

Applied Clinical Trials spoke with Norman Stockbridge, MD, PhD, Director of the Division of Cardiovascular and Renal Products in CDER's Office of New Drugs, about this new development and potential future developments in the assessment of cardiac safety of drugs in development.

10 Years?

Stockbridge noted that it has always been a known that TQT studies are inefficient. He said, "It led to sponsors doing a separate study instead of piggybacking onto an existing study. Then because it was a special study, it was only conducted late in development. Also, the previous by-time-point analysis doesn't use all the information; it just uses the information where the QT interval is the worst."

"The bigger factor was the FDA sitting down, talking and getting agreement on a validation making process for exposure response modeling," noted Stockbridge. And to that forward motion, he credits FDA colleague Christine Garrett. "She was largely responsible for getting us to work through

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What Problems ECGs Can Uncover in Clinical Trials

ECG Feature	Area of Myocardium	Main Abnormalities Seen in Clinical Trials
P-wave	Atrium	Ectopic atrial rhythm
		Atrial fibrillation
		Atrial flutter
PR interval	Atrium	AV-blocks
Q Wave	Ventricle	Myocardial infarction (old)
QRS Complex	Ventricle	Right bundle branch block
		Left bundle branch block
		Incomplete right bundle branch block
S-T Segment	Ventricle	Ischemia, Infarction
T-wave	Ventricle	Electrolyte changes
QT-Interval	Ventricle	Prolonged ventricular repolarization

Source: Biomedical Systems, 2014

Table. Twelve-lead electrocardiograms provide information about the functioning of the heart. Features, both waveforms and intervals on the ECG correlate to the structure and function of different segments of the myocardium.

it." And she led them through the intellectual-thinking and achieving an acceptable confidence level in the new approach. "It's been close to a decade to settle on an approach with enough pre-specification to talk about exposure-response analysis with the same confidence level as the older style TQT.

In the end, according to Stockbridge, FDA asked for a trial that formally compared the two approaches. The CSRC and IQPharma members initiated the IQ-CRSC study, of which the FDA was heavily involved in the design. Of the results, Stockbridge said, "What surprised me was how small a sample size study was able to capture drugs with modest QT effects, even using only the data for the usual maximum clinical dose."

Thus, the 10-year history of the TQT. "We nibbled away at the edges of the problem of ICH E14, made some community advancements of TQT designs, but it's really only been the last couple of years that we've had a real renaissance to assess proarrhythmia more effectively, and birth the initiative to get rid of TQT," noted Stockbridge.

There are certain issues that still need to be ironed out with the TQT vs. ECG Concentration studies. Just a cursory review of the CSRC/FDA Workshop: The Proarrythmic Assessment of New Chemical Entities agenda from early April shows a number of presenters focusing on that next step. Stockbridge led a session discussing proposed methods to replace the positive control (moxifloxacin) in QT studies. (When any pharmacologic control is introduced into a trial, it automatically makes the trial more complex and expensive, thus the incentive to eliminate moxifloxacin in small studies). Also on the agenda are non-clinical ways to assess cardiac safety, with the Comprehensive In Vitro Proarrhythmia Assay (CiPA).

Future Cardiac Safety Assessments

CiPA is being developed to use non-clinical cardiac safety evaluations to determine a drug's proarrhythmic potential, irrespective of effects on the QT interval. Stockbridge said, "CiPA is predicated on our assertion that we understand the molecular basis why some drugs are torsadogenic and others are not. I am confident that we can make reliable decisions based on assessment of the drug effects on the major human cardiac ion channel types in vitro," said Stockbridge. "It will always be more difficult to predict exactly who is going to get an arrhythmia and when, but we should be able to do better than QT assessment to rank drugs according to their risk."

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Are You Prepared to Replace the Thorough QT Study?

Amy Furlong

Planning ahead can save time and money later, thanks to recent regulatory changes in cardiac safety guidance.

Drugs that produce torsade de pointes, a potentially fatal arrhythmia, also prolong the QTc interval measured on the electrocardiogram (ECG). The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), which brings together global regulatory authorities and the pharmaceutical industry to clarify scientific and technical aspects of drug registration, adopted the ICH E14 guidance in 2005 to address this important safety issue. Since then, regulatory bodies like the FDA, EMA, and more recently the PDMA have mandated the evaluation of a new drug's effect on QTc in a formal Thorough QT (TQT) trial.

In December 2015, the ICH E14 Working Group released an update to the ICH E14 Guidance for Industry as a "Q&A" document. This anticipated revision discusses the use of concentration-QTc effect modeling (also referred to as Pharmacokinetic/Pharmacodynamic or PK/PD modeling) of data obtained during Phase I single and multiple ascending dose SAD/MAD clinical studies to characterize a new compound's effects on QTc. In the right circumstances, the ICH update indicates that such data may be adequate to replace a TQT trial for regulatory submission and

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review – which is welcome news for biopharmaceutical companies looking for ways to reduce development time and costs.

This strategy is not new, but the guidance revision offers new options to consider in development. Since 2005, regulatory bodies have required a TQT trial for new compounds with the exception of drugs for which a TQT study is not feasible, most notably for cytotoxic oncologic agents, atypical antipsychotics, and some biologics. In these cases, the industry has assessed QTc liability via PK/PD analysis during Phase I ascending dose studies. What is new is simply that the ICH now acknowledges that these techniques which have been used on oncologic and other agents are robust enough for use on less toxic drugs.

Options to assess cardiac safety early and at lower cost

The new ICH E14 revision gives you the option of using either Phase I SAD/MAD data or data from a standard TQT trial to assess the QTc liability of new agents. Since the cost of adding the required ECG collection to a SAD/MAD trial are a tiny fraction of the cost of a TQT trial, this is a great opportunity to potentially collect QT data earlier while also reducing costs. However, as only a small percentage of compounds that have a SAD/MAD trial progress to Phase III and drug approval, it is important to work with an experienced advisor so as to not increase overall costs even though the cost for a particular compound will be less.

A trusted partner to guide you

ERT has performed over 1,000 Phase I studies, securing multiple TQT waivers for our customers, and we have several different technical solutions for collecting required ECG data. Our precision analysis delivers the highest quality data, and we offer unique analytics and integration solutions to support a complete risk-based approach to your study conduct.

ERT also offers different strategies which allow you to choose the timing of ECG data analysis. You may analyze all data and perform statistical analysis as soon as your SAD/MAD trial is completed. After determining the safety of the product, you may decide to delay the intensive analysis until a drug has completed Phase II studies, thereby not analyzing QT data for drugs which are halted in development early in Phase I.

Ultimately, we recommend a flexible, customized approach since there is no silver bullet or one-size-fits-all approach. ERT will work with you to determine the optimal strategy that makes the most sense for your compound.

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