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REVIEW

How can we improve our understanding of cardiovascular safety liabilities to develop safer medicines?

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Report on the Medical Research Council Centre for Drug Safety Science workshop on 'Cardiovascular Toxicity of Medicines'.

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Given that cardiovascular safety liabilities remain a major cause of drug attrition during preclinical and clinical development, adverse drug reactions, and post-approval withdrawal of medicines, the Medical Research Council Centre for Drug Safety Science hosted a workshop to discuss current challenges in determining, understanding and addressing '*Cardiovascular Toxicity of Medicines*'. This article summarizes the key discussions from the workshop that aimed to address three major questions: (i) what are the key cardiovascular safety liabilities in drug discovery, drug development and clinical practice? (ii) how good are preclinical and clinical strategies for detecting cardiovascular liabilities? and (iii) do we have a mechanistic understanding of these liabilities? It was concluded that in order to understand, address and ultimately reduce cardiovascular safety liabilities of new therapeutic agents there is an urgent need to:

- Fully characterize the incidence, prevalence and impact of drug-induced cardiovascular issues at all stages of the drug development process.
- Ascertain the predictive value of existing non-clinical models and assays towards the clinical outcome.

- Understand the mechanistic basis of cardiovascular liabilities; by addressing areas where it is currently not possible to predict clinical outcome based on preclinical safety data.
- Provide scientists in all disciplines with additional skills to enable them to better integrate preclinical and clinical data and to better understand the biological and clinical significance of observed changes.
- Develop more appropriate, highly relevant and predictive tools and assays to identify and wherever feasible to eliminate cardiovascular safety liabilities from molecules and wherever appropriate to develop clinically relevant and reliable safety biomarkers.

Abbreviations

ABPI, Association of the British Pharmaceutical Industry; ADR, adverse drug reaction; AE, adverse event; AERS, Adverse Events Reporting System; BP, blood pressure; CD, candidate drug; CDSS, Centre for Drug Safety Science; FDA, Food and Drug Administration; hERG, human ether-a-go-go-related gene; ICH, International Conference on Harmonization; IMI, Innovative Medicines Initiative; MHRA, Medicines and Healthcare products Regulatory Agency; MRC, Medical Research Council; nda; no data available; PK/PD, pharmacokinetic and pharmacodynamic, TdP, Torsades de Pointes

Introduction

Pharmaceutical industry surveys have revealed that over the last decade the number of new medicines being launched has fallen sharply despite significant investments in Research and Development (Munos, 2009). Over the same period, non-clinical and clinical safety has remained a major cause of drug attrition. Such attrition can occur during preclinical or clinical development and post-approval stage, resulting in withdrawal of marketed drugs accounting for approximately one-third of all drug discontinuation (Figure 1; Kennedy, 1997; Lasser *et al.*, 2002; Kola and Landis, 2004; Shah, 2006; Redfern *et al.*, 2010). A recent literature review of the reasons for drug attrition in non-clinical and clinical development, serious adverse drug reactions (ADRs) and withdrawal from the market place revealed that cardiovascular toxicity occurred more frequently than hepatotoxicity (Figure 2; Redfern *et al.*, 2010). The data indicate that Phase I clinical trials are very safe at least from a cardiovascular point of view; this may reflect the effective preclinical testing and elimination of high-risk cardiovascular safety liabilities prior to entering clinical development. More worrying is the identification of more subtle, but high-risk, cardiovascular events either not detected in earlier clinical trials or not deemed to be biologically significant or clinically meaningful that emerge when drugs are administered for longer periods of time to larger patient populations (Figure 2; Lewington *et al.*, 2002; Joy and Hegele, 2008; Paul *et al.*, 2010; Redfern *et al.*, 2010). Such high incidence and/or severity of cardiovascular ADRs in late-stage clinical development can lead to prescribing restrictions, additional pre- and/or post-approval monitoring, dose limiting toxicity, or ultimately drug discontinuation or withdrawal. Interestingly, the hepatic and cardiovascular toxicity profiles are somehow different. The incidence of hepatic ADRs is low and consistently lower than cardiovascular ADRs; this may reflect our ability to detect and discard drugs associated with hepatic more so than cardiovascular type A-ADRs during preclinical development. However, the high incidence of liver-related attrition observed in late clinical development or post-approval might be indicative of idiosyncratic reactions, not identified during preclinical or early clinical development. The difference in incidence of cardiovascular-related attrition post-approval noted between Fung *et al.* (2001) and Stevens and Baker

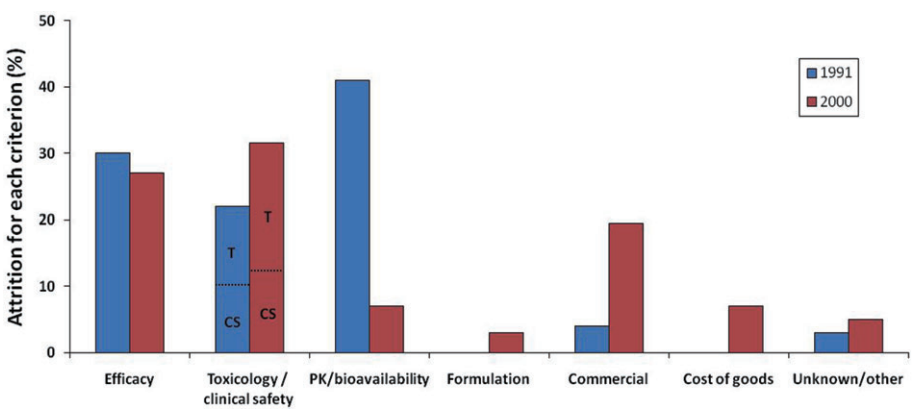

Figure 1

Reasons for drug attrition in 1991 and 2000. PK, pharmacokinetics; T, toxicology; CS, clinical safety. Modified from Kola and Landis (2004). Over the 10 year period safety, combining non-clinical toxicology and clinical, has remained a major cause of drug attrition accounting for approximately 30% of all drug discontinuation; during the same period attrition due to pharmacokinetics and bioavailability reasons has been reduced significantly, probably reflecting in part the effort placed on front-loading Drug Metabolism and Pharmacokinetics activities in the early discovery phases.

Phase	Non-clinical	Phase I	Phase I-III	Phase III/ post-approval	Post-approval	Post-approval	Post-approval
Information	Causes of attrition	Serious ADRs	Causes of attrition	ADRs on label	Serious ADRs	Withdrawal from sale	Withdrawal from sale
Source	Car (2006)	Sibille et al. (1998)	Olson et al. (2000)	BioPrint® (2006)	Budnitz et al. (2006)	Fung et al., (2001)	Stevens & Baker (2009)
Sample size	88 CDs stopped	1,015 subjects	82 CDs stopped	1,138 drugs	21,298 patients	121 drugs	47 drugs
Cardiovascular	27%	9%	21%	36%	15%	9%	45%
Hepatotoxicity	8%	7%	21%	13%	0%	26%	32%

0% 1-10% 10-20% >20%

Figure 2

Evidence, prevalence and occurrence of safety liabilities relating to the cardiovascular and hepatic systems. Information was collated from published articles (Sibille *et al.*, 1998; Olson *et al.*, 2000; Fung *et al.*, 2001; Budnitz *et al.*, 2006; Car, 2006; Stevens and Baker, 2009) and from the commercially available database BioPrint® (Krejsa *et al.*, 2003) to provide a guide to the prevalence of adverse drug reactions (ADRs) and their impact in terms of attrition, across the cardiovascular and hepatic systems. Some datasets relate to frequency (i.e. percentage) of candidate drugs or marketed drugs associated with the toxicity; others contain data on prevalence of the ADRs in volunteer subjects or patients. Cardiovascular data do not include haematological related attrition, withdrawal or ADRs. The data were collected over different time periods, so that there is no analysis of trends over time. Attrition has a greater financial impact than ADRs *per se*, and the further advanced a candidate drug (CD) or drug is in clinical development, the greater the financial impact. Therefore, cardiovascular toxicity has a greater impact than hepatotoxicity in terms of its contribution to drugs withdrawn from sale and CD attrition during clinical preclinical or clinical development. Some of the adverse events (AEs) contributing to the data are functional in nature, and so would be predictable from primary, secondary or safety pharmacology studies, whereas others are pathological in nature, so would be predictable from toxicology studies (histopathological end-points). Some AEs might be indicative of idiosyncratic reactions not identified during preclinical or clinical development (e.g. hepatotoxicity-related attrition observed in late clinical development or post-approval). The difference in incidence of cardiovascular-related attrition post-approval noted between Fung *et al.* (2001) and Stevens and Baker (2009) may reflect the increased cardiovascular-related attrition over the last ~15 years particularly in relation to arrhythmias. Modify from Redfern *et al.* (2010).

