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Methods of collecting and evaluating non-clinical cardiac electrophysiology data in the pharmaceutical industry: results of an international survey

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Abstract

Objective: To assess current practice in the pharmaceutical industry for assessing the potential for QT interval prolongation by non-cardiovascular medicinal products. **Methods:** The survey was based on responses from the Toxicology and (Safety) Pharmacology laboratories (a total of 74 laboratories) of 54 companies based in Europe, Japan/Asia and the USA, received between January and March 1999. **Results:** All 54 companies conducted preclinical in vivo electrocardiography (EGG) evaluation of new active substances (NASs). Thirty of these companies also conducted in vitro cardiac electrophysiology studies on their compounds. The majority of in vivo work was done in conscious beagle dogs. There was no consistency within the industry in defining the magnitude of change in QT interval that is considered biologically important. Most companies considered a change greater than 10% to be important, although the design of the studies suggested that group sizes used may not give sufficient statistical power to detect this size of change. Bazett's formula was used by 41% of laboratories to correct QT for changes in heart rate, despite the fact that this formula is generally deemed to be unsuitable for use in dogs. For studies in anaesthetised dogs, the majority of laboratories used barbiturate anaesthesia, but researchers should be aware of the effects of this and some other anaesthetic agents on QT interval. As for in vitro cardiac electrophysiology, there was wide diversity in the testing methodologies, particularly with regard to the test species and tissue type. As with QT prolongation, there was no consensus on the degree of action potential prolongation to cause concern. For both in vitro and in vivo testing, the majority of companies tested a minimum of three dose (or concentration) levels in order to ascertain any dose–response relationship. **Conclusions:** The survey provides a snapshot of the practice in the industry prior to any internationally-agreed consensus on the most effective and efficient approaches to minimising the risk of QT prolongation by new drugs in man. It must be stated that for any given methodology, the 'majority view' in the industry is not necessarily best practice.

Keywords: EGG; Ion channels; Long QT syndrome; Purkinje fiber; Sudden death

1. Introduction

The occurrence of *torsade de pointes* with various non-cardiovascular agents such as terfenadine, terodiline and cisapride prompted the Committee for Proprietary Medicinal Products (CPMP) to issue a 'Points to Consider' document in 1997 [1]. There has since been much debate within the pharmaceutical industry as to the most predictive in vitro and in vivo techniques to detect such activity, and indeed as to whether the in vitro tests are worthwhile.

This paper contains the results of a survey conducted in

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the pharmaceutical industry between January and March 1999. The aim of the survey was to assess current approaches, practices and methodologies within the phannaceutical industry relating to the detection of delayed ventricular repolarization by all new active substances (NASs), prior to human exposure. The survey was not designed to ask opinions on the merits of the various CPMP-recommended tests. The survey involved two questionnaires, on cardiac electrophysiology techniques in vivo and in vitro, respectively.

Where we have made recommendations, they are based on our own experience of the methodology and knowledge of the literature.

2. Methods

The 'in vivo' and 'in vitro' questionnaires comprised 28 and 38 primary questions, respectively. Copies of the original questionnaires are available on request to the corresponding author. In the tables, 'Number' refers to 'Number of laboratories'. Where percentages are given, these have been rounded-off to the nearest whole number.

3. Results

A total of 54 companies responded, ranging from small private companies to large multinationals. Although this might give undue influence to smaller companies (with a smaller number of annual submissions to regulatory authorities), on the other hand the larger companies generally returned responses from more than one site. Of the global top 25 pharmaceutical companies worldwide in terms of Pharma sales in 1998 [2], all companies ranked in the top five responded, and a total of 16 of the top 25 responded.

3.1. In vivo electrocardiogram (ECG) data

Where clearly indicated on the completed questionnaires, the entries were separated into (Safety) Pharmacology and Toxicology Laboratories. Therefore, from a total of 54 companies, there were responses from 74 laboratories. Nearly half of the laboratories (35) were European-based although adequate representation from Japan (26) and the USA (13) give confidence that the responses reflect practices worldwide.

3.1.1. Choice of species and model

All companies collected in vivo ECG data as part of the preclinical evaluation of NASs. The beagle dog was the main species used (Table 1).

