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# Integrated and translational nonclinical *in vivo* cardiovascular risk assessment: Gaps and opportunities

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ABSTRACT

Cardiovascular (CV) safety concerns are a significant source of drug development attrition in the pharmaceutical industry today. Though current nonclinical testing paradigms have largely prevented catastrophic CV events in Phase I studies, many challenges relating to the inability of current nonclinical safety testing strategies to model patient outcomes persist. Contemporary approaches include a spectrum of evaluations of CV structure and function in a variety of laboratory animal species. These approaches might be improved with a more holistic integration of these evaluations in repeat-dose studies, addition of novel endpoints with greater sensitivity and translational application, and use of more relevant animal models. Particular opportunities present with advances in imaging capabilities applicable to rodent and non-rodent species, technical capabilities for measuring CV function in repeat-dose animal studies, detection and quantitation of microRNAs and wider use of alternative animal models. Strategic application of these novel opportunities considering putative CV risk associated with the molecular drug target as well as inherent risks present in the target patient population could tailor or 'personalize' nonclinical safety assessment as a more translational evaluation.

This paper is a call to action for the clinical and nonclinical drug safety communities to assess these opportunities to determine their utility in filling potential gaps in our current cardiovascular safety testing paradigms.



## 1. Introduction

It is widely recognized in the drug development community that adverse cardiovascular (CV) effects plague the development of many novel pharmaceuticals and marketed drugs. These effects are often varied in their presentation, insidious in their onset, multi-factorial in their pathogenesis and occur at all stages of development complicating their recognition in both nonclinical animal studies and in human patients. Accordingly, CV safety concerns are a major contributor to a debilitating drug development attrition challenging the pharmaceutical industry today (Laverty et al., 2011).

Standard approaches to CV risk assessment in pharmaceutical development have largely been driven by ICH Guidances (e.g. S7a, S7b) primarily intended to prevent acute and catastrophic adverse drug effects in Phase I clinical trials conducted in healthy human volunteers (International Conference on Harmonisation, 2001; Cavero and Crumb, 2005). These approaches have been effective in protecting that population of patients as illustrated by lack of reports of significant adverse CV effects in Phase I trials. Paradoxically, the more vexing CV challenges in contemporary drug

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development relate to adverse CV findings in non-acute nonclinical studies or longer duration clinical trials. Indeed, some of the most concerning current manifestations of CV effects in human patients are those that occur in small numbers of patients during late stage clinical development or after registration when large and heterogeneous patient populations have been exposed (e.g. increased incidence of myocardial infarction or stroke, drug-induced valvulopathy, decreased ejection fraction, etc.). Many of these populations have underlying diseases and co-medications that confound interpretation of outcomes. Individual patient susceptibility to cardiotoxicity is often not recognized preventing risk avoidance in these patients. Recent clinical experiences with these issues (e.g. rofecoxib, torcetrapib, trastuzumab, anti-neoplastic tyrosine kinase inhibitors) resulting in late stage discontinuation, post-marketing withdrawals or the need for enhanced clinical monitoring suggest that traditional approaches fall short of efficiently identifying and managing these important risks (Burnier, 2005; Chien and Rugo, 2010; Chu et al., 2007; Jnni et al., 2004; Kerkel+ñ et al., 2006).

Accordingly, these authors believe that there is a need to re-examine pharmaceutical CV risks in their varied manifestations, our current strategies for assessing those risks, and exploring opportunities for improving those strategies. Specifically, improvement is needed in the earlier recognition of potential risks, a better understanding of mechanisms and pathogenesis, and design of more translational biomarker strategies. Also, there is a need for nonclinical strategies that have a high concordance with clinical outcomes and can be translated to the clinical development context. Nonclinical recognition of important clinical risk will aid in early discontinuation of drug candidates with unacceptable risks or meaningful risk mitigation for compounds with acceptable risk: benefit profiles. Mitigation of risk may include designing safer compounds, avoiding patient populations at greatest susceptibility (i.e. personalized medicine), or designing sensitive and specific translational biomarker strategies to facilitate early clinical detection and drug withdrawal. Development of effective nonclinical assay or modeling systems requires scientists at all stages of the drug development process to understand these risks and to collaborate to develop more effective strategies.