(2009) may reflect the increased cardiovascular attrition related to arrhythmias over the last ~15 years. Because of these unanticipated cardiovascular complications at the population scale, cardiovascular safety is of paramount importance in contemporary drug development. Cardiovascular safety liabilities are observed with both cardiovascular and non-cardiovascular pharmaceuticals and affect all components of the cardiovascular system, namely, the heart, blood vessels and blood constituents; in addition, the key role of the nervous and renal systems in modulating cardiovascular function should not be neglected. Cardiovascular side effects can occur after acute (i.e. single dose administration) or chronic treatment and can be functional and/or structural (i.e. histopathology) in nature. In an era marked by increased public scrutiny, escalating industry costs and finite resources at regulatory agencies, the need for efficient yet safe drug development is more important than ever.

Cardiovascular safety liability is seen by many to be an important area where non-competitive collaboration would bring benefits to all parties involved in terms of improving patient safety, increasing the numbers of new medicines registered and reducing drug development times and costs. On 28 January 2010, a workshop was hosted by the Medical Research Council (MRC) Centre for Drug Safety Science (CDSS; http://www.liv.ac.uk/drug-safety), University of Liverpool, in conjunction with the Association of the British Pharmaceutical Industry (ABPI) and the Medicines and Healthcare products Regulatory Agency (MHRA). It discussed current challenges in determining and understanding '*Cardiovascular Toxicity of Medicines*'. The MRC CDSS is a non-profit organization that brings together academic, industry and government scientists in the collaborative identification and resolution of emerging issues in drug safety (Park, 2008). The key aims of the workshop were to identify those areas of cardiovascular safety testing where our knowledge and understanding should be further strengthened and to recommend areas as to where collaborative efforts should be focused on. The workshop was attended by representatives from pharmaceutical companies, contract research organizations, regulatory agencies, world-leading cardiologists, oncologists and academics. Besides contributing to a range of stimulating presentations and discussion sessions, attendees were asked to provide information on our current understanding of cardiovascular toxicity (summarized in Tables 1–3) to allow a gap analysis to be performed. This analysis attempts to address three major areas:

- What are the key cardiovascular safety liabilities in drug discovery, drug development and clinical practice?
- How good are preclinical and clinical strategies for detecting cardiovascular liabilities?
- Do we have a mechanistic understanding of these liabilities?

Table 1

What are the key cardiac liabilities?

Tissue	Toxicity	Drug discovery	Drug development	Clinical practice	Drug class/disease specific
Heart	Proarrhythmic potential	hERG screening strategies are in place in most pharmaceutical companies leading to a reduced number of QT prolonging drugs in development pipelines. Primary focus on hERG/QT. Screening other ion channels (e.g. NaV1.5 and KCNQ1/KCNE1) and profiling in cardiac tissue is also being undertaken (Gallacher *et al.*, 2007; Pugsley *et al.*, 2009; Pollard *et al.*, 2010).	QT prolongation is a developability issue as opposed to a reliable predictor of TdP risk. On occasion other arrhythmias mediated through non-hERG mechanisms, for example, conduction slowing. hERG trafficking effects or non-hERG-related issues are found in telemetry studies; this can be a big issue when detected late, for example, trafficking effects that show up only after prolonged exposure. QT shortening associated type arrhythmia is an emerging issue (Pollard *et al.*, 2010; Shah, 2010; Valentin *et al.*, 2010).	QT determination and prediction on likely outcome of TQT study. If interval signals have been detected this may translate to rhythm changes in patient groups. Better understanding of this translation is required (Darpo, 2010; Wallis, 2010). In addition to QT/TdP ADRs the ECG provides valuable parameters reporting other ECG/cardiac disorders. (Gussak *et al.*, 2004).	Class specific tends to be dealt with in drug discovery as in some cases it is chemically related (hERG) or target related (e.g. ion channel projects for disease modulation). The problem is exacerbated by certain diseases, for example, diabetes, pre-existing heart conditions.
	Myocardial ischaemia	Rare event. Currently detected via ECG morphology changes (Detweiler, 1983) and sometimes radionuclide scanning.	Rare clinical event. Detected through clinical signs	The consequences of ischaemia (angina pectoris and myocardial infarction) may only be detected through post-marketing observations.	Exacerbated in 'at-risk patients' with pre-existing disease.
	Myocardial necrosis	Quite frequent finding. Identified in standard histological examination as part of early repeat dose tox studies. There are currently few predictive *in vitro* methods (Partridge *et al.*, 2005). Standard and non-standard histological examination (LM, EM).	Can be monitored via troponin and other biomarkers. Potential for imaging (e.g. echocardiography) to follow functional consequence of CV damage. Radionuclide markers can also be used. This method is translatable (Hanton *et al.*, 2008).	Unlikely to be detected in clinical practice – dependent on post-marketing observations (Borer *et al.*, 2007). Require biomarkers that predict rather than report damage (e.g. troponin). Imaging provides translational bridge from preclinical observations.	Some examples with characteristic haemodynamic profiles (e.g. increased heart work). Some non-specific mechanisms that are diffuse throughout heart and more likely due to direct cell tox as opposed to a response to functional/haemodynamic change.
	Heart failure	Rare event. Heart weight is used as a crude index during pathology. There may be functional end-points (e.g. contractility) that flag risk of heart failure.	Rare clinical event. Usually detected through clinical signs. Potential to include imaging (e.g. ultrasound and echocardiography) to assess heart failure markers – however, this is currently a non-standard assessment.	Unlikely to be detected in clinical practice – dependent on post-approval observations Imaging can be used if flagged from non-clinical work.	nda

Table 1

Continued.