It should be noted that 26% of laboratories collected ECG data from the rat, which is not generally considered to be a suitable species to detect alteration of the QT interval as a consequence of blocking effect on I_{Kr} (the rapid component of the delayed rectifying potassium current) — see Summary and recommendations. However, only one laboratory in the survey used the rat exclusively for deriving ECG data, but another laboratory within the same company was using non-rodents. The majority of laboratories evaluated ECGs from conscious dogs or monkeys. Regardless of species, telemetry techniques were used by 28 out of 74 laboratories (38%) (Table 2).

Table 1
Species used in in vivo studies[a]

	Number
Dog – beagle	63
Dog – beagle/mongrel	6
Dog – breed not stated	3
Rat	19
Cynomolgus	24
Marmoset	2
Guinea-pig	4
Cat	1
Minipig	1
Pig/piglet	2
Rabbit	3
Total	128

[a] Not mutually exclusive.

Of those companies using anaesthetised preparations, the majority (51%) used intravenous barbiturate as the anaesthetic of choice. Most of the anaesthetics recorded in the survey have either overt or subtle effects upon cardiovascular function, and many also increase QT interval (see Summary and recommendations). According to the survey returns, 11 laboratories relied entirely on anaesthetised preparations for evaluation of effects of NASs on the ECG.

3.1.2. Experimental design

The majority of laboratories (72%) tested three or more dose levels. Surprisingly, several laboratories (17%) used only one or two dose groups, although no information to justify this (such as vaccine evaluation) was given.

The group sizes used predominantly ranged between three and six with very few using group sizes below three (Table 3). Of the 69 laboratories that used three or more animals per dose group, 44 (64%) applied statistical analysis to the QT interval data. However, in one labora-

Table 2
General methods used in in vivo studies

	Dog	Cynomolgus	Rat
Anaesthetised (*sole method*)	13	1	5
Conscious (*sole method*)	22	12	2
Telemetry (*sole method*)	1	1	2
Combination of above	32	9	9
Not stated	4	1	1
Total	72	24	19

Table 3
Group sizes used in in vivo studies

	Number	%Total
$n = 1$	1	1
$n = 2$	4	5
$n = 3$	23	31
$n = 4$	22	30
$n = 5$	6	8
$n = 6$	9	12
$n = 8$	4	5
$n = 10$	1	1
not stated	4	5
Total	74	100

tory, statistics on QT interval (see later in report) were apparently applied to a group size of two!

The majority of laboratories (70%) included a negative control group of similar size to the test groups. The reason for the lack of controls in the remainder is not apparent but may be due to experimental design with animals acting as their own control.

Of those laboratories that conducted multiple dose studies, the majority (86%) recorded ECGs both pre- and post-dose. Those who did not (recording either pre- or post-dose only) all used concomitant negative controls. Post-dose recordings were usually timed to relate to toxicokinetic/pharmacokinetic profiles of the NAS (Figs. 1 and 2).

3.1.3. Techniques

There was wide variability between laboratories in the positioning of animals for EGG recording (Table 4).

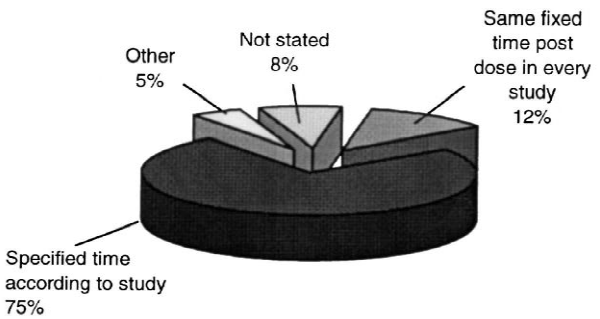

Fig. 1. Time points for ECG recording.

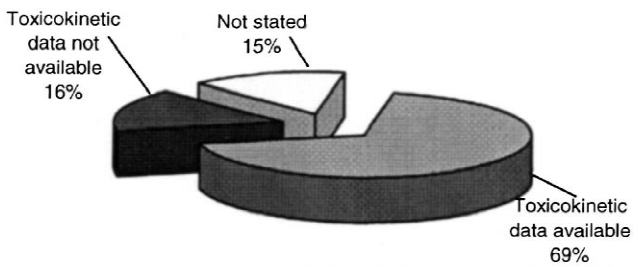

Fig. 2. Availability of toxicokinetic data prior to study.

