

## Drug Research Predictions - iCardiac Technologies Drug Discovery & Development - November 01, 2008

To mark its 10th anniversary, Drug Discovery & Development magazine invited pharmaceutical and biotechnology companies to reflect on the history and made predictions about future of the industry. Featured here are verbatim comments from this company.

### iCardiac Technologies, Inc.

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#### About the company/organization

iCardiac is a research-based company that offers advanced tools for measuring ECG-based biomarkers in pharmaceutical cardiac safety trials. iCardiac offers two distinct service areas: 1) An advanced ECG-based QT analysis to meet the FDA's E14 QT/QTc guidance for the industry 2) An advanced analysis based on novel biomarkers which complement the FDA mandated QT prolongation results and, at the same time, enable a more in-depth and personalized approach to cardiac safety analysis.



In addition, iCardiac offers a full range of clinical trial services for acquisition, analysis, regulatory compliance and quality control of ECG data in clinical trials in collaboration with its Cardiac Safety Network Partners: Charles River Clinical Trials Services, a 250-bed Phase I facility, and Spacelabs Healthcare, a full service ECG clinical research organization.

iCardiac's novel ECG biomarkers provide rigorous characterization of a drug's effect on the repolarization process of the heart and significantly improve the ability to evaluate the risk of drug-induced arrhythmias such as torsades de pointes (TdP). The technology, developed at the University of Rochester Heart Research Follow Up program and at Pfizer, Inc, relies on the digital quantification of the heart's repolarization morphology and dynamics.

#### A 10-year perspective: Advances and roadblocks

The importance of cardiac safety testing increased in the last 15 years with the discovery that many drugs—whether in development or on the market—have the potential to cause a life-threatening arrhythmia, a condition known as torsades de pointes (TdP). Although the issue of cardiac safety in drug development appeared in the 1980s when drugs began to be withdrawn from the US market for safety concerns, the advanced cardiac safety industry only began to take shape in the last 5 years.

iCardiac Technologies formation as a company was precipitated by the emergence of cardiac safety as a critical issue in drug development. For a broad range of products from antibiotics to antipsychotic medications, drug induced changes in cardiac repolarization – a hallmark of dangerous arrhythmias – have become a major cause for attrition of drugs in the pipeline, adverse labeling changes and even post-market withdrawal.

In October 2005, the FDA adopted a new guidance for industry (ICH E14) requiring the evaluation of pro-arrhythmic potential of all new drugs in development by measuring the QT segment of ECGs collected in clinical trials. This method of evaluating cardiac safety risk is relatively crude, leaving drug developers, regulators, doctors and patients with uncertainty. Development of safe drugs can be unnecessarily terminated while unsafe ones can take too long to be identified. The need for a better cardiac safety test has driven innovation.

Breakthroughs in cardiac safety have stemmed from electrophysiology research and the use of sophisticated ECG signal processing algorithms. One key finding was that drug induced arrhythmias manifest on an ECG in the same way as arrhythmias caused by congenital Long QT Syndrome. This discovery made decades of data on congenital Long QT Syndrome extremely useful in the study of cardiac safety.

### **R&D Challenges in the next 10 years**

Life-threatening arrhythmias triggered by a patient's reaction to a drug are extremely rare. In cases where drugs were pulled off the market because they triggered dangerous drug-induced arrhythmias, the percentage of people who experience those adverse effects is extremely low. Moreover, the people tested in clinical trials most often are healthy whereas those who take the prescribed drugs often have conditions for which they are taking other medications. Adverse reactions may be triggered by a combination of drugs. Both the rarity of life-threatening reactions and the difference between clinical trials and post marketing conditions pose a major challenge for researchers who are trying to determine the cardiac risk of drugs in development in the clinical trial setting. The biggest challenge for research and development in the cardiac safety arena is to find a method of determining risk for each individual because the clinical trial settings cannot be used to rule out rare occurrences.