Tissue	Toxicity	Drug discovery	Drug development	Clinical practice	Drug class/disease specific
	Coronary artery disorders	Rare event.	Rare clinical event. Detected through clinical signs.	Clinical consequences are currently only detected at the post-approval stage.	Dependent on 'at-risk patients' with pre-existing disease.
	Cardiac valve disorders	Rare event. 5-HT2B agonism has been implicated in valvulopathy (proliferative type) seen with norfenfluramine (metabolite of fenfluramine 'Fen-Phen'), pergolide and others (Roth, 2007). Alerts may come from receptor binding data (e.g. pergolide-like pattern).	Imaging can be used to follow progression and impact of valve damage on valve function. Potential to use echocardiography but rarely included in preclinical studies (Hanton *et al.*, 2008). Preclinical assessment relies on careful histopathological examination of cardiac valves.	Imaging and echocardiography can be used.	5-HT2B link and associated QSAR. Migraine prophylaxis, Parkinson (dopamine agonists) appetite suppressant and, hyperlipidaemic disorders have all been linked.
	Endocardial disorders	Although rare, examples do exist (Belhani *et al.*, 2006). Identification of endocardial disorders is not part of standard assessment. Detected during pathology if present (Chekmarev *et al.*, 2008).	May be detected during histopathological assessment at end of repeat dose tox studies.	nda	nda
Vessel	Hypo/ hypertension	Common findings in non-clinical studies. Receptors involved in vascular control routinely included in secondary pharmacology screens (Whitebread *et al.*, 2005). BP screening in telemetered rats is a frequently used approach. Isolated vessel assessment can be performed. Often lack an understanding on whether BP effect is due to change in cardiac output or peripheral vascular resistance (Taylor *et al.*, 2007). One issue for studies is that in early phases there is seldom enough test material to conduct experiments in larger animals.	Quite common and detectable in first in human studies. Question of assay sensitivity to detect small changes that may have a long-term consequence. Require repeat dose assessment of BP risk and to understand relationship to clinical stopping criteria and clinical symptoms (e.g. syncope for hypotension or increased CV events. BP measurements are a standard part of the ICH S7 compliant safety pharmacology studies in non-rodents. New technology may soon allow measurement of BP also in toxicity studies (JET technology, i.e. implanting a monitor in the femoral artery). Some regulators see even small increases of BP as problematic, which will make accurate BP measurements an important part of preclinical safety studies.	Postural hypotension can be detected symptomatically (and investigated with tilt-table testing clinically), but hypertension may not. Powering of clinical studies important to detect BP signal. Single dose and repeated dose Phase I studies tend to identify trends. Combining preclinical and clinical BP data in PKPD models can be beneficial. The key challenge faced is the translation from non-clinical studies to man and also defining the magnitude of effect that is a concern.	Impact in patients with pre-existing disease, for example, drug-induced increased in BP in patients with high BP and CV risk factors. Class effects are known, although for novel targets some upfront work understand potential involvement of target in CV function may be necessary (requires tool compounds). Impact of BP effect in patient populations is currently not well incorporated in risk management plans.

Table 1

Continued.

Tissue	Toxicity	Drug discovery	Drug development	Clinical practice	Drug class/disease specific
	Vascular disorders	nda	nda	nda	nda
	Arteriosclerosis/ stenosis	Overt drug-induced changes are very rare. However, potential for indirect risk, for example, change in plasma lipid levels. Platelet function can be assessed for cause.	Potential to use imaging techniques	nda	nda
	Vascular insufficiency	nda	nda	nda	nda
	Necrosis	Identified in standard histological examination as part of early repeat dose tox studies.	Identified in standard histological examination as part of early repeat dose tox studies.	nda	nda
	Vascular inflammation	Vasculitis is a relatively common finding preclinically but difficult to manage going forward. The issue is clinical relevance (Brott *et al.*, 2005; Louden *et al.*, 2006).	Rare clinical event that probably has a distinct pathology from drug-induced injury in non-clinical species.	nda	nda
Blood	Embolism and thrombosis	Quite rare findings non-clinically	May be detected in the clinic via coagulation times, blood/platelet aggregation, etc.	nda	nda
	Vascular haemorrhagic disorders	nda	nda	nda	nda
	Coagulation	nda	nda	nda	nda
	Aggregation	nda	nda	nda	nda

hERG, human ether-a-go-go-related gene; TdP, Torsades de Pointes; ADR, adverse drug reaction; ECG, electrocardiogram; nda, no data available; BP, blood pressure; PK, pharmacokinetic; PD, pharmacodynamic; ICH, International Conference on Harmonization; CV, cardiovascular; QSAR, quantitative structure-activity relationship.

Table 2

How good are preclinical and clinical strategies for detecting cardiovascular liabilities?

Tissue	Toxicity	How effective are current strategies at detecting and dealing with identified toxicities? Preclinically	Clinically	How effective are current biomarkers (e.g. diagnosis, prognosis, etc.) Preclinically	Clinically
Heart	Proarrhythmic potential	The QT focus has improved ECG monitoring in non-clinical safety studies and so we have a higher chance of detecting rhythm disturbance non-clinically. In addition, ECG intervals are better quantified and therefore any changes can be used as an early marker of potential arrhythmias. Non-hERG – improving understanding and development of appropriate strategies.	With improved ECG monitoring for QT reasons, there is a higher chance of detecting rhythm disturbance in healthy volunteers. Non-hERG – improving understanding and development of appropriate strategies. However, the TQT study may be too restrictive. It may be important to monitor factors other than repolarization prolongation (Bass *et al.*, 2007; Gallacher *et al.*, 2007).	ECG interval changes are essentially biomarkers for arrhythmias. However, the magnitudes of ECG intervals changes that are a cause for clinical concern are not fully defined. hERG and QT are good markers for flagging development risk, but not so effective in defining TdP risk. New biomarkers predicting TdP risk are required as are new tools to integrate preclinical and clinical data to address need for TQT. The importance of the contribution of genetics to drug-induced QT/TdP problems should be considered.	ECG interval changes are essentially biomarkers for arrhythmias. However, the magnitude of change that would be a concern and is predictive for arrhythmias is not defined. hERG/QT – good for flagging development risk, not so effective for TdP risk. Not ideal but the best tool we currently have for assessment.
	Myocardial ischaemia	Unlikely that ischaemic events would be detected unless such changes cause T-wave changes and overt histological damage.	Improved ECG monitoring would detect T-wave changes. However, more subtle effects, not relevant to healthy volunteers may be missed, but these may be relevant to certain patient populations, for example, tegaserod.	ECG morphology change would be a biomarker in addition to troponin. ST segment is a potential translatable biomarker but currently has limited preclinical validation.	ECG morphology change could be a biomarker in addition to troponin.
	Myocardial necrosis	Can be detected in toxicology studies and also through use of biomarkers, for example, troponin (current gold standard). Histopathology does not predict risk, it simply reports outcome. Need progressive approach from *in vitro* models. Molecular imaging of necrosis and apoptosis should be considered (Chun *et al.*, 2008).	Can be monitored via troponin and other biomarkers.	Troponin is used as a biomarker, but cTn reports damage, need predictive biomarker. Imaging could be used but not routinely used preclinically.	Troponin is used as a biomarker. Although not routinely used molecular imaging of necrosis and apotosis is available in expert clinical centres.

Table 2

Continued.

Tissue	Toxicity	How effective are current strategies at detecting and dealing with identified toxicities? Preclinically	Clinically	How effective are current biomarkers (e.g. diagnosis, prognosis, etc.) Preclinically	Clinically
	Heart failure	Can be detected via monitoring LV function and cardiac contractility in animals (routine in some companies, but not all). Otherwise dependent on monitoring the impact of any changes in cardiac output via effects on BP.	In the absence of non-clinical signals detection would be dependent on clinical signs.	Measurement of left ventricular function and ejection fraction as well as using echocardiography and MRI.	Left ventricular function and ejection fraction as well as echocardiography.
	Coronary artery disorders	Unlikely that ischaemic events would be detected unless such changes cause T-wave changes and overt histological damage. Techniques are available to investigate drug effects on coronary blood flow, but these are not routinely used unless other signals are detected.	Improved ECG monitoring would detect T-wave changes. However, more subtly effects, not relevant to healthy volunteers may be missed, but these may be relevant to certain patient populations, for example, tegaserod.	No obvious biomarkers. Coronary diameter and flow can be measured in animals.	No obvious biomarkers. Measure coronary artery diameter.
	Cardiac valve disorders	Structural changes can be detected in toxicology studies. However, the experience with Fen-Phen demonstrates that this can be difficult. Histopathology and 5HT2B screening detects problematic compounds.	nda	Echocardiography can be used to detect functional changes in valve function. However, it is a rare event normally detected by histopathology.	Echocardiography can be used to detect functional changes in valve function. But this may require repetitive echos at the time of treatment to determine the precise cause of the problem.
	Pericardial disorders	Structural changes can be detected in toxicology studies.	nda	nda	nda
	Endocardial disorders	Structural changes can be detected in toxicology studies.	nda	nda	nda

Table 2

Continued.

