BY DENISE MYSHKO

ECG Goes **Digital**

With regulatory agencies placing a greater emphasis on cardiac safety, pharmaceutical companies are now required to test all drugs for their impact on cardiac repolarization. **Electronic data capture and transfer technologies are making this a much more manageable endeavor.**

Paper ECGs in clinical trials are but a blip away from becoming nonexistent. Regulatory guidances for definitive QT interval testing pretty much assure that paper electrocardiograms are soon to become a thing of the past. In fact, core labs — and even some CROs — now have the capability to provide digital ECGs and digital transmission.

Cardiac safety effects have become one of the most common causes of product withdrawal from the market. As a result, regulatory authorities around the globe have been placing greater emphasis on cardiac safety. Regulators have asked sponsors to incorporate an assessment of the QT interval in all of their development programs, not just cardiac products. A thorough QT trial is described as a single trial dedicated to evaluating the effect a drug has on cardiac repolarization as a way to predict the risk of sudden death.

"Regulatory agencies have become increasingly concerned with drug-induced QT prolongation and serious cardiac arrhythmia — known as 'Torsades de Pointes' — in the past decade," says Marilyn Agin, Ph.D., associate director of clinical biostatistics at Pfizer Global Research and Development. "Several products have been removed from the market — terfenadine, astemizole, cisapride, and mibefradil — because of QT prolongation-related safety issues."

According to Toby Barbey, M.D., medical director of core lab cardiology at Medifacts International, all sponsors should have the equivalent of a "QT dossier."

"Sponsors need to be able to explain to the FDA what their drug does or does not do to the QT interval based on quality preclinical and clinical work," he says. "All drugs have to be tested to show that they don't affect the QT interval, or if they do, they have to be unique enough to justify a small or medium risk."

Larry Lawson, president and CEO of eCardio Diagnostics LLC, says companies shouldn't overlook the possibility that a drug, even if it is considered safe within the specified range, could have an effect on the heart or the arrhythmia of the heart when coupled with another drug. This is why physicians are optimizing processes for cardiac event monitoring and drug titration.

At a meeting in May 2005 in Brussels, the International Conference on

The ICH guidances have established new standards regarding QT prolongation that prompt sponsors to design studies to detect the potential for QT prolongation in the preclinical phases. This will assist companies in making critical go/no-go decisions earlier in the drug-development process.

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Harmonization (ICH) Steering Committee and its expert working groups adopted two final guidances related to the testing for QT interval prolongation. (For more information on the guidances, visit ich.org.)

These documents provide recommendations to sponsors concerning the design, conduct, analysis, and interpretation of clinical studies (E14) and preclinical testing (S7B) to assess a drug's potential to delay cardiac repolarization.

The guidances provide a clear path to sponsors on how to assess the potential effects of non-antiarrhythmic drugs on the QT interval, Dr. Agin says.

"Obviously these requirements increase the cost and complexity of drug-development programs, but regulatory expectations are now well-defined and sponsors have a better understanding of how regulators will interpret QT data and the potential labeling implications," she says. "As a result, the ICH E14 guidance will help sponsors design and execute optimal strategies for QT interval testing. In my view, this is the most positive development in the past couple of years with respect to QT assessment. Another positive is the harmonization of these requirements — again with some exceptions acknowledged in the guidance — across the three major regulatory agencies, the FDA, EMEA, and Japan."

Pushing Past the Paper

"Thorough QT trials are expensive, and the logistics are challenging, which is pushing a lot of sponsors toward digital ECG capture," says Tony King, director of core lab services at Medifacts International. "We simply could not use paper ECGs in this context."

While recent advances have made the acquisition of these data easier, they also have provided new challenges.

"The last decade has seen the evolution from paper ECGs and intervals recorded on CRFs by hand to data captured completely on digital systems," says Pierre Wicker, M.D., executive director, site clinical therapeutic area head, worldwide clinical development, at Pfizer Global Research and Development. "Manufacturers of ECG machines are continually improving the automatic algorithms for measuring the QT and other intervals. Reliable data management tools are also critical. Because of the sheer number of ECGs in a thorough QT study, the technology must also keep an accurate record of when the ECG was recorded and for which subject."

Rick Gallisa, VP of sales and marketing at Gentiae Clinical Research Inc., says about 20% of what is spent on ECG cardiac safety testing and analysis goes to digital methods. The overall cardiac safety market is between $1 billion and $1.2 billion.