Table 4
Positioning of animals for ECG recordings

Table for the two main species used:		
	Dog	Cynomolgus
No standard position	8	2
Anaesthetised – supine	9	0
Standing freely	5	0
Standing in a sling (dog)	12	
Lying on side (dog)	22	
Telemetry – ambulatory	5	1
Telemetry – restrained (dog)	1	
Restraining chair (cynomolgus)		11
Other	2	3
Not stated	1	0
Total	65	17

Although this may cause difficulty in interpretation of waveform morphology [3], it is unlikely to have major consequences for measurement of EGG intervals. The importance of heart rate was probably not being addressed adequately, with 32% of companies taking no measures to ensure that heart rate was recorded at 'resting' heart rate (Fig. 3).

Eighteen laboratories recorded EGG at paper speeds of 25 mm/s or less although, of these, only 7 relied on manual measurement and could be expected to have had difficulty with accuracy of measurement. Similarly, 8 laboratories appeared to use a 1 mm/mV amplitude calibration which could be expected to cause difficulty with assessment of waveform, especially T-wave.

The majority of laboratories (73%) did not use chest leads. Most laboratories recorded six limb leads, presumably to assess morphology (Table 5). Twenty-nine laboratories used either lead II alone or in combination with leads I and III. However, the majority of laboratories (78%) measured EGG intervals from lead II only (Table 6).

Automated EGG data capture and analysis was widely used (Fig. 4). The majority of these laboratories had validated their data acquisition systems, reflecting a similar proportion conducting their studies in a 'Good Laboratory Practice' (GLP) environment (Fig. 5).

Despite the fact that 69% of laboratories used validated

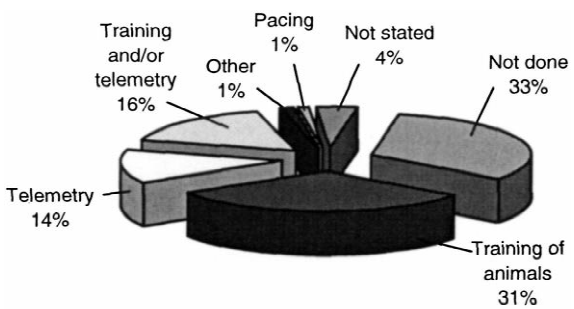

Fig. 3. Method of achieving 'resting' heart rate.

Table 5
ECG limb leads recorded

	Number	% Total
Lead II only	20	27
Leads I, II & III only	9	12
Leads I, II, III, aVL, aVR, aVF	39	53
Other	3	4
Not stated	3	4
Total	74	

Table 6
Derivation of QT interval

	Number	% Total
Lead II	58	78
Median of all leads	2	3
Longest measurement from all leads	4	5
Other	6	8
Not stated	1	1
Total	74	

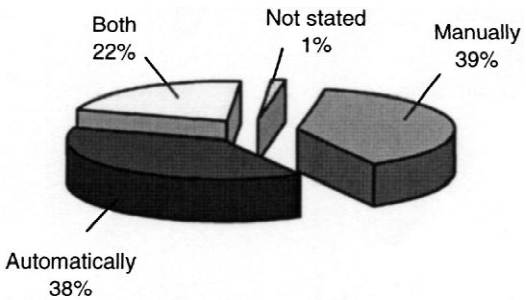

Fig. 4. Method of measurement of ECG parameters.

methods (manual or automatic), only 53% had acceptance/rejection criteria based on trace quality. The methodology used to record ECG data has been changed significantly in the last 5–10 years in 39 laboratories (i.e. 52%). This included 17 of the 25 laboratories that have experienced regulatory issues with compounds that prolong QT interval.

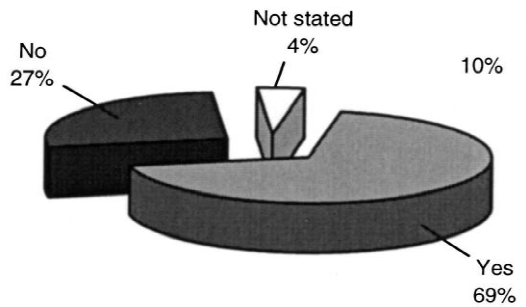

Fig. 5. Validation of recording systems.