Tissue	Toxicity	How effective are current strategies at detecting and dealing with identified toxicities? Preclinically	Clinically	How effective are current biomarkers (e.g. diagnosis, prognosis, etc.) Preclinically	Clinically
Vessel	Hypo/hypertension	Good systems are in place to detect effects that may impact the safety of first in human studies. However, there are questions related to the sensitivity of the assays to detect 'small effects' that may be relevant to longer-term toleration and risk. Tends to detect BP risk, but not always in the right direction as clinical. Acute assessment routinely performed, repeat dosing to determine cause – may be missing chronic BP effects.	BP and HR can be easily monitored through clinical development. However, the ability to detect and respond to small changes that may be clinically relevant is variable.	BP is translatable biomarker. Uncertainty exists in terms of sensitivity and magnitude of change related to clinical concern (e.g. hypertension and CV events).	nda
	Vascular disorders	nda	nda	nda	nda
	Arteriosclerosis/stenosis	Risk factors can be detected in animals, for example, lipid changes as well as any pathology changes.	Risk factors can be detected and monitored in the clinic.	nda	Blood vessel imaging.
	Vascular insufficiency	nda	nda	nda	nda
	Necrosis	Histopathology can detect necrosis.	nda	nda	nda
	Vascular inflammation	Identified in standard histological examination as part of early repeat dose tox studies.	Can be detected though clinical signs.	A lot of work is being done in this area to validate biomarkers, although none has been universally accepted.	A lot of work is being done in this area to validate biomarkers, although none has been universally accepted.
Blood	Embolism and thrombosis	Potential to detect effects in pathology.	Can be detected though clinical signs.	Investigate effects on clotting times and coagulation pathway.	Investigate effects on clotting times and coagulation pathway.
	Vascular haemorrhagic disorders	Potential to detect effects in pathology.	Can be detected though clinical signs.	nda	nda
	Coagulation	Can study drug effects on clotting times and coagulation pathway.	Can study drug effects on clotting times and coagulation pathway.	Can study drug effects on clotting times and coagulation pathway.	Can study drug effects on clotting times and coagulation pathway.
	Aggregation	Drug effects on platelet function can be studied non-clinically.	Drug effects on platelet function can be studied clinically.	Drug effects on platelet function can be studied non-clinically.	Drug effects on platelet function can be studied clinically.

ECG, electrocardiogram; hERG, human ether-a-go-go-related gene; TdP, Torsades de Pointes; BP, blood pressure; nda, no data available; MRI, magnetic resonance imaging; HR, heart rate.

Table 3

Do we have a mechanistic understanding of the liabilities?

Tissue	Toxicity	Do we have a mechanistic understanding of the toxicity?
Heart	Proarrhythmic potential	For some but not all arrhythmias our knowledge is limited to QT and not to how arrhythmias translate to TdP.
		Broad profiling of drugs against cardiac ion channels, action potential morphology on isolated tissues (e.g. Purkinje fibre, isolated hearts) and also ECG morphology are all available methods.
		Have not been successful at converting mechanistic understanding in to new, regulatory accepted, biomarkers.
		The contribution of genetics to the problem must also be considered.
		Often when compound development is stopped due to proarrhythmic potential the exact mechanism is not completely known.
	Myocardial ischaemia	Ischaemia can occur from increased oxygen demand and/or reduced supply and both of these have been studied non-clinically, for example, changes in vascular tone/coronary blood flow as well as cardiac function (heart rate and contractility).
	Myocardial necrosis	Knowledge of mechanisms is limited.
	Heart failure	Generally no, however, effects on cardiac contractility can be measured, but understanding the mechanisms that can change contractility is limited at the cellular level.
	Coronary artery disorders	Pharmacological mechanisms that can cause coronary artery constriction are well defined although the effects on endothelial function are less clear.
	Cardiac valve disorders	Only in some rare cases do we have an understanding of mechanisms but in general we have a poor understanding of drug effects on valve function.
	Pericardial disorders	Some inflammatory mechanisms can cause pericardial damage.
	Endocardial disorders	Some inflammatory mechanisms can cause endocardial damage.
Vessel	Hypo/hypertension	Classical pharmacological mechanisms that affect vascular tone are well defined. However, others are not well defined.
		Complex multifactorial control of BP often confounds identification of a specific mechanism. Some examples where site of action understood (e.g. vascular resistance and/or cardiac output change) centrally versus peripherally mediated and the role of some receptors is understood.
	Vascular disorders	Causes are not well defined.
	Arteriosclerosis/stenosis	Changes in lipids and other factors are defined, but impact of inflammatory mechanisms is less clear.
	Vascular insufficiency	Causes are not well defined.
	Necrosis	Causes are not well defined.
	Vascular inflammation	Causes are not well defined.
Blood	Embolism and thrombosis	Causes are not well defined.
	Vascular haemorrhagic disorders	Causes are not well defined.
	Coagulation	Causes are not well defined.
	Aggregation	Causes are well defined.

TdP, Torsades de Pointes; ECG, electrocardiogram; BP, blood pressure.

Information was gathered using the headings defined by the Food and Drug Administration's (FDA) Adverse Event Reporting System (AERS) for cardiovascular-related adverse events (AEs; Anon, 2010a; Figure 3). The data represent the cumulative number of cardiac (top panel) or vascular (bottom panel) AEs reported over the last 40 years; over that period there has been a large number of cardiac and vascular AEs reported. Within each category, the AEs are ranked by decreasing order of incidence. As shown in Figure 3, there are six main AE categories of cardiac and vascular side effects for which over 10 000 reports are available. The very large number of AERS reports related to arrhythmias is likely to reflect the increased scrutiny around drug-induced QT prolongation and associated arrhythmias over the last decade. The highest incidence of AEs in each category (i.e. the top six categories) have been considered as part of the questionnaire and analysis conducted prior to and during the workshop. Although such AEs data should be taken with caution, as a causal relationship between an AE and a medicine is not always demonstrated, they do provide some indication on where to focus our efforts in order

