



## **Proving Cardiac Safety, the Right Way**

***Accuracy and Flexibility are Critical in  
ECG Acquisition, Interpretation,  
Clarification and Verification***

By Covance Inc. (Cardiac Safety Services)

*Helping to bring miracles to market sooner.*

**COVANCE**  
THE DEVELOPMENT SERVICES COMPANY

The pressure on biopharmaceutical companies today to prove drug safety has perhaps never been greater. In this post-Vioxx environment, drugs are falling under a much higher level of regulatory scrutiny. One area in particular that is gaining significant regulatory attention is cardiac safety, or a drug's effect on the human heart. In fact, recent guidance<sup>1</sup> from both the U.S. Food and Drug Administration (FDA) and the International Conference on Harmonization (ICH) strongly recommends that sponsors must prove a drug's cardiac safety, or risk having the drug delayed or even denied marketing approval.

While this increase in regulatory vigilance will likely translate into an increase in the demand for cardiac safety testing, the big question is whether or not the ECG testing and analysis community is adequately prepared to support this need. That is, do they have the right tools and resources to produce data of a quality that can withstand the rigor of stricter regulatory scrutiny?

**Drugs can face approval delay or denial without proof of cardiac safety**

According to the FDA, seven drugs currently awaiting full marketing approval are being delayed until their sponsors can allay all cardiac safety concerns regarding the new drugs.

While many ECG core labs (the main service providers of ECG testing and analysis) do offer these services, they are often using outdated, inflexible or imprecise methods to produce cardiac safety data. This can lead to inexact results and potentially leave the sponsor in a tenuous situation when it files for marketing approval.

In order to obtain the high quality, on-time data sponsors need to support most of their studies, they need an ECG core lab that can provide full cardiologist review of every ECG that comes in. They need a lab that offers precise and efficient ECG analysis and is flexible enough to meet the particular needs of a study protocol. The specific expertise and tools such a lab should have include:

1. Board Certified Cardiologists on staff that can review every ECG
2. Precise, automated digital annotation systems that offer optimum accuracy, flexibility and consistency
3. Highly accurate ECG waveform measurement systems that can provide high-resolution measurements for the most precise readings possible
4. A fully integrated data environment – from ECG acquisition to interpretation to clarification and on through validation – to preserve data integrity and increase processing efficiency, every step of the way
5. Ability to standardize processes for global acquisition of ECGs

Covance, a worldwide leading provider of cardiac safety services, is one provider that can deliver this superior performance, across the board. Covance Cardiac Safety Services utilizes an open-ended, integrated information technology (IT) infrastructure comprised of Covance-pioneered tools that maximize performance throughout the entire ECG testing and analysis process.

In this article we will further explore Covance's ECG core lab solution which provides sponsors with unparalleled accuracy, efficiency and flexibility in proving cardiac safety. We will also discuss the heightened regulatory environment around cardiac safety and the many challenges most ECG core labs face in terms of supporting these emerging drug development needs.

## Pressure to prove cardiac safety, accurately and on time

Every additional day a drug remains in clinical studies costs a biopharmaceutical company on average US\$600,000 in lost sales (Research and Markets, June 2005). To help avoid potential marketing approval delays, the FDA and ICH now recommend that sponsors conduct full ECG testing and analysis. Recent guidance specifically states:

*“In general, drugs should receive an electrocardiographic (ECG) evaluation, beginning early in clinical development, typically including a single trial dedicated to evaluating their effect on cardiac repolarization. Failure to perform an adequate non-clinical and clinical assessment (of standard ECG intervals and waveforms) of a drug can be justification to delay or deny marketing authorization.”*

The primary measurement used to identify cardiac repolarization is the QT interval. At a heart rate of 60 beats per minute (bpm) the QT interval is about 400 milliseconds in duration. Drugs that prolong the QT interval can lead to a cardiac arrhythmia known as Torsades de Pointes (TdP). This serious cardiac condition can quickly degenerate into ventricular fibrillation, leading to sudden death. For this reason, the desire to accurately measure a new drug’s QT prolongation effect is growing. Figure 1 below illustrates the QT measurement.