3.1.4. Data analysis

The majority of laboratories statistically analysed data for heart rate, PR/PQ interval, QRS duration and QT interval. Most did not analyse amplitudes. It should be noted that, while 92% of laboratories measured QT interval, 28% did not statistically analyse the data (Table 7). Most laboratories (66%) did not assess the U-wave, and rhythm was not assessed by 43% of laboratories. Very few laboratories (5 in all) measured QT interval dispersion.

The use of formulae to correct QT for changes in heart rate (Fig. 6) was widespread (63% of laboratories), and frequently included statistical analysis of the derived data.

3.1.5. Data interpretation

There were 4 types of analysis used by laboratories to assess drug-induced changes in QT (Table 8). However, of possible concern is that 26% of laboratories did not appear to have predetermined criteria to assess changes in QT interval. For those that have established criteria variability in the method of assessment exist (Table 9). Thirteen laboratories considered a 10% increase in QT interval to be significant (i.e. biologically significant) with a wide range of 'thresholds for concern' amongst the remaining laboratories.

3.2. In vitro cardiac electrophysiological data

In contrast to the in vivo section of the survey, none of the companies in the survey performed in vitro cardiac electrophysiology in more than one in-house facility, so the term 'company' rather than 'laboratory' is used in this section. Of the 54 companies polled, 30 (56%) conducted in vitro cardiac electrophysiology studies, and a further 5 (9%) planned to do so (Fig. 7).

The data presented here are based on replies from the 30 companies that did carry out such studies at the time of the survey. Of these 30 companies, 20 had the capability to perform the studies in-house. Most of the 30 companies were located in Europe (53%), with fewer in Japan/Asia and the USA (30% and 17%, respectively). The geographical distribution of companies that had in-house capability to carry out in vitro cardiac electrophysiology showed approximately 20% to be located in the USA, with 40% each in Japan/Asia and Europe. The majority (67%) of the 30 companies conducted these in vitro investigations prior to first administration to man.

3.2.1. Species and tissues

There was a broad diversity between companies in the choice of species and tissues used for these studies. The most commonly used tissues were Purkinje fibre and papillary muscle. The distribution of tissues and species is shown in Fig. 8. A small number of companies reported

Table 7
Analysis of ECG variables

	Not assessed (%)	Visually assessed (%)	Measured (%)	Analysed statistically (%)
Heart rate	0	3	19	78
P wave height	24	35	19	22
P wave width	30	24	22	24
PR/PQ interval	7	5	27	61
QRS width	4	9	31	55
R wave height	18	32	20	30
ST segment	31	34	19	16
QT interval	3	5	28	64
T wave height	24	39	19	18
T wave width	45	35	8	12
U wave	66	34		
Rhythm	43	57		

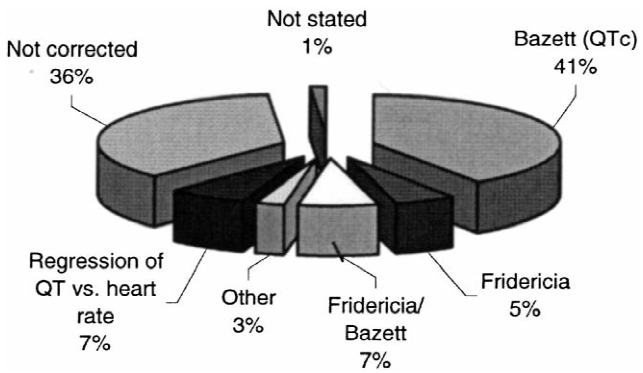

Fig. 6. Correction of QT for heart rate.

using other species (one each for pig, human, monkey) and other tissues [ventricular muscle (1), sino-atrial node (1), right ventricular myocardium (1), perfused or isolated heart (3) and myocytes (3)]. Only one group used neonatal animals (pigs); the remainder used adults. Only one company used female animals only, all others used males only or both sexes. In many instances, especially for the larger species, animals were killed with an overdose of anaesthetic, usually barbiturate. This may be a concern because it has been shown that anaesthetics can affect myocardial ion channels involved in action potential duration [4–6] and it is not clear whether, and how quickiy, the effects of an anaesthetic administered to an animal will diminish when tissues are removed for in vitro studies.