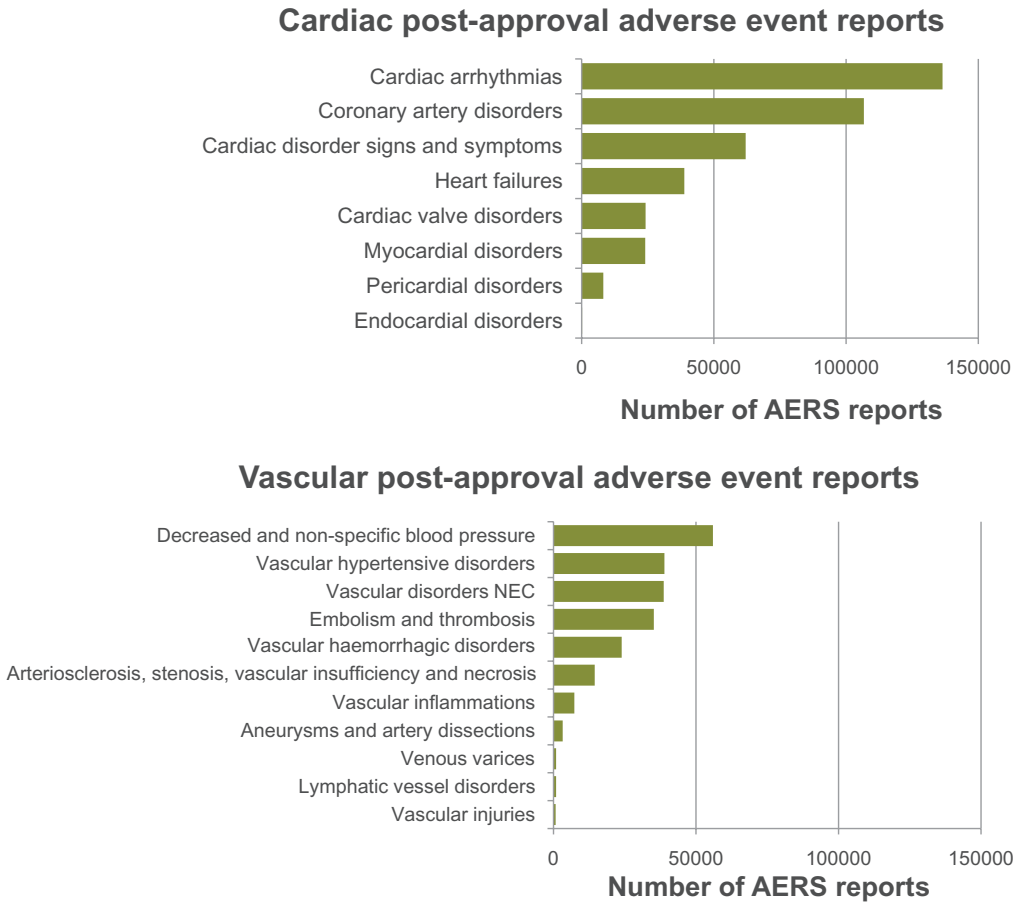

Figure 3

Cumulative cardiac and vascular adverse events (AEs) reported to the US Food and Drug Administration Adverse Event Reporting System (AERS) since 1969; the documents compiled in *PharmaPendium* (https://www.pharmapendium.com) refer to the Spontaneous Reporting System prior to 2000 and to the AERS from 2000 onwards, so the reports prior to that are more sporadic and less detailed. The annual number of AERS reports that exist in *PharmaPendium* has more than doubled over the last decade from a value of ~200 000 in 2000. The data represent the cumulative number of cardiac (top panel) or vascular (bottom panel) AEs reported over that period of time. Within each category, the AEs are ranked by decreasing order of incidence. Such AEs data should be taken with caution, as the linkages with drugs are not always demonstrated. Overall there are six main AE categories of cardiac and vascular side effects, for which over 10 000 reports are available. Note the very large number of AERS reports related to arrhythmias probably reflects the increased scrutiny around drug-induced QT prolongation and Torsades de Pointes over the last decade. NEC, not elsewhere classified.

to reduce cardiovascular-related safety liabilities. This publication incorporates the key issues highlighted during the workshop along with the gap analysis and identifies key areas where a concerted effort could make a real difference by reducing cardiovascular liabilities of new medicines.

What are the key cardiovascular safety liabilities in drug discovery, drug development and clinical practice? Table 1

Using cardiovascular safety-related terms as outlined in the FDA's AERS, workshop attendees were invited to provide information on the key cardiovascular liabilities that pharmaceutical companies faced (Table 1). Information was segregated into data for the different stages of the drug development process, from discovery through to reaching market and clinical practice; information on whether drug classes had specific problems associated with them or specific diseases impacted on cardiovascular safety was also requested. The gap analysis revealed that the majority of AEs reported in the FDA's AERS are often not well described and the relationship between an AE and a drug is not necessarily established. It is worth highlighting that the frequency of serious ADRs leading eventually to discontinuation or withdrawal of a drug can be extremely low [e.g. less than 1 in 100 000 patients experienced Torsades de Pointes (TdP) with terfenadine].

Using the data summarized by Shah (2006), drug-induced TdP, a potentially fatal arrhythmia, was the reason for around one-third of all drug withdrawals between 1990 and 2006. Indeed, even though TdP is extremely rare, for all the agents

withdrawn there was evidence of TdP; these drugs were associated with prolongation of the QT interval on the electrocardiogram (ECG) and block of the human ether-a-go-go-related gene (hERG) channel (Redfern *et al.*, 2003). Shah's data in 2006 are further supported by the high number of cardiac arrhythmias-related AEs reported in the FDA's AERS (Figure 3; Anon, 2010a); although predominantly populated by QT-related arrhythmias (i.e. TdP), such dataset also includes non-QT-related arrhythmias (data not shown). Furthermore, Stevens and Baker (2009) reported a higher incidence of cardiovascular-related drug withdrawal compared with Fung *et al.* (2001) (45% vs. 9%, respectively); this may reflect the increased withdrawal related to arrhythmias over the last ~15 years. Myocardial ischaemia, myocardial necrosis, heart failure and coronary artery disorders do not always appear to be highlighted during drug development, rather they are reported at the post-approval stage indicating that current preclinical assays and clinical development studies are failing to capture all these liabilities. Whereas myocardial necrosis is sometimes observed in development and is relatively well understood, for some drugs myocardial necrosis is not detected during development, only for it to be reported at the post-approval stage. The detection of myocardial necrosis in development would be improved by employing biomarkers that ideally would predict the onset of myocardial necrosis, as the currently accepted marker reports damage that has already occurred (Baubuin and Jaffee, 2005; Reinhold *et al.*, 2010; Thygesen *et al.*, 2010; Tijsen *et al.*, 2010). Analysis of the data collected suggests that cardiac valve, pericardial and endocardial disorders, as well as disorders affecting blood components (e.g. embolism and thrombosis, vascular haemorrhagic disorders, coagulation and aggregation; see Tables 1–3) are rare events with few instances reported during drug development; however, these serious AEs are reported post-approval.

The information gathered indicates that at all stages of the drug development pipeline compounds that cause hypo- or hypertension and tachy- or bradycardia, can be detected and these data used to manage risk during subsequent development. It is becoming increasingly recognized that small cardiovascular changes may be very relevant to longer-term clinical outcomes. For example, it has been suggested that increases in blood pressure (BP) as small as 2 mmHg may be associated with increased morbidity and mortality (Lewington *et al.*, 2002), although this view is not shared by all especially as convincing clinical studies are not readily available. However, more recent studies suggest that patients experiencing small, chronic drug-induced increases in BP (5 mmHg) or heart rate (5 beats·min^{-1}) have a 6–23% greater risk of suffering heart failure, cardiac ischaemia or cerebral stroke events (Paul *et al.*, 2010). Interestingly, preclinical studies conducted prior to first in human trials may only be powered to identify relatively large changes in a given parameter (Guth *et al.*, 2009). The true meaning of any observed change is often only understood when a sufficiently large number of patients have been exposed to a given drug often for a prolonged length of time. It is possible that even small changes in these parameters result in the impairment of cardiovascular function and/or loss of cardiovascular homeostasis with the potential to damage cardiovascular organ systems as well as other organs (e.g. kidney), precipitating increases in cardiovascular-related mortality and morbidity (Lewington *et al.*, 2002; Valentin *et al.*, 2009b; Chalmers and Arima, 2010). Likewise, vascular inflammation and injury is often reported in preclinical models (Brott *et al.*, 2005; Louden *et al.*, 2006), while the clinical relevance and consequence of these observations remains unclear, as compounds with a drug-induced vascular injury liability have been successfully developed (e.g. potassium channel openers; phosphodiesterase inhibitors; endothelin receptor antagonists). Surprisingly for many vascular disorders reported preclinically (e.g. arteriosclerosis, vascular insufficiency and vascular necrosis); there remains a lack of data to confidently translate from preclinical observations to man (Valentin *et al.*, 2009a,b).

How good are preclinical and clinical strategies for detecting cardiovascular liabilities? Table 2

Information was gathered on our understanding of the issues that had been highlighted in Table 1 and whether we have the tools to be able to identify all cardiovascular liabilities (summarized in Table 2). Data requested addressed the effectiveness of current strategies at detecting and dealing with identified adverse effects clinically and/or preclinically, and whether we have effective preclinical and clinical biomarkers to allow for diagnosis and prognosis of cardiovascular liabilities (Valentin *et al.*, 2009a,b). It should be noted that preclinical safety evaluation is almost always conducted in young healthy animals that do not carry the pathophysiological background underpinning disease conditions, and a key question is whether these preclinical models accurately reflect the patient population that will be exposed to a drug.

