

Drug-induced cardiotoxicity: screening methods, regulatory context, commercial environment.

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Overview

This report identifies and discusses methods, products and services 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. The primary focus is on identification of proarrhythmia, but some discussion is provided on identification of other forms of cardiotoxicity.

We start by providing a primer on cardiac anatomy / physiology. Particular consideration is given to the various ion fluxes that contribute to the cardiac action potential.

Next, drug-induced cardiotoxicity is discussed under two 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 which may predispose to drug-induced cardiotoxicity, and outline current / proposed cardioprotective approaches.

We then outline 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, we discuss some of the main factors which may impact the regulators' decisions regarding drug non-approval due to cardiotoxicity.

Next, we provide 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 torsades de pointes (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 also is provided on mechanisms of screening for 'direct' (non-proarrhythmic) cardiotoxicity.

In addition, we provide and discuss the results of an industry survey undertaken for this report by online questionnaire and by one-to-one interviews with key experts. Questions were aimed at, *inter alia*, 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.

An overview of 50 commercial entities offering cardiotoxicity screening products / services is provided. 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, we provide a subjective opinion on the future of cardiotoxicity screening, suggest how regulatory guidelines might change in the future, and outline some commercial opportunities that might be associated with the current / future cardiotoxicity screening environment.

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