Table 8
Approaches to assessing drug-induced changes in OT

	Number	% Total
% change in QT	22	30
change in QT	9	12
absolute QT (ms)	10	14
'statistical significance'	14	19
not stated	19	26
Total	74	

3.2.2. Experimental design

There was no consensus on criteria for selection of a concentration range for the test compound (Fig. 9). Thirty-seven per cent of companies tested multiples of a plasma

Table 9
Magnitude of change in OT interval considered to be significant

	Number
(i) % change in QT	
>5	3
>10	13
>15	2
>20	1
>25	1
>30	1
not stated	1
Total	22
(ii) Change in QT (from pre-dose, control group, or predicted value).	
>8 ms	1
>10 ms	3
>20 ms	2
>22 ms	1
>30 ms	1
>50 ms	1
not stated	0
Total	9
(iii) Absolute QT (dog)	
>220 ms	1
>240 ms	1
>250 ms	1
>270 ms	1
>280 ms	1
>320 ms	1
>500 ms	1
outside normal range for that particular heart rate	3
not stated	0
Total	10

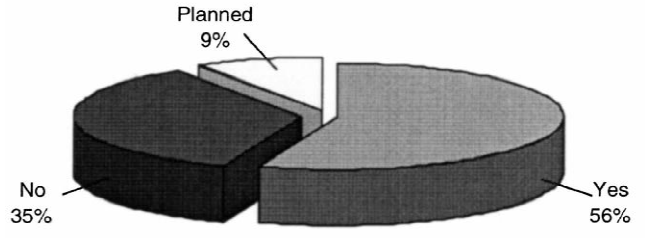

Fig. 7. Companies conducting in vitro cardiac electrophysiology studies on non-cardiovascular compounds (% of 54 companies).

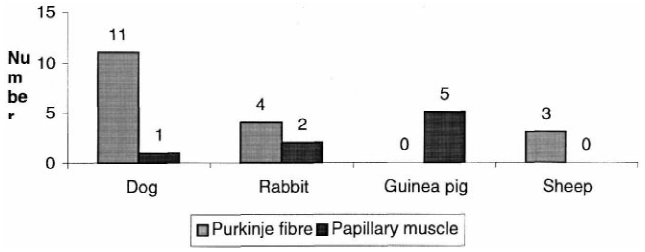

Fig. 8. Most commonly-used species and tissues.

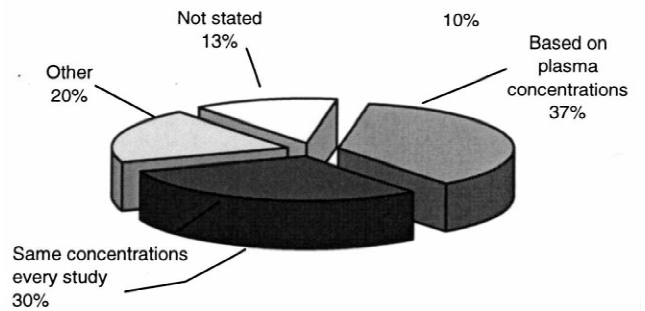

Fig. 9. Test concentration selection criteria.

concentration (therapeutic or pharmacologically effective), whereas in 30% of companies a fixed range of concentrations was used, irrespective of the potency of the compound. Most companies tested between three and six concentrations of test compound, in three to six preparations per compound (Figs. 10 and 11).

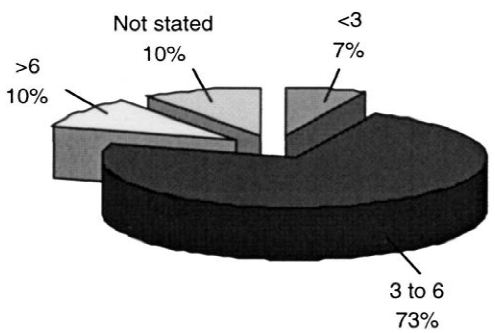

Fig. 10. Number of concentrations tested.

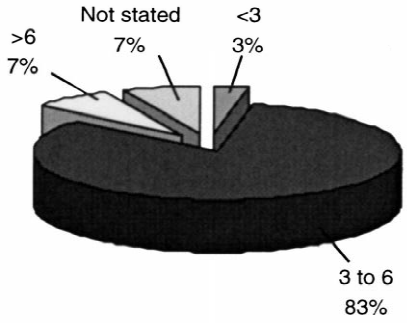

Fig. 11. Number of preparations per study.

