Monitoring Cardiac Safety:

MINIMIZING RISK FOR YOUR NEXT CLINICAL TRIAL

Many drugs used to treat non-cardiac conditions are known to have off-target cardiovascular effects including arrhythmias, hypertension, and reduced ventricular function, which may lead to increased cardiac risk and possibly death. This presents a major challenge not only for clinicians who administer these medications, but also for sponsors who have invested significant time, resources, and money to develop effective therapeutic treatments. As such, cardiac safety monitoring has drawn considerable attention from the pharmaceutical and biotech industries, clinicians and regulatory agencies and has led to the establishment of regulatory guidelines by the International Conference on Harmonization (ICH). For example, the ICH-E14 guideline, ratified by the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA), calls for a rigorous evaluation of new drugs for potential repolarization (QT) related cardiotoxicity.

Cardiac Safety Endpoint Measurements

There are several different modalities and endpoint measurements available for assessing the cardiac safety of a new drug during clinical trials. Choices for sponsors include electrocardiogram (ECG) measurements (for determining QT intervals), ambulatory blood pressure monitoring (ABPM) (for measuring hypertension), echocardiograms (for LV and valvular function) and other image-based modalities such as MUGA and MRI (for measuring ventricular function), and serum biomarker levels (for monitoring cardiac injury). Although cardiac safety monitoring necessitates additional resources, strategies, expertise, and expenses for pharmaceutical and biotech drug sponsors, it is ultimately in their best interest to add these studies to drug development programs as they provide key benefits to help maximize the success of clinical trial outcomes.

Patient Safety

At the forefront of successful therapeutic development is patient safety. Even the most efficacious drug cannot progress through clinical trials without demonstrating its safety in large patient populations. Cardiovascular safety monitoring can define both short-term and long-term patient risks associated with novel drugs and provide added assurance that a drug does not adversely affect the cardiovascular system. As a result, these types of studies have become an integral part of clinical trial safety assessment. Monitoring for cardiotoxicity early in clinical development has the added benefit of identifying drugs with potential cardiovascular liability, identifying patients at higher risk, as well as providing opportunities for selecting safer drug administration regimens, thereby minimizing drug liabilities and making clinical trials safer for participants.

Cardiac Safety Testing Can Reduce Overall Development Costs

Pharmaceutical companies invest tremendous amounts of money and resources in developing approved therapeutics, with the average cost to bring a drug to market estimated at almost $1 billion. In particular, cardiotoxicities that arise during drug development exact a heavy toll on sponsors, with up to 45% of drug withdrawals and non-approvals in the U.S. over the last two decades arising from the presence of cardiac side effects in patients. Implementing cardiac safety studies into clinical trials is one way in which sponsors are minimizing the inherent risk of cardiotoxicity associated with new drugs. In particular, cardiac safety studies implemented in the early phases of clinical trials can identify potential risks and red flags early in the process, preventing expensive testing in later phases of trials, late-stage program termination, or post-market withdrawal.

In addition to minimizing financial losses, cardiac safety monitoring can also provide important mechanistic information to both clinicians and drug sponsors. Cardiac safety data not only provides insight into the interaction of a drug or drug class with the heart, but also can help guide the development of safer drugs with fewer cardiac side effects. With the help of the Cardiac Safety Research Consortium (CSRC), a public-private partnership developed in response to a recent FDA initiative, scientific findings on cardiac safety are being shared between industry, academia and regulatory agencies to advance awareness of cardiac safety studies. More recently, cardiac safety studies may also have the potential to inform drug efficacy during clinical trials. There is now some evidence from oncology studies of kinase inhibitors which suggests that particular cardiovascular pharmacodynamic responses (i.e. elevated blood pressure) are associated with increased efficacy and improved clinical outcomes. Thus cardiac safety monitoring may provide sponsors with valuable information regarding not just safety but also efficacy during clinical trials.