"I would expect this spend to accelerate

ROBERT BROWN

The guidances provide a consistent framework for doing cardiac safety evaluations within a company or across the industry. They should also decrease the overall time required to make decisions on the cardiac safety of individual compounds.

based on the QT guidelines that have come out from ICH and FDA," he says. "Additionally, the inherent advantages of digital acquisition and management of cardiac safety data will drive this trend."

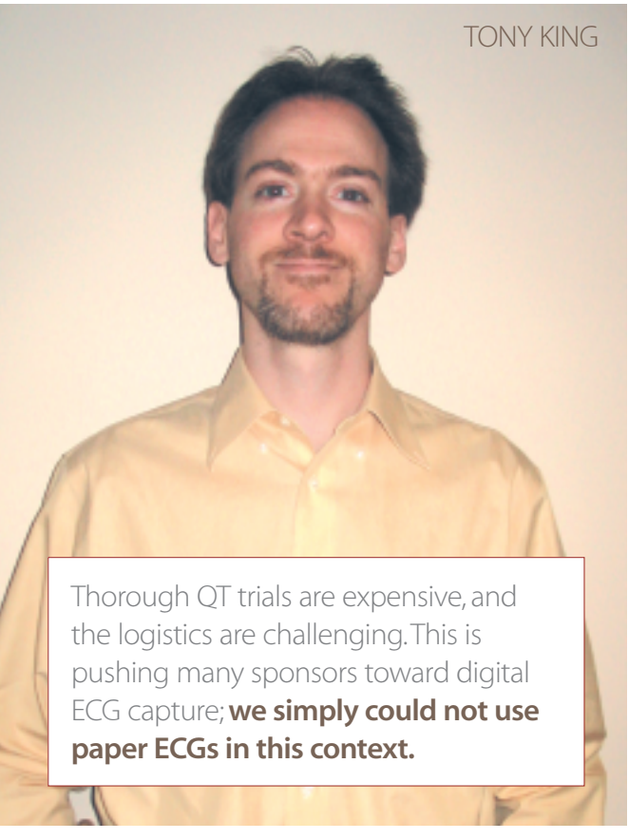
But Robert Brown, senior VP of outsourcing partnerships at eResearchTechnology Inc., says paper ECGs will be around for some time.

"Although digital ECG collection, transmission, and analysis represent best practices, our belief is that sponsors are still working with paper; therefore, there needs to be a system in place to process paper," he says. "There will be certain studies in third-world countries or huge studies over many sites over many

The ECG/Cardiac Monitoring Market

- The market includes: resting ECG products and services; stress testing products and services; Holter monitoring products and services; cardiac event products and services; ECG data management systems; and pacemaker monitoring services.
- The market for products was $295.7 million in 2004. It is expected to expand at a CAGR of 3.8% from 2004 to 2011.
- ECG data-management systems that offer the ability to interface with existing healthcare information systems will drive the product market.
- The market for services was $3.24 billion in 2004. It is expected to increase at a CAGR of 2.3% from 2004 to 2011.
- There is an increasing demand for integrated data management systems.
- There is increased adoption of PC-based ECG systems

Source: Frost & Sullivan, San Antonio. For more information, visit healthcare.frost.com.



Thorough QT trials are expensive, and the logistics are challenging. This is pushing many sponsors toward digital ECG capture; **we simply could not use paper ECGs in this context.**

Optimal timing of the QT study is one of the most important challenges faced by sponsors: not too early at a development stage when attrition is still high and the compound may be terminated for other reasons and not too late when substantial resources have already been expended.

years where sponsors may not choose to collect digital electrocardiograms. For these studies, centralized coordination and processing of paper ECGs is still more beneficial than a decentralized, non-core lab approach."

Industry experts say the pivotal QT studies are generally outsourced, either to a core lab or a CRO that either has a core lab or strategic partnership with a core lab.

"To reduce data variability, thorough QTc studies are usually done in a single site that has the capacity to run the entire trial," Mr. Brown says. "Sponsors select an ECG core lab to support thorough QTc studies to meet both the ICH guidelines and the specific requirements of the FDA standard for data delivery. They base their selection in part on the core lab's consultation expertise coupled with its overall experience in similar studies, experience with the site, experience with certain ECG technologies, and a demonstrated track record for the ability to get all aspects of the job done accurately and efficiently."

Some contract research companies have been offering ECG monitoring services for some time. Quintiles Transnational Corp. and Covance Inc., for example, both made acquisitions in 1998 that gave them the capabilities to do ECG monitoring. Quintiles acquired Cardiac Alert, and Covance acquired GDXI Inc.