Although the mechanisms underpinning drug-induced TdP are far from being fully understood, over the last 15 years a significant scientific understanding has been gained into the molecular mechanisms and predisposing factors of drug-induced QT prolongation. So despite an imperfect biomarker of drug-induced TdP, QT prolongation is accepted as a surrogate marker of TdP. Indeed all the drugs that do induced TdP are associated with prolongation of the QT interval (Redfern *et al.*, 2003). Industry, academia and regulatory agencies have worked closely together in developing a rigorous QT testing paradigm (Pugsley *et al.*, 2008; 2009; Vik *et al.*, 2008; Pollard *et al.*, 2010; Valentin, 2010; Valentin *et al.*, 2010; Wallis, 2010). Genetic and pharmacological evidence highlighting the pivotal role of hERG was a critical step in understanding how to start addressing this issue. It led to the development of hERG assays with the rapid throughput needed for the short timescales required in early drug discovery. The resulting volume of hERG data has fostered *in silico* models to help chemists design compounds with reduced hERG potency. In early drug discovery, a pragmatic approach based on exceeding a given potency value has been required to decide when a compound is likely to carry a low QT risk, to support its progression to late-stage discovery. At this point, the *in vivo* efficacy and metabolism characteristics of the potential drug are generally defined, as well as its safety profile, which includes usually a dog study to assess QT interval prolongation risk. The hERG and *in vivo* QT data, combined with the

likely indication and the estimated free drug level for efficacy, are put together to assess the risk that the potential drug will prolong QT in man. Further data may be required to refine the risk assessment before making the major investment decisions for full development (e.g. assessment of the proarrhythmic potential *per se*). The non-clinical data are essential to inform decisions about compound progression and to optimize the design of clinical QT studies; a negative clinical 'thorough QT study' provides reassurance regarding the torsadogenic potential of a drug. Emerging data indicate that preclinical QT-related assays are overall good predictors of the clinical outcome (Wallis, 2010). However, even with this well-defined system, there are substantial gaps in our knowledge in terms of understanding the genesis of TdP and non-TdP arrhythmia in preclinical and clinical setting and their relationship to changes in the QT interval and other ECG changes (Hoffmann and Warner, 2006; Pollard *et al.*, 2010; Shah, 2010; Valentin *et al.*, 2010).

The picture is much less clear with regard to other AEs such as myocardial ischaemia and myocardial necrosis. In the case of ischaemia it is unlikely to be detected unless there are changes to the ST wave of the ECG or overt histological damage. In the case of myocardial necrosis, troponin release into the serum can be used as a biomarker of damage, but this current gold standard of histopathological assessment does not predict risk, it simply reports cardiac myocytes damage. The risk of heart failure, cardiomyopathy and coronary artery disorders can be detected by monitoring left ventricular function and coronary blood flow. Sensitive and predictive imaging technologies such as ultrasound, echocardiography and magnetic resonance imaging can be used to measure changes in heart function that might precede myocardial damage. These technologies and parameters are directly translatable to humans; however, they are not available routinely in all laboratories and therefore not consistently included in drug development programmes unless triggered by other signals (Hanton *et al.*, 2008). Drug effects on the cardiac inotropic and lusitropic state can be monitored routinely via the invasive measurement of left ventricular function and derived parameters (i.e. LV dP/dt max & min; Pugsley *et al.*, 2008), although such end-points are not routinely accessible in the clinic, they are assumed to be translatable to humans. The role of calcium handling in myocytes, endothelial and smooth muscle cells is still little understood but could prove to be a rich avenue for investigation (Bers, 2002). Other disorders such as cardiac valve, pericardial and endocardial disorders can be detected in toxicology studies via histopathological examination. However, the current inability to translate between species means it is often difficult to predict how these preclinical observations may manifest in patients. As has been noted previously, the acute absence of predictive biomarkers of cardiovascular side effects at all stages of drug development is again emphasized by the data collected here. Many different initiatives and much research is being devoted to the identification of novel biomarkers; however, to date none has been universally accepted either clinically or preclinically (e.g. troponin, Baubuin and Jaffee, 2005; Omland *et al.*, 2009; Thygesen *et al.*, 2010; miRNA, Tijsen *et al.*, 2010; brain natriuretic peptides, Reinhold *et al.*, 2010). An additional challenge is to determine the sensitivity and specificity of these clinical biomarkers when applied in the non-clinical setting.

In relation to BP changes, there are good preclinical methods in place that detect effects that may be useful in the design of first in human studies. BP measurements are important in terms of monitoring vital physiological function and relatively straightforward, and therefore they are routinely used clinically, providing a good example of a translatable biomarker. However, there are questions as to the sensitivity and specificity of preclinical and clinical measures of BP in current use and whether the small changes in BP can be accurately detected, and if so whether they translate into a clinically meaningful risk especially following chronic drug treatment (Lewington *et al.*, 2002; Valentin *et al.*, 2009a,b; Chalmers and Arima, 2010). It is also likely that this risk depends on the patient population, for example a higher risk may be anticipated in elderly patients with cardiovascular risk factors compared with young healthy individuals. Moreover, certain aspects of drug-induced cardiovascular disturbances (e.g. orthostatic hypotension, baro-reflex dysregulation) are not routinely addressed during preclinical development. Other vascular disorders captured by preclinical testing and observations are translatable to the clinic, such as, arteriosclerosis where plasma changes in lipids can be measured in animals and changes detected in the clinic; likewise blood coagulation and aggregation are amenable to both preclinical and clinical assessment. However, some disorders can only be confirmed by histopathology such as necrosis, while others although observed preclinically, are of disputed relevance to the clinic (e.g. vascular inflammation and injury; Brott *et al.*, 2005; Louden *et al.*, 2006).

Do we have a mechanistic understanding of the liabilities? Table 3

Chemical liabilities

Finally, data were gathered on whether we have a mechanistic understanding of the toxicities described (Table 3). As we have discussed, the most studied effects are those that are associated with QT interval prolongation and associated proarrhythmic potential and much has been learnt regarding some of the underlying mechanisms. It has been shown that a vast majority of compounds prolong the QT interval through the inhibition of a single molecular target – the hERG-encoded potassium ion channel. This has enabled medicinal chemists to develop structure–activity relationships such that few compounds are synthesized that have high potency as hERG channel inhibitors (Gavaghan *et al.*, 2007; Pugsley *et al.*, 2008; Pollard *et al.*, 2010; Valentin *et al.*, 2010; Wallis, 2010). This was achieved by concerted efforts involving industry and academic scientists and regulators, often working closely together (Valentin *et al.*, 2010). However, cardiovascular safety is responsible for a large number of drug withdrawals only a small proportion of which are due to arrhythmias. Much is understood regarding changes in BP and classical pharmacological mechanisms that affect vascular tone are well defined. But even when parameters such as BP are well understood the often complex multifactorial control of BP frequently confounds the identification of a specific mechanism of a drug-induced effect. This

situation is exacerbated by variation in the patient population and underlying cardiovascular risk, making prediction of injury to a patient due to drug-induced BP changes extremely difficult.