### **Business/regulatory challenges for the next 10 years**

Currently the industry takes a one-size-fits-all approach – that is, every drug must be “heart safe” to every person. The problem, however, is the inherent diversity of the human geno- and phenotype precludes a uniform standard. Even a drug proven safe for the vast majority of humans is likely to have adverse effects on some small portion of the population. Just as a patient's genetic make-up can determine his or her reaction to a drug, so too can underlying disease, smoking status, electrolyte imbalance and other medications that the patient may be taking. Finding a way to individualize cardiac safety testing would have profound effects on the productivity and cost of drug development.

The quest for absolutely safe medicines for all humans in all disease categories, leads to many undesired outcomes. Specifically, the current risk threshold for regulatory concern in “thorough QT” clinical trials is set at approximately 1 case of TdP arrhythmia per 105 to 106 drug exposures. This threshold seems arbitrary, as no explanation or justification for the threshold of regulatory concern has been published. Furthermore, it is clear that life-saving drugs or drugs that help control and manage dangerous or debilitating conditions may justifiably carry a greater risk of TdP and still be beneficial for patients. For instance, if a particularly efficacious cancer drug prolongs the QT interval in one out of 100,000 patients, would it not be worth the risk? Regulatory guidance as to how this risk-benefit analysis may be performed for a given therapeutic area, however, is lacking.

### **Bold Prediction: Where will the company/organization be in 10 years?**

*Hospital and Medical Office Diagnostics:* We believe that our ECG-based cardiac safety analysis will migrate to the diagnostic and clinical settings. When a patient is admitted to the hospital or visits the doctor's office with cardiac related problems, advanced ECG markers can be measured to better characterize the person's individual predisposition to drug-induced arrhythmias. For example, it may be possible to pin-point problems that are related to specific combinations of medications. This would offer an opportunity for the healthcare profession to adjust the regimen of medications to treat the underlying condition.

*Home Monitoring of At Risk Patients:* As the U.S. population ages, a larger number of individuals are taking medications at a stage in their lives where age-related cardiac problems are also occurring. Additionally, baby boomers will be expected to take a number of medical products in combination at the same time. This is creating a large number of possible permutations between inherent age-related cardiac problems and an increasing large regimen of various medications. In the clinical trial setting, it is impossible to test all of these combinations in addition to the variations that are introduced by individual patient's genetic makeup. This will likely result in patient specific and potentially fatal cardiac problems developing and going undiagnosed. We expect to be in the position to offer at risk patients and medical providers the option to monitor for the development of these types of cardiac problems in a home setting using simple ECG monitoring devices in combination with advanced ECG signal processing software.

### **Bold Prediction: Where will the industry will be in 10 years?**

Just as medicine will become more personalized, we believe cardiac safety will move to a personalized approach. Instead of attempting to find an absolutely “heart safe” compounds, this new approach will take into account the differences in each individual's heart. Specifically, the new approach will measure the individual heart's ability to manage the stress introduced by pharmaceutical molecules' interacting with the ion channels in the heart, the phenomenon also known as “repolarization reserve”. Recent advances in the fields of genomics and proteomics have led to the understanding that certain drugs tend to be more efficacious in specific sub-groups of patients. Similarly, cardiovascular safety biomarker research indicates it is possible, with a simple and inexpensive test, to separate those patients that can safely take a particular drug from those who cannot.

Current studies on cardiac safety biomarkers have demonstrated that certain patients have a lack of robustness within the repolarization mechanism of the heart. That lack of robustness can be caused by multiple factors, including genetics, health history and other medications. Patients who are not able to take certain drugs can be identified through a disruption of their cardiac ion channel flow, which can be determined with a simple electrocardiogram (ECG) test.

Novel advanced ECG-based cardiac safety biomarkers that comprehensively assess a patient's phenotype and cardiac function show great potential for developing an accurate, inexpensive, broadly available and easy-to-implement

personalized safety testing. We believe that with the support of advanced ECG analytics, testing can easily be administered in physicians offices because it does not introduce new procedures. Physicians already administer ECGs routinely.