### Accurate, consistent measurement leads to accurate, consistent data

ECG core labs receive ECG data from site investigators. Once the ECG is received, in whatever format or from whatever capture device, advanced core labs input the data into a digital system and apply a computerized annotation algorithm to measure QT and other intervals. This software produces numerical results which can then be evaluated by human experts. These automated systems can now process - in minutes - what it once took lab technicians weeks to accomplish. However, with most ECG core labs, this technology isn’t very flexible in terms of its ability to support the intake of varying formats of ECG data. There is also an issue of inconsistency from one software product to another. Most labs use one or more of a variety of annotation systems on the market. Each system uses its own mathematical algorithm to calculate results, and they cannot interoperate from one system or type of equipment to the next. With multiple different products on the market, this can be problematic. For example, if a sponsor were using several different ECG core labs for the same study, the ECG interval

### Depiction of QT interval analysis

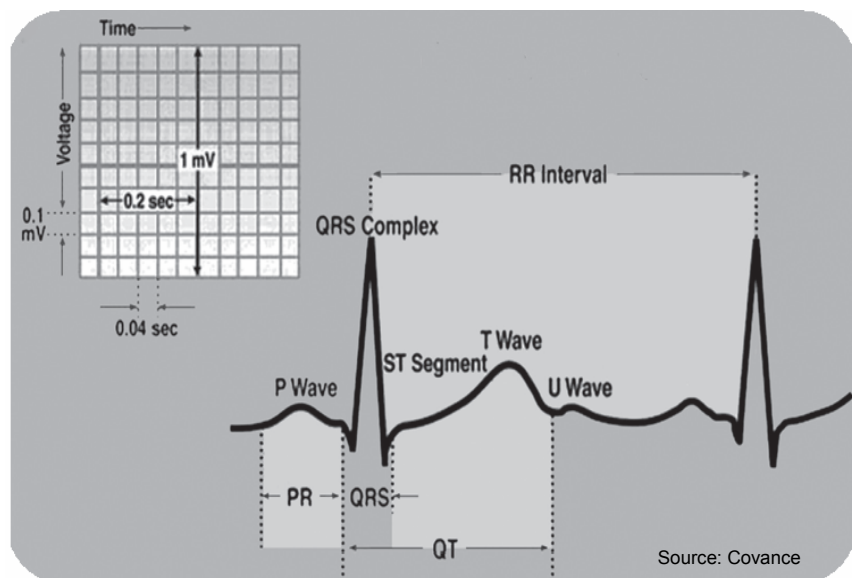
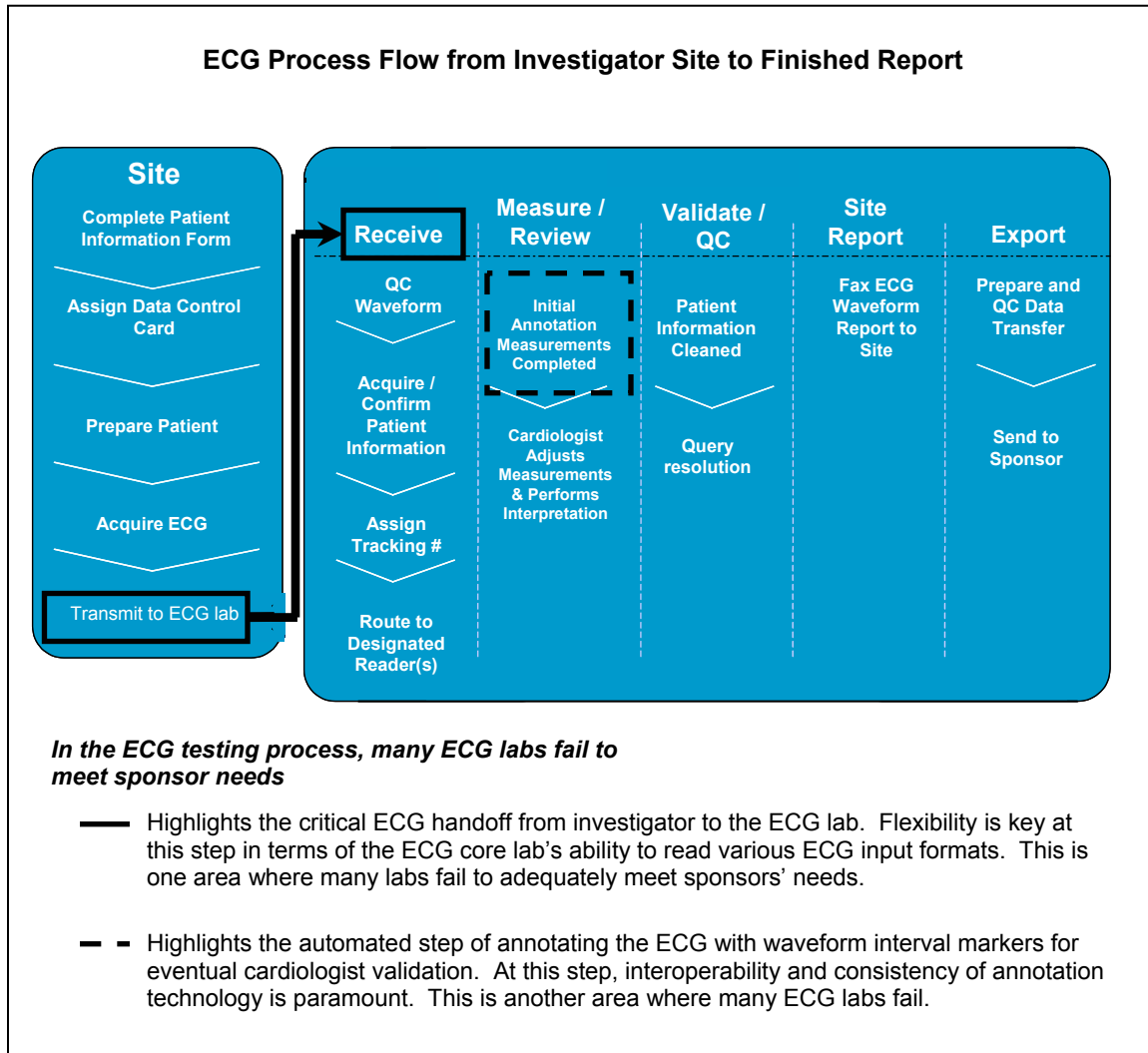