From the biological information collected for the safety liabilities listed, it is clear that in most cases we understand the processes that are affected but we currently lack the understanding of why certain compounds produce a given ADR. When the chemical structures of compounds that have been withdrawn have been analysed it is clear that they show structural diversity; that is, they cover most of the 'drug-like' space outlined by the medicinal chemist. Only a few structural motifs have been reported that are associated with cardiovascular safety liabilities (Gavaghan *et al.*, 2007; Aronov, 2008; Chekmarev *et al.*, 2008; Frid and Matthews, 2010), making it very difficult for medicinal chemists to develop structure–activity relationships, although there are emerging data that suggest an association between physicochemical drug properties and *in vivo* or *in vitro* toxicological profiles (Krejsa *et al.*, 2003; Leeson and Springthorpe, 2007; Price *et al.*, 2009). However, in most instances, we do not understand the mechanistic basis that underlies why only some compounds produce cardiovascular safety liabilities. This combination of a lack of a chemical motif and an incomplete understanding of the biology results in compounds with a cardiovascular liability being able to progress through the drug development process before ultimately failing late in clinical development, at considerable costs to both companies and patient safety.

Emerging evidence suggests that cardiac drug disposition and/or local cardiac drug concentration might play a role in drug-induced cardiac side effects. For instance, many transporters and metabolizing enzymes are expressed in the heart; several of these transporters and P450s are associated with evidence of drug transport or metabolism in the heart. Furthermore, several drugs transported and/or metabolized by these transporters or enzymes are associated with cardiovascular toxicities (McBride *et al.*, 2009; Reiss *et al.*, 2009). Moreover, drug cardiac tissue concentration appeared to be a key factor in exacerbating the arrhythmogenic proclivity of drugs (Titier *et al.*, 2004). Although current technology exists to perform tissue distribution studies, they are not routinely conducted during the early phases of drug discovery due to the need for radioactive compound but tend to be performed late in the drug discovery phases; clearly compounds that do accumulate in the heart or vasculature may deserve a closer look. To this effect, the use of novel technology such as Positron Emission Tomography might be valuable. Further research is required to understand the full impact of such observations.

Target liabilities

One emerging problem in cardiovascular safety is the increasing prevalence of toxicity from targeted cancer therapies, notably protein kinase inhibitors (Cheng and Force, 2010; Zuppinger and Suter, 2010). These synthetic small molecular weight compounds inhibit the activity of several protein kinases, either associated with neoplastic transformation of cells within the tumour, or present in the associated vascular endothelial cells of blood vessels supplying the tumour leading to angiogenesis inhibition (Holmes *et al.*, 2007). However, these kinases are also expressed in cardiac myocytes and cardiac endothelial cells and play a crucial role in normal homeostasis within the cardiac tissue. Consequently, inhibition of these kinases within cardiac tissue due to 'on-target toxicity' has the potential to result in cardiovascular AEs. Furthermore, such liability can be compounded by the fact that kinase inhibitors such as sunitinib (Sutent®) and sorafenib (Nexavar®) often display broad selectivity increasing the potential for 'off-target toxicity' (Zuppinger and Suter, 2010). A major challenge is to understand how we predict and manage the ADRs associated with kinase inhibitors. Novel *in vitro* screens that can detect cardiovascular adverse effect liability with these agents at the preclinical stage are needed.

In some instances it might not be possible to remove the cardiovascular risk associated with a compound, for example for some anti-cancer agents, as the pathways that a given drug targets in the tumour are also intrinsic to the proper functioning of cardiac tissue (Cheng and Force, 2010; Zuppinger and Suter, 2010). It is a paradox of current therapy that as it has become more effective, with better survival rates with some drugs, such as anthracyclines, higher rates of heart failure are being observed 6–7 years post treatment. As healthy heart tissue can defend against stress by several different mechanisms (e.g. NO, GF, gp130, Neu/HER), the risk of cardiovascular AEs is also heightened by newer drugs that target some of these defence mechanisms (e.g. anti-HER2: trastuzumab – Herceptin®). With improved understanding of the mechanism by which drugs work and the mechanism by which toxicities arise, it is possible to manage and wherever feasible to mitigate the risk of cardiovascular side effects. For example, when concomitant treatment of chemotherapy and trastuzumab is used then high incidence (i.e. 25%) of cardiac dysfunction are observed. However if trastuzumab is used after completion of the chemotherapy course then the level of cardiac dysfunction falls (3–18%). In this instance the risk is manageable by changing clinical treatment design with a reduction in the level of AEs observed (De Keulenaer *et al.*, 2010; Peng *et al.*, 2010). Other treatments target cardiac tissue due to their intrinsic mechanism of action (e.g. bevacizumab – Avastin®), which binds the VEGF ligand and inhibits angiogenesis; therefore, it is difficult to envisage how risk can be avoided. A clear understanding of the benefit to risk ratio is needed for these promising new medicines and a realization that the naturally risk averse approach of our society may be denying potentially beneficial compounds from reaching the market; all those involved in development medicines may need to adopt a new approach to cardiovascular risk assessment (Borer *et al.*, 2007).

Discussion

This document represents an important step towards the identification of the problems surrounding drug-induced cardiovascular side effects at all stages of drug discovery, clinical development and post-approval. It is clear that in some areas we have a good understanding of potential liability (e.g. drug-induced QT prolongation and associated proarrhythmic risk). However, as highlighted in this manuscript, there are other areas that we do not understand fully (e.g. tissue exposure, pharmacokinetic and pharmacodynamic relationship,

metabolism, transporters, structural changes and the interrelationship between vascular biology and cardiac structural changes due to drug treatment). The authors acknowledge that the gap analysis outlined in this manuscript is obtained from information collected from one meeting and that other data may be available from other sources to complement and expand the analysis. We recognize that this is the beginning of an ongoing process and welcome correspondence with other interested parties regarding data available for cardiovascular safety and further discussions on how to progress the field. However, it is beyond dispute that cardiovascular AEs is an area of significant need both in terms of patient safety and its impact upon drug attrition, drug withdrawal and ADRs. For the field to progress several areas were identified where action must be taken to:

- Fully characterize the incidence, the prevalence and the impact of drug-induced cardiovascular issues at all stages of drug discovery, development and post-approval. This could be achieved by retrieving, sharing, analysing and interrogating cardiovascular safety-related data hold in privately own or publicly available repositories and databases.
- Ascertain the predictive value of existing non-clinical models and assays towards the clinical outcome. This could be achieved by building and expanding on existing initiatives; by sharing, interrogating, analysing and interpreting complex preclinical and clinical pharmacodynamic and pharmacokinetic cardiovascular datasets.
- Understand the mechanistic basis of cardiovascular liabilities; by addressing those areas where it is currently not possible to predict clinical outcome based on preclinical safety data and that are most likely to succeed and to have the highest impact on patient safety and drug attrition. Research collaborations, cooperations and consortia efforts between scientists of pharmaceutical companies, contract research organizations, non-profit organizations and academic institutions are required.
- Provide scientists in all disciplines (e.g. clinician, pharmacologist, physiologist, toxicologist and pathologist) with additional skills to enable them to better integrate preclinical and clinical data and, to better understand the biological and clinical significance of any changes observed. Significant investments in cross-functional, pan disciplines training and educational programmes at national and international levels are required.
- Develop more appropriate, highly relevant and predictive tools and assays to identify and wherever feasible to eliminate cardiovascular safety liabilities from molecules and wherever appropriate to develop clinically relevant and reliable safety biomarkers. This includes a better understanding of the pharmacology of drugs, their targets, pharmacokinetic and pharmacodynamic relationship, metabolism and disposition. This would require concerted efforts and investments from academia, service and technology providers as well as biopharmaceutical companies.