The percentage of companies that used negative and positive controls in their studies is shown in Fig. 12. It is noteworthy that while 57% of respondents included negative controls, 37% did not. It is of less concern that 30% did not run a positive control group. Where control groups (positive or negative) are used, they generally consist of three to six preparations.

Regarding timing of electrophysiology recordings, 60% of companies used pre-selected or specified times, while the remainder used variable time points, or did not answer this question. In 60% of companies, the identity of key metabolites was not known at the time of initial studies, so where they were tested at all (in 53% of companies) this was done at a later time.

Most companies (63%) acquired their action potential recordings by continuous impalement of the tissue, but 20% used serial sampling (i.e. successive impalement of several cells during the experiment). Slightly over half the companies (57%) used a ‘normal’ stimulation frequency (in this context, ‘normal’ is taken to be 1 Hz) while 27% used low and/or high frequencies in addition. Again, 57% used more than one frequency of stimulation in their study design; 65% allowed an adjustment period of 1 to 5 min following any change in stimulation frequency, whereas others used 6 to 10 min (12%), or greater than 10 min (6%). The majority of companies (70%) used either Tyrodes, Krebs or Krebs–Henseleit solutions in their

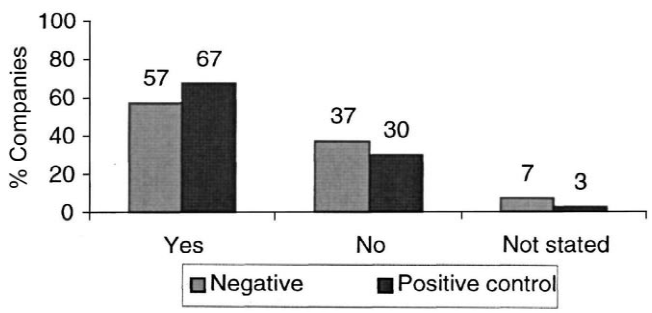

Fig. 12. Inclusion of negative and positive controls.

Table 10
Control APD_{90} ranges

Species/preparation	APD_{90} range	Number of companies
Dog Purkinje fibre	229–350 ms	8
Rabbit Purkinje fibre	220–275 ms	4
Guinea-pig papillary muscle	186–359 ms	7

studies, and the concentrations of potassium, magnesium, calcium and glucose used reflected this. Most companies used a temperature over 35°C, but some (13%) used a temperature below 35°C.

3.2.3. Data analysis and interpretation

Most of the key action potential parameters were measured and/or analysed by the majority of companies, including, importantly, resting membrane potential, maximum upstroke velocity, amplitude and action potential duration at 90% repolarisation (APD_{90}). Probably the single most important parameter to be measured in order to assess activity at the I_{Kr} channel is APD_{90}. The range of control values obtained for this parameter is shown in Table 10.

However, 13% of companies did not appear to measure APD_{90}, and there were differences in what degree of change in APD_{90} companies thought was a 'cause for concern' (Fig. 13). This varied from $<$10% (by 10% of companies), 10–20% (by 47% of companies) to $>$20% (by 10% of companies). It may also be of some concern that, in 17% of companies, data were not subject to peer review.

Finally, nearly half of the companies stated that they had changed the methods that they used for in vitro electrophysiology studies over the past 5 to 10 years, but it did not seem that this was related to any particular experience with the regulatory authorities.

4. Summary and recommendations

For both in vitro and in vivo testing, the majority of companies tested a minimum of three dose (or concentration) levels in order to ascertain any dose-response relationship. We consider this to be appropriate.

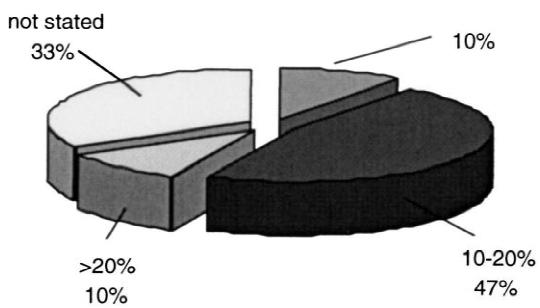

Fig. 13. % increase in APD_{90} to raise concern.

