

# Executive Summary

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## **Cardiotoxicity**

Ion currents across a cardiac myocyte cell membrane cause a sequence of voltage changes known as the action potential, which is the basis of the heartbeat. Drug-mediated interference with 1 or more of the ion channel types that give rise to the action potential may cause potentially lethal arrhythmias. This could be brought about by direct binding of drug to ion channel proteins or by indirect interference with ion channel function. The clinical outcome of drug-ion channel interactions could be potentiated by a variety of predisposing factors, for example, concurrent disease, medication, genetic variations, age, and gender.

Additionally or alternatively, drugs may have more directly cytotoxic effects on cardiac cells, for example, pro-apoptotic effects. In particular, the anthracyclines are commonly used in pediatric malignancies and breast cancer, and are associated with chronic cardiotoxicity. Hence, many cancer survivors have a higher risk of cardiovascular disease than of recurrent cancer. In most cases, the mechanisms and predisposing factors involved in “direct” cardiotoxicity are not well understood.

## **Regulatory Environment: Proarrhythmia Screening**

The regulatory environment is largely defined by guidelines ICH S7B and ICH E14, from the International Conference on Harmonisation, which are accepted in North America, Europe, and Japan. Our interpretation of S7B suggests that, at present, preclinical QT studies should use ion current assays (including an IKr [rapid rectifier potassium current] assay) in single cells, action potential assays in multicellular systems, and in vivo studies such as electrocardiographic (ECG) recordings/QT measurements from animal models. However, the authors of S7B acknowledge that it may be revised in the light of new data; in

particular, the guideline suggests that instability, temporal and/or spatial dispersion of refractoriness, reverse use dependency, changes in action potential configuration, and predisposed animal models might become recognized as having utility in assessing proarrhythmia.

Our interpretation of E14 suggests that the thorough QT/QTc study is used to determine if drug effects on QT/QTc interval should be studied intensively during later clinical trials, not to determine whether or not a drug is proarrhythmic. Drugs that prolong the mean QT/QTc interval by 5 months or less do not appear to cause torsades de pointes (TdP) and will not be required to undergo extensive QT studies in later clinical trials. Drugs that prolong the mean QT/QTc interval by greater than 20 ms are said to have a substantially increased likelihood of being proarrhythmic and are likely to require extensive and time-consuming expanded QT studies in later trials.

### **Assessing Drug-Induced Cardiotoxicity**

At present, surrogate markers for TdP risk suggested by the regulatory guidelines primarily comprise IKr blockade and QT/QTc prolongation. There has been some criticism of these surrogates. For example, it is known that channels other than hERG (human homolog of the ether-à-go-go related gene) are involved in the action potential, that blockade of channels other than hERG may be torsadogenic, and that hERG blockade does not always result in TdP. Similarly, there is no clear link between QT prolongation and human TdP. Furthermore, manual QT readings introduce variability and the potential for error, and are of low throughput.

Alternative surrogates for TdP risk have therefore been proposed. These include instability and transmural dispersion of repolarization and combinations of measures (TRIaD) that include these markers. However, these can only be measured in relatively complex, low-throughput multicellular systems, such as ventricular wedges and Langendorff perfused whole hearts, and often require a degree of expertise that has hindered their broad application.

Other methods for assessing proarrhythmic cardiotoxicity during the drug development process include the following:

- *In silico methods*: These have been designed mainly to identify hERG binders, not other cardiac ion channels; they generally suffer from false positives and negatives, and cannot yet substitute for studies in living cells.
- *Single-cell in vitro methods*: These may allow automated, higher-throughput screens on a single ion channel, but cannot identify the potentiating/mitigating effects that may arise when a single drug interacts with multiple ion channels. Data from automated systems are increasingly accepted as valid, but at present, manual patch clamping remains the gold standard single-cell technique for regulatory approval purposes.
- *In vivo systems*: These primarily involve dog, pig, or monkey models, and have the advantages of modeling the effects of hormonal/neuronal secretions and drug metabolites. However, they are expensive and low throughput, and suffer from interanimal variability. Some predisposed animal models are said to be particularly sensitive for the identification of drugs with TdP liability, for example, the methoxamine-sensitized rabbit, the canine chronic atrioventricular (AV) block, and canine pharmacological IKs (slow rectifier potassium current) block.

“Direct” (nonproarrhythmic) cardiotoxicity screens are mainly based on *in vivo* assays of biomarkers, for example, troponins. Toxicoproteomics may have a role in the future.

## **Industry Attitudes and Survey Results: Proarrhythmia Screening**

It is common practice to screen against multiple ion channels, using multiple assessment platforms. Besides hERG, other channels of interest include L-type calcium channels, Nav1.5, Kv4.3, KvLQT1, Kv1.5, and HCN4. However, the exact number and identity of cardiac ion channels that should be tested in a cardiotoxicity screening program are still debated.

There is least pessimism and most optimism about regulatory acceptance of instability and dispersion of repolarization as TdP risk surrogates. Similarly, there is significant optimism over the utility of multicellular models that allow measurement of instability or dispersion.

There is some feeling that regulatory authority behavior, if not official guidelines, is changing or will change over the next few years. In the Insight Pharma Reports cardiotoxicity survey conducted in December 2007, 25 of 49 (51%) respondents said that they expect a substantial change to S7B within 5 years, and 30 of 54 (55%) expect a substantial change to E14 within 5 years.

Possible changes to the S7B guideline include increased acceptance of automated patch clamping data, but decreased emphasis on single-channel studies as compared with multiple-channel studies, and perhaps a decreased focus on in vitro data. In addition, there may be an increased emphasis on multicellular/whole organ or whole animal studies, in particular, those using the ventricular wedge, the Langendorff perfused whole heart, or the SCREENIT model.