Figure 1: This diagram highlights key annotation points typically made by computer software. Covance’s AEA annotation algorithm leads the industry in terms of accuracy and flexibility (more information later in the article).

measurements from one lab to the next wouldn't be consistent. This can lead to inaccurate, inconsistent data analysis.



Covance has developed a one of a kind industry solution that eliminates problems of this sort. Cardiac Safety Services' Algorithm-Assisted ECG Annotation (AEA) system - the industry's most efficient, accurate and flexible ECG annotation system - is an open (fully interoperable) system, compatible with any ECG input, from any device. This interoperability provides the sponsor with a higher level of flexibility in how and where it chooses to conduct its trial.

### Industry's Most Accurate, Efficient and Flexible Cardiac Safety Solution

A comprehensive, high-performing digital ECG solution is the most effective means to obtaining quality cardiac safety data to support your trial. This equates to an integrated ECG annotation and measurement process that is accurate, efficient, consistent and flexible.

Covance's total cardiac safety solution is comprised of the following core components, all developed by Cardiac Safety Services to better service client needs:

- Acquisition – **Covance's MTX-2** is the industry standard in portable ECG acquisition devices.

MTX-2 is the industry's first and most utilized digital ECG reading device. It is portable, handheld and permits digital acquisition. The MTX-2 stores the ECG on the device itself, transmits the data remotely, automatically collects subject demographics and provides real-time quality control of waveforms. The MTX-2, due to its ease of use, is ideal for studies that cover wide geographies.

- Interpretation – **Covance's AEA** annotation algorithm provides unparalleled flexibility and precision in automated ECG waveform marking.

AEA (an automated ECG mark-up algorithm) - the industry's most efficient, accurate and flexible annotation algorithm - can read ECGs and automatically place annotation marks on any ECG format (including MTX-2, MAC 1200, Eli-250, H12+, Digipaper scanned paper, etc). This interoperability eliminates variability of ECG interval measurement between proprietary devices, a common restriction other ECG core labs face.

AEA is a very unique system capable of measuring waveform intervals on each individual lead – independently of other leads. It can leverage lead simultaneity and can mark every QRST complex or a selection of complexes on the digital ECG. AEA determines the sponsor's methodology requirements and presents annotation only on the appropriate leads and beats to be over-read in Covance's Digitography measurement tool (explained below).

AEA provides highly precise waveform measurements and is capable of marking up a virtually unlimited number of ECGs in one day.

- Clarification and Validation – **Covance's Digitography™** is the industry's first and most accurate interactive ECG analysis and annotation system for clinical trials.

Digitography is Covance's on-screen digital measurement tool providing our cardiologists with a high resolution ECG waveform analysis display – the most precise resolution in the industry. This totally integrated digital, paperless process includes measurement and interpretation of the Rate, PR, QT and QRS intervals, with unparalleled accuracy.

Furthermore, beyond all of this technology, Covance goes a step further. At Covance, every ECG is reviewed thoroughly by a Board Certified Cardiologist to ensure the most accurate measurements possible.

## Conclusion

As industry and regulatory pressures mount to ensure patient safety, and the need increases to bring new drugs to market as quickly and safely as possible, so should the desire to prove cardiac safety. To best address this critical need, sponsors will need accurate, consistent and timely ECG data that supports their drug filing. The most effective way to obtain this high-quality, on-time data is to find a service provider that has the tools, technology and professionals to help you prove cardiac safety, the right way.

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<sup>i</sup> June 2004 FDA guidance (re-released by ICH in May 2005) – The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Antiarrhythmic Drugs