Other CROs, such as Kendle, are just starting to do ECG monitoring for clients.

"As we continue developing the technology and expertise, we're able to offer ECG services to an increasing number of customers," says Melanie Bruno, Ph.D., VP of global regulatory affairs at Kendle.

Pharmaceutical companies, such as Lilly, also are bringing the expertise in house.

"We wanted to make the process better," says

QT/QTc Background

- An undesirable feature of some non-antiarrhythmic drugs is their ability to delay cardiac repolarization, an effect that can be measured as prolongation of the QT interval on the surface electrocardiogram (ECG). The QT interval represents the duration of ventricular depolarization and subsequent repolarization, beginning at the initiation of the QRS complex and ending where the T wave returns to isoelectric baseline. A delay in cardiac repolarization creates an electrophysiological environment that favors the development of cardiac arrhythmias, most clearly torsade de pointes, but possibly other ventricular arrhythmias as well. Torsade de pointes (TdP) is a polymorphic ventricular tachyarrhythmia that appears on the ECG as continuous twisting of the vector of the QRS complex around the isoelectric baseline. A feature of TdP is pronounced prolongation of the QT interval in the supraventricular beat preceding the arrhythmia. TdP can degenerate into ventricular fibrillation, leading to sudden death.
- While the degree of QT prolongation is recognized as an imperfect biomarker for proarrhythmic risk, there is a qualitative relationship between QT prolongation and the risk of TdP, especially for drugs that cause substantial prolongation of the QT/QTc interval.
- Because of its inverse relationship to heart rate, the QT interval is routinely transformed (normalized) by means of various formulae into a heart rate independent "corrected" value known as the QTc interval. The QTc interval is intended to represent the QT interval at a standardized heart rate of 60 bpm. For drugs that prolong the QT/QTc interval, the mean degree of prolongation has been roughly correlated with the observed risk of clinical proarrhythmic events. It is not clear, however, whether arrhythmia development is more closely related to an increase in the absolute QT interval or an increase in the relative ("corrected") QT interval (QTc). Most drugs that have caused TdP clearly increase both the absolute QT and the QTc. The combination of QT/QTc interval prolongation and documented cases of TdP (fatal and nonfatal) associated with the use of a drug has resulted in regulatory actions, including withdrawal from the market, relegation to second-line status or denial of marketing authorization. Because prolongation of the QT/QTc interval is the ECG finding associated with the increased susceptibility to these arrhythmias, an adequate premarketing investigation of the safety of a new pharmaceutical agent should include rigorous characterization of its effects on the QT/QTc interval. The relevant nonclinical and clinical data will be used to make an integrated assessment of proarrhythmic risk for novel drug therapies.

Source: The Food and Drug Administration, Rockville, Md. For more information, visit fda.gov/cber/gdlns/iche14qtc.htm.


DR. MARILYN AGIN

Researchers need to help their colleagues in data management understand ECG parameters so they will be able to spot obvious inconsistencies in the data. **They should also transmit test data sets from the site or vendor throughout the study to avoid surprises at the end.**

Theressa Wright, M.D., cardiovascular safety officer at Eli Lilly & Co. "To date, we've done several thorough QTc studies, but our use of a standardized process for ECG assessments was in place before the current ICH E 14 guidance for conducting thorough QTc studies."

In the development of new drugs, cardiovascular safety is a key component and electrocardiographic assessments are its major tools.

"From our experience, Lilly recognized and decided many years ago to create a standardized process for conducting and analyzing ECGs," Dr. Wright says. "This process is required of all our ECG vendors and applied to the majority of our clinical studies. The standardized ECG process has helped to maintain consistency and improved the quality of electrocardiographic assessments within and across all clinical studies.

"This allows us to enhance our understanding of a compound's cardiovascular safety profile by integrating data over multiple studies," she continues. "Technology has played a big part in the standardized process. We do not encourage paper ECGs for any studies that potentially might be used for regulatory submission. If the study is just for observation or the data will not be part of a registration submission, paper ECG assessments are fine. We are basically trying to become paperless. A few years ago, the Lilly Cardiovascular Safety Committee drew a line in the sand and said from this day forward everything will be electronic."


RICK GALLISA

With digital ECGs, there is the ability to manage, manipulate, and mine the data. If it is in paper, it's suboptimized in terms of the ability to do scientific research across clinical studies, across trials, across patient populations, or for new indications.