4.1. In vivo techniques

4.1.1. Choice of species

Generally, the species used were appropriate to detect QT change of relevance to man, with beagle dogs being the most popular. Other species were used less frequently than the dog, but with the exception of the rat, there is no particular reason why other species such as pig/minipig, rabbit or guinea-pig would not be as predictive of effects on ventricular repolarisation in man. However, the rat should not be used to assess QT interval changes. Whereas the rat is of some value in cardiovascular assessments, this species will probably not be susceptible to action potential lengthening and QT prolongation as a consequence of blockade of the rapid component of the delayed rectifying potassium current (I_{Kr}). Although the consensus view is that ventricular tissue from this species does express this ion channel protein [7,8], a dominant transient outward current (I_{to}) will rapidly restore membrane potential to negative voltages, thus reducing the time for I_{Kr} activation. As a consequence, the adult rat lacks a prominent action potential plateau and therefore agents blocking I_{Kr} will not prolong action potential duration in this species [7,9,10]. In short, the current patterns during repolarization are quite different in the rat myocardium compared with humans and other mammalian species, such as guinea-pig [11,12].

4.1.2. Choice of anaesthetic (for EGG measurements in anaesthetised preparations)

Anaesthetised preparations are an acceptable adjunct to the conscious studies, permitting a more thorough evaluation of cardiovascular effects. Choice of anaesthetic is important, as several agents in common use have direct effects on QT interval or the cardiovascular system (Table 11).

It is, therefore, worth noting that the presence of anaesthetic during cardiovascular evaluations may alter the sensitivity of the model to detect effects on ventricular repolarisation and consequently QT duration. Consideration should be given to the effects of the anaesthetic agent used on the cardiovascular system and on cardiac ion channels, particularly when anaesthetised preparations are to be the only model for ECG assessment.

4.1.3. EGG leads

The number of leads used to collect ECG data varied between laboratories. We propose that only one lead (generally lead II) is necessary for measuring QT interval, but that the recording of three leads will enable choice of the clearest waveform for interval measurements, and will permit assessment of morphology. Chest leads are not required for ECG interval analysis. Few laboratories assessed U-wave, probably reflecting its rare occurrence in

Table 11
Effects of anaesthetics on QT interval

Anaesthetic agent	Cardiovascular/autonomic	QT (or QTc) interval (dog)
Isoflurane	Tachycardia [17]	↑ [22]
Halothane	Bradycardia [17]	↑ [22]
Pentobarbitone	Respiratory depression	↑ [23]
Ketamine	Tachycardia [17]	no effect [24]
Alpha-chloralose	Tachycardia and hypertension	↑ [25]
Propofol + alfentanil	Hypotension during induction but normotensive thereafter [18,19]	No effect in man [26]; no literature found indicating an effect in dogs
Urethane	Hypotension, release of adreno-medullary catecholamines [20,21]	No literature found indicating an effect (in any species)

dogs. The large majority of laboratories in the survey did not measure QT interval dispersion. There is little published data to support the value of QT dispersion in animals presently.

4.1.4. Quality of data

Methodology used to evaluate ECG in animals is evolving. Some of the improvements appear to be in response to regulatory issues and recent guidelines. Generally, the quality of data generated is considered to be adequate to permit evaluation of drug-induced changes in QT interval. Wide variability existed in the positioning of dogs for EGG recording, although we do not consider this to be important for measuring ECG intervals per se.

4.1.5. Correction of QT interval for changes in heart rate

Whereas 41% of laboratories used Bazett's formula to correct QT for changes in heart rate, in the literature this formula is generally deemed to be unsuitable for use in dogs. Use of correction formulae was not consistent and in some instances inappropriate. In those cases where a statistically significant change in heart rate is seen, QT should be corrected and the method of correction must be justified. Bazett's formula is unlikely to be suitable for dogs, and other methods of correction have been proposed [13–15]. Alternatively, a regression approach may be applied, based on in-house data of QT-heart rate relationships in the individual beagles under drug-free conditions. Measures should be taken to ensure that, as far as possible, recordings are taken at 'resting' heart rates. This will reduce the need for correction formulae, reduce the variance of the data, and ensure that QT prolongation is not masked at high heart rates by the effects of reverse use-dependence.