Possible changes to the E14 guideline include methodological updates, for example, to recommend the use of automated systems to measure QT intervals. In the longer term, there may be acceptance of surrogates such as transmural/spatial dispersion of repolarization (perhaps measured as changes in T-wave morphology) and instability.

For both S7B and E14, such changes seem more likely to take the form of unwritten understandings between regulators and sponsors, rather than the issue of revised documents.

## **Commercial Environment**

At least 50 companies have a claimed product or service relevant to cardiotoxicity screening, of which 29 have some clear focus on proarrhythmic cardiotoxicity or ion channel screening. Of these 29 companies, about 83% include services in their offering, and only about 17% focus exclusively on products; approximately 66% are privately held.

Among companies that offer services for cardiotoxicity screening, 14 are involved in providing low-throughput services and 15 provide medium-/high-throughput services. There may be some consolidation opportunities in the cardiotoxicity screening services subsegments, particularly where a merger can offer the market a broader “one-stop shop” for cardiotoxicity screening services.

Similarly, it seems unlikely that the market will continue to support all 10 providers of high-/medium-throughput cardiotoxicity screening instrumentation. There may be merger and acquisition (M&A) activity in this subsegment in the future.

## **Cardiotoxicity Screening in Drug Development: The Future?**

Beat-to-beat variability and spatial or transmural dispersion of repolarization may be good surrogates for TdP risk. These signals arise at the level of multiple cell-tissue interactions. At present, their measurement requires intrinsically high-cost, low-throughput procedures involving laboratory animals and technically complex/time-consuming laboratory preparations.

Such procedures do not address the throughput requirements of early-stage drug development. These requirements probably will continue to be met in the near term by systems that are based on less adequate TdP risk surrogates, such as hERG blockade, whether measured by in vitro or in silico systems.

Commercial opportunities in proarrhythmia screening may exist as follows:

- Improvement of single-cell high-throughput methods to allow assessment of interactions of a compound with multiple ion channels in a single cell, probably via the development of new cell lines and software
- Development of ventricular wedge-type systems, or systems that provide equivalent data, that are capable of broader uptake (require less technical expertise) and/or are higher throughput
- Development of systems to accurately measure transmural/spatial dispersion of repolarization in the human
- Development of “automated” Langendorff systems to compete with SCREENIT
- Development of systems for the electronic reading and assessment of cardiac parameters such as ECG profiles and T-wave morphology, and software/algorithms for superior correction of QT data

Commercial opportunities in systems to screen for direct (nonproarrhythmic) cardiotoxicity may be limited by poor understanding of the mechanisms by which such toxicity arises, but could include identification of superior serum biomarkers or toxicoproteomic serum profiles for use during in vivo and clinical stages of drug development, and development of apoptosis or other cytotoxicity screens specifically refined for cardiac myocytes, and/or the development of standardized cell lines that can substitute for cardiac myocytes.

## **Overview of This Report**

This report identifies and discusses methods, products, and services that are designed to identify cardiotoxic compounds before they reach the market, discusses the current and possible future regulatory environment, outlines main commercial competitors, and suggests broad types of commercial opportunity and future M&A activity in this subsector. Although the primary focus is on identification of proarrhythmia, identification of other forms of cardiotoxicity is also discussed.

Chapter 1 provides a primer on cardiac anatomy/physiology. Particular consideration is given to the various ion fluxes that contribute to the cardiac action potential.

In Chapter 2, drug-induced cardiotoxicity is discussed under 2 headings: “direct” cardiotoxicity (i.e., where the primary symptom of cardiotoxicity is not arrhythmia) and proarrhythmic cardiotoxicity. In each category, we provide extensive lists of drugs associated with cardiotoxicity, discuss factors that may predispose to drug-induced cardiotoxicity, and outline current/proposed cardioprotective approaches.

Chapter 3 outlines the history and status quo of the current regulatory environment pertinent to drug-induced proarrhythmia, with particular reference to guidelines S7B and E14. In addition, some of the main factors that may impact the regulators’ decisions regarding drug nonapproval due to cardiotoxicity are discussed.

Chapter 4 provides a detailed discussion on methods for assessing the potential for drug-induced cardiotoxicity, with a primary focus on proarrhythmia screening. Various recommended and proposed surrogates for TdP risk are compared. Preclinical and clinical proarrhythmia screens are discussed, including in silico methods, in vitro single-cell/

multicellular methods, in vivo methods, and early clinical trial methods. Some discussion is also provided on mechanisms of screening for direct (nonproarrhythmic) cardiotoxicity.

Chapter 5 and Appendix D provide and discuss the results of an Insight Pharma Reports cardiotoxicity survey undertaken for this report in December 2007 by online questionnaire. Questions were aimed at, among other things, gathering information on attitudes to preclinical models and surrogates for TdP risk, and opinions as to how and when current guidelines might change. Results from previous industry surveys also are noted. These subjects are further discussed in one-on-one interviews with key experts in the field, transcripts for which can be found in Appendix A.

Chapter 6 provides an overview of 50 commercial entities that offer cardiotoxicity screening products/services. Further analysis is included regarding the competitive positioning and ownership of 29 companies that have some clear cardiotoxicity screening focus. Broad consolidation/M&A opportunities are outlined in general terms.

Finally, Chapter 7 provides a subjective opinion on the future of cardiotoxicity screening, suggests how regulatory guidelines might change in the future, and outlines commercial opportunities that might be associated with the current and future cardiotoxicity screening environment.