This paper outlines relevant opportunities for providing greater insight into drug-related effects on the CV system in nonclinical safety studies enabling earlier and more effective design of risk mitigation strategies for both chronic toxicity studies and clinical trials. It is intended to be a call to action by an interdisciplinary group of cardiovascular risk assessment experts under the auspices of the ILSI–HESI Cardiac Safety Technical Committee. This group of safety scientists has examined our traditional nonclinical strategies, identified important gaps, and is suggesting opportunities to fill those gaps. The authors acknowledge the lack of data to support the clinical predictivity of these strategies but believe a more holistic approach to nonclinical CV safety offers better opportunity for decreasing CV safety related attrition than current practices. The opportunities offered here are relevant for contemporary CV safety challenges as we know them but would require further characterization to demonstrate their usefulness.

## 2. Defining the risk

An important component of designing effective strategies to identify risk- non-clinically or clinically- is to have a sense of what those risks are and how they present. Undesirable drug-induced CV effects identified in nonclinical animal studies and patients run the spectrum of altered cardiac electrophysiology (e.g. QT prolongation, arrhythmias), changes in cardiac and/or peripheral hemodynamics (e.g. change in blood pressure or heart rate), cardiac contractile dysfunction, vascular injury, valvulopathy, and cardiomyocyte injury. Many of these effects are of sufficient concern to stop the progression of novel drugs from nonclinical testing to clinical trials in human patients. Though patient safety is always the primary consideration, the concordance or predictivity of drug effects in animal models for human patients is often unknown resulting in discontinuation of potentially safe and efficacious drugs. Further complicating clinical progression of these putative risks is lack of sensitive and specific biomarker strategies that allow detection prior to irreversible harm to patients.

Conversely, there are drug-associated cardiac effects that occur in human patients that are not modeled or predicted with traditional nonclinical strategies. Some of these toxicities do not reliably reproduce in animal models (e.g. anorexigen-induced valvulopathy) or present clinically as imbalances in naturally occurring adverse CV events (e.g. myocardial infarctions, strokes, cardiac death) in long duration clinical trials or post-marketing (Barkin et al., 2010; Basaria et al., 2010; Besag and Stiefel, 2010).

This variability in presentation is illustrated in a wide variety of published accounts in both nonclinical species and human patients. An increased incidence of adverse CV events was associated with small increases in blood pressure in patients given torcetrapib (Barter et al., 2007). Thrombo-embolic events occurred in patients given the selective cyclooxygenase-2 inhibitor rofecoxib (Solomon et al., 2004). Changes in cardiac contractility are recognized risks in patients taking anti-neoplastic anthracyclines or tyrosine kinase inhibitors (Force and Kolaja, 2011). Vascular injury has been reported with a variety of vasoactive compounds in nonclinical animal studies (Zhang et al., 2006). Valvulopathy has been described in patients taking ergot derivatives or phentermine–fenfluramine combinations as well as in animals given ALK receptor inhibitors (Anderton et al., 2011; Elangbam, 2010).

Clinical tolerance for cardiovascular safety risks is variable. For example, drug-induced myocardial injury – though concerning in any target patient population – may be of more concern in a patient with non-life threatening disease (e.g. diabetes) than a patient with terminal cancer. Risk tolerance also differs for short duration treatments versus drugs intended for daily use over long periods of time. Aside from these issues, societal and regulatory tolerances for risk are fluid. The pharmaceutical industry is under considerable societal pressure to develop novel drugs that are distinguished from existing drugs by their effectiveness but that also have equal or improved side effect profiles. Accordingly, the FDA recently issued guidance for development of drugs for diabetes where there is a greater expectation for demonstrating CV safety in longer duration clinical trials than in previous guidances (Hennekens et al., 2010; Joffe et al., 2010; Preiss et al., 2011). Likewise, recent successes in the treatment of some forms of cancer have resulted in the birth of the clinical field of 'cardioncology' – a focus on the cardiac sequelae of oncology drug therapy (Curigliano et al., 2010; Lenihan et al., 2010; Zambelli et al., 2010). Cancer patients treated with cardiotoxic anti-neoplastic drugs are living longer resulting in the need to manage the long term adverse cardiac effects of those drugs.

## 3. Traditional paradigms

Contemporary approaches to nonclinical safety assessment of novel pharmaceuticals include a number of *in vivo* assessments of CV structure and function. In general, evaluations of drug-induced changes in CV function are conducted in focused single dose safety pharmacology studies while clinical pathology (hematology, hemostasis, clinical chemistry, urinalysis, cytology) and morphologic pathology assessments of structural effects are done in repeat-dose general toxicity studies.

For the past decade, assessments of CV function in nonclinical safety studies have largely been driven by regulatory recommen-