4.1.6. Study design/power

ECG recording/analysis was usually conducted at intervals that reflected pharmacokinetic/toxicokinetic profiles. The study designs are generally acceptable with respect to numbers of dose groups, although a minimum of three dose levels is required to detect dose-related changes. Investigators need to perform statistical power calculations based on in-house data, in order to build-in sufficient *n* numbers to detect the magnitude of changes in QT interval that they consider to be 'biologically significant'. Based on preliminary estimates of sample sizes, using a standard formula for power calculations [16] we believe that group sizes of $n=4$ may be inadequate to detect changes in QT interval of 10% in conscious dogs, but may detect changes of ~20% (for control QT=200 ms; control S.D.=19 ms; $P<0.05$, 2-tailed, unpaired test; 80% power). This can be improved upon if QT is corrected using the formula of Van de Water et al. (1989), where group sizes of five are sufficient to detect changes in QTc of 10% (control QTc= 236 ms; control S.D.=13 ms; $P<0.05$, 2-tailed, unpaired test; 80% power). However, the degree of change in QT (or QTc) considered to be 'biologically significant' was not universally consistent. Not all laboratories used statistical analysis of their QT data. We consider a lack of statistical analysis to be undesirable.

4.2. In vitro techniques

Only 30 companies investigated their compounds using in vitro cardiac electrophysiology tests. There was wide diversity in the testing methodologies, particularly with regard to the test species and tissue type. The survey was initiated in response to the CPMP Points to Consider [1] which did not include assessment of activity in cloned human ion channels. It is recognised that this methodology is becoming increasingly important.

4.2.1. Choice of species

As with the in vivo testing, there is no compelling reason to use one species rather than another on the basis of ion channel function, with the exception of the rat, which is of limited value for predicting electrophysiological effects on the human myocardium, and was not in any case used for in vitro studies by any of the companies in the survey.

4.2.2. Tissue preparation

The use of in vitro techniques may require that the experimental tissue be removed under terminal anaesthesia, often using a high dose of barbiturate. This is especially true in the case of larger species such as the dog, which cannot reasonably be killed by any other method. It

is not established whether, or how rapidly, the effects of an anaesthetic administered to the intact animal will wear off once tissue has been removed into an organ bath and bathed with a physiological salt solution. Therefore, there would have to be some degree of caution implicit in the use of tissue harvested from anaesthetised animals (and thus from dogs).

4.2.3. Action potential characteristics

We recommend that APD_{90} is the most appropriate marker of action potential duration. However, careful evaluation of drug effects on V_{max} and upstroke amplitude is as important as assessment of APD. As with QT prolongation, there was no consensus on the degree of action potential prolongation to cause concern.

4.2.4. Quality of data

Seventeen percent of companies did not subject their data to peer review; this may give cause for concern regarding the quality of the data from the studies. Sixty percent of companies did not carry out the studies to GLP; this could be an issue if the information is used to support administration of the substance to humans. Thirty-three percent did not have acceptance criteria (e.g. action potential morphology/characteristics) for whether they would accept data from a tissue preparation. Sixty-three percent did not correct for electrode drift over the time course of the experiment. In four companies, experiments were carried out at a temperature of less than 35°C, which will markedly influence ion channel biophysics and kinetics. Up to 13% of companies may not have been measuring or analysing APD_{90}; 53% did not output their action potential waveforms to a chart recorder; this would make proper assessment for early after-depolarisations difficult. Use of continuous impalements rather than serial sampling techniques to improve data accuracy and quality is recommended.

4.2.5. Rate dependence

While a majority of those responding carried out some testing at a range of frequencies, it is doubtful that there is significant added value in doing this during routine screening. However, in the event of a drug effect at (say) 1 Hz, it would then be worthwhile exploring rate-dependence.

4.2.6. Time-matched controls

Thirty-seven percent of companies did not routinely include a negative (time-matched) control group. Use of appropriate time-matched negative (i.e. vehicle– perfused) control preparations is recommended. Routine inclusion of a positive control (i.e. reference substance) would be desirable.

5. Conclusions

The survey provides a snapshot of the practice in the pharmaceutical industry prior to any internationally-agreed consensus on the most effective and efficient approaches to minimising the risk of QT prolongation by new drugs in man. The survey has revealed a wide spectrum of approaches to addressing this issue in the pharmaceutical industry, and there is clearly a need for a degree of consensus on ‘best practice’ in terms of methodology [27,28]. It must be stated, however, that for any given methodology, the ‘majority view’ in the industry is not necessarily best practice.

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