Digital Benefits

The shift from paper ECGs to digital ones is impactful because companies will have the ability to manage, manipulate, and mine the data, Mr. Gallisa says.

"If it is in paper, it's suboptimized in terms of the ability to do scientific research across clinical studies, across trials, across patient populations, or for new indications," he says. "There are considerable advantages for drug manufacturers that use digital acquisition and centralized core laboratories for cardiac safety in clinical trials."

According to Mr. Brown, sponsors would decrease their costs for evaluating ECG data in other non-thorough QTc studies just by hiring a core lab to coordinate and centralize the ECG collection, processing, and reporting activities plus manage the tasks related to equipment provisioning, technical and logistical support of sites, database management, and project management.

He estimates that sponsors are currently using a centralized process for ECGs to support about 10% to 15% of the ECGs collected in non-thorough QT studies, and in the process are reducing ECG-related costs compared with sponsors that are still operating in a decentralized fashion.

"Much of the savings can be attributed to the elimination of certain activities that the sponsor would normally perform, for instance, in the query-resolution area and the data-entry area," Mr. Brown says. "The core lab is able to do these activities more efficiently and more rapidly. In addition, use of a single data evaluation methodology across a study or program improves data consistency and reduces data variability compared with a decentralized approach."

Dr. Wright says digital ECGs allow companies to assess the safety and quality of the data in real time as the information comes in.

"We don't want to find out when we are two-thirds or almost done with a study that the ECG data exhibited a safety issue or the ECG tracing was unreadable or the file was corrupt," she says. "We request that the data be transmitted as soon as possible; we prefer this to be transmitted within a 24-hour timeframe so that the ECG data can be assessed for safety and quality, and feedback to the sites can be provided as soon as possible."

Dr. Wicker points out that the timing of conducting the test is critical.

"The thorough QT study is expensive, and it is important to get its design right with respect to ECG collection and doses," he says. "No sponsor would want to repeat the study because the ECG data were not collected at the appropriate time points or wrong doses were selected. While every compound is unique, most ECG studies are typically conducted after basic pharmacokinetic data are available and the expected therapeutic dose range has been reasonably defined. Pfizer now includes an extensive QT evaluation in first in human (FIH) studies to identify a QT signal very early in the clinical-development process, which will guide subsequent decisions."

The Selection Process

Dr. Agin says when the use of an ECG supplier is indicated, selecting the appropriate vendor may be a challenge for companies with no in-house expertise and no prior QT experience.

"Companies often choose a vendor based on its reputation or other nontechnical criteria," she says. "Expert advice is very helpful when selecting a vendor, however, to ensure quality data at a reasonable cost."

Mr. King says what is more important than how the vendor does the testing is its quality program and whether it is compliant with current regulations.

"If we're doing electronic data interchange it's absolutely critical that we know that the ECG data were collected accurately at the site and can be attributed to the correct subject all the way along the electronic data stream; we know who the data belong to, who analyzed the data, when they analyzed the information, and who changed the data and when," he says.

Sponsors should have what I call a "QT dossier." They need to be able to explain to the FDA what their drug does or does not do to the QT interval based on useful quality preclinical and clinical work.

"Those issues are important because it is easy with electronic data transfer to potentially make an error, and we don't have a nice paper ECG in the subject folder to fall back on."

Companies shouldn't overlook the possibility that a drug, even if it is considered safe within the specified range, could have an effect on the heart or the arrhythmia of the heart when coupled with another drug.

Dr. Wicker says significant cost savings in the future will come from the regulatory authorities' willingness to use preclinical data coupled with FIH testing to determine the need for a thorough QT study.

"A paradigm based on preclinical testing combined with an intensive QT assessment in FIH studies, including a measure to validate study sensitivity as well as statistical analysis and exposure-response modeling, has been proposed," he says. "Negative preclinical and FIH results will then be sufficient to establish the lack of a QT effect and obviate the need for a thorough QT study. Similarly, the presence of a QT prolongation in the FIH studies with a positive exposure- or dose-response relationship — with or without a preclinical signal — will definitively establish the presence of a QT effect, thus making the thorough QT study redundant."

Lawrence Satin, M.D., chief medical officer and president of Cardiocore, says technology that improves the transmission and analysis of ECG data is the next step forward.

"Wireless data transmission, user-friendly computer programs for hysteresis management, and high-speed transmission of large data files from flash cards are some of the leading challenges that technology faces today in this area," he says. ✦

PharmaVOICE welcomes comments about this article. E-mail us at feedback@pharmavoice.com.

Experts on this topic

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