Cardiac Safety Studies the Heartbeat of Research

The pharmaceutical drug development environment continues to evolve, focusing on benefit and risk considerations based on therapeutic indication and patient populations, as well as comprehensive cardiac safety monitoring across early-phase, late-phase, and post-marketing clinical trial data. The information resulting from such cardiac safety studies are proving to be beneficial not only to sponsors that have a vested interest in the success of drug candidates, but also to regulatory agencies that guide the process, clinicians who prescribe medications, and ultimately patients who take new drugs on a daily basis. PV

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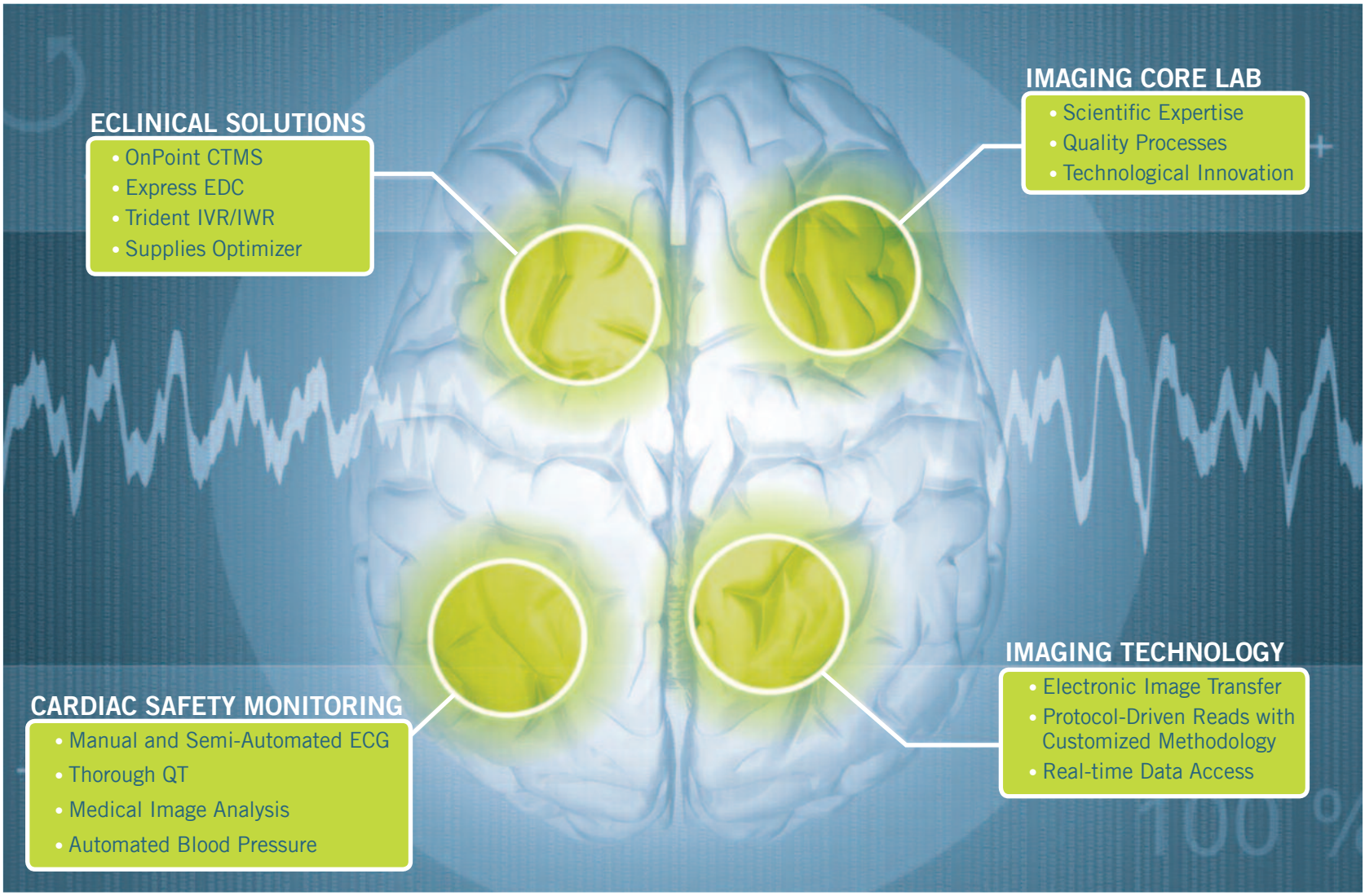

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