Currently there are several initiatives in the cardiovascular safety area as outlined in Table 4 (Bass *et al.*, 2008; Piccini *et al.*, 2009; Stummann *et al.*, 2009; Cavero, 2010; Pettit *et al.*, 2010); most of these tackle some of the issues that have been described in this manuscript but tend to focus on known liabilities that have been well described and mechanisms proposed. Other initiatives have produced positions or white papers describing aspects of cardiovascular safety that would benefit from being followed up with concrete research projects. Some offer a 'pragmatic approach' that will inform regulatory processes; however, what is required are approaches that discover the fundamental mechanisms of cardiovascular liability that will allow a step change in the detection and assessment of cardiovascular liability in drug discovery and development. Few if any of the current initiatives are addressing the identification and characterization of cardiovascular liabilities and the impact that they have on late-stage clinical development. Several of the initiatives are also under pressure financially or have not been progressed due to the fiscal pressures on industry and governments. So although it is clear that those in industry are aware of the issue, not enough is being done and that is why it is believed that a new initiative is required. By presenting and recognizing existing initiatives, we clearly highlight the importance of ensuring complementarity and wherever feasible additivity if not synergistic effects with existing initiatives.

Having reviewed the field and other initiatives in this area it is believed that what is currently missing is a true pharmacological approach to define the issue. We simply do not understand enough about the mechanisms that result in cardiovascular dysfunction and key to being able to address this are well-defined chemical reagents that are highly selective for the pathways important for cardiovascular liability. To achieve this the definition of a training set of compounds that will allow us to link the chemistry of the compounds to biological perturbation of the pathways is proposed. This new initiative will need to collect information from the pharmaceutical industry on compounds with associated liability and build training sets of compounds that can then be tested in current and novel models, assays and screens. It is believed that it will be too time-consuming a task to collect this information for every cardiovascular liability so it is proposed that in the first instance a small number of liabilities are selected (e.g. cardiac contractility), and the relevant information and compounds are collated. These compounds can then be tested in the same relevant test systems that have been selected by the stakeholders and the signatures of cardiovascular liabilities can be looked for.

Clearly the issue of cardiovascular safety liability in drug development is an area that would benefit from Innovative Medicines Initiative (IMI) support. Cardiovascular toxicity was announced as being one of the IMI indicative call topics earlier in 2010; however, it has not progressed to the proposal stage. The reasons for this are unclear; however, the area is ideally suited to an IMI approach as it is an emerging problem for the development of safe medicines in which both academia and industry scientists have the opportunity to synergize and innovate in tackling the problem. The authors ask that European Federation of Pharmaceutical Industries and Associations members and IMI look again at this issue. By better coordinating our activities and focusing on key drug development challenges there is an opportunity to advance our understanding of the causes of cardiovascular safety, improve the likelihood of success in drug development and ultimately improve patient safety. Organization such as the MRC CDSS and the IMI have a key role to play in fostering

Table 4

Background information and objectives of key initiatives focusing on cardiovascular safety liabilities

Identification	Background	Objectives	References
Animal Model Framework – Association of the British Pharmaceutical Industry (ABPI)	Cross pharmaceutical companies initiative under the auspice of the ABPI aimed at developing a conceptual framework to define and classify key models used in safety pharmacology with respect to specific end-points that are evaluated in animals and humans.	To investigate the translation of non-clinical safety pharmacology assays and models (including cardiovascular models) to the phase I clinical outcome.	Valentin JP *et al.*, 2009a. J Pharmacol Toxicol Methods 60: 152–158.
Top Institute (TI) Pharma	Public–private partnership aimed at improving development of socially valuable medicines. Formed by Dutch Government, Universities and Pharmaceutical Industry.	To investigate the translation of non-clinical assays of QT prolongation to the clinic and patient outcome. Use mechanistic PK/PD modelling to predict risk from non-clinical data. Examine relationship between QT prolongation and sudden death.	Anon (2010b) http://www.tipharma.com/about-our-institute/about-ti-pharma.html
European Centre for the Validation of Alternative Methods (ECVAM)	To promote acceptance of alternative methods to reduce, refine or replace the use of laboratory animals.	'Alternative Methods for Drug-induced Cardiotoxicity' workshop. Recommendations published. However, ECVAM no longer focusing on pharmaceuticals.	Stummann TC *et al.*, 2009. Cardiovasc Toxicol 9: 107–125.
Cardiac Safety Research Consortium (CSRC)	To advance scientific knowledge on cardiac safety for new and existing medical products by building a collaborative environment based upon the principles of the FDA's Critical Path Initiative as well as other public health priorities.	Intent is to develop evaluative tools, standards, validated tests and cardiovascular biomarkers related to broader aspects of cardiac safety including, but not limited to arrhythmia, thrombosis, myocardial infarction and heart failure.	Anon (2010c) https://www.cardiac-safety.org/ Piccini JP *et al.*, 2009. Am Heart J 158: 317–326.
Safety Pharmacology Society (SPS)	Best practice initiative led under the auspice of Safety Pharmacology Society involving Pharmaceutical companies, CROs and Regulatory agencies	'Cardiovascular Best Practices Workshop' aimed at improving the quality and consistency of cardiovascular *in vivo* Safety Pharmacology studies and cardiovascular end-point measurement in toxicology studies.	Cavero I, 2010. Expert Opin 10: 319–333.
Stem Cell for Safer Medicines (SC4SM)	Public–private collaboration, established through the vehicle of a not-for-profit company, whose mission is to enable the creation of a bank of stem cells lines.	The aim of the SC4SM programme is to develop stem cell technology for use at an early stage in safety testing, to eliminate new drug candidates, which may have side effects in humans, before animal or human trials are conducted. Stem cells may provide a route to deriving sufficient quantities of hESC-derived cardiomyocytes that can be used in high-throughput *in vitro* cardiac safety screens.	Anon (2010g) http://findarticles.com/p/articles/mi_hb5255/is_16/ai_n35675936/
HESI – Cardiac Technical Committee	Global scientific, non-profit, organization since 1989. Focus on human and environmental risk assessment and toxicology. The Cardiac Technical Committee encompasses four sub-committees.	Cardiac Biomarkers. Focus on cardiac troponin as a marker of cardiac injury. Evaluate current experimental practice in assessment of haemostasis. Predictive Cardiovascular Safety. To identify and pursue opportunities to develop a more predictive/translational approach to cardiovascular safety evaluation. Functional Cardiovascular Toxicity Evaluation. Facilitate discussion around the use of functional measures of cardiovascular effects for safety evaluation. Proarrhythmia Models. Understand of the value of non-clinical repolarization assays for predicting drug-induced QT prolongation.	Anon (2010f) http://www.hesiglobal.org/i4a/pages/index.cfm?pageid=1 Pettit SD *et al.*, 2010. J Pharmacol Toxicol Methods 61: 1–2.
Critical Path institute's Predictive Safety Testing Consortium (PSTC)	PSTC is a public–private partnership established in 2006 and directed by the non-profit Critical Path Institute.	Consortium of pharmaceutical companies who share and validate each other's safety testing methods. Current working groups include vascular injury and cardiac hypertrophy.	Anon (2010d) http://www.c-path.org/pstc.cfm
Innovative Medicine Initiative (IMI)	Public–private partnership between the pharmaceutical industry represented by the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the European Union represented by the European Commission.	Cardiovascular liabilities were originally included in the IMI JU Scientific Priorities 2010 (published on IMI website 16/03/2010): Safety Pillar: General Safety, Scientific Priority A: 'Assessment of drug induced toxicity in relevant organs – surrogates for early drug failure'. However, it was subsequently not included in the final '2010 Call for proposals' (published online 04/10/2010) that specified DILI.	Anon (2010e) http://www.imi.europa.eu/

this non-competitive collaborative approach involving pharmaceutical companies, academic institutions and the regulators. It is proposed to host a follow-up workshop to define the liability to be selected and put in place a mechanism for the collection of the data from companies, its safe storage and interrogation followed by compound selection and testing. We would welcome all interested stakeholders to join this venture and their contribution to moving the field forward.

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Conflict of interest

Some authors of this paper are employed in the pharmaceutical industry or serve as consultants to the pharmaceutical industry. However, the subjects presented in the paper do not advocate or support purchase of any of the products offered by the respective organizations.

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