the cardiac myocyte, the currents being mediated by the coordinated activities of different ion channels. The ion currents manifest themselves as a sequence of transmembrane voltage changes known as the action potential.

1.4. The Action Potential

The action potential is the name for the characteristic signature of electrical activity in a contracting/relaxing cardiac myocyte. It can be separated into 5 phases (Figures 1.2 and 1.3).

**Figure 1.2. Typical Action Potential of a Cardiac Myocyte**

Source: Insight Pharma Reports
Table 2.2. Potentially Proarrhythmic Drugs (cont.)

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Example</th>
<th>Cardiac Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other (cont.)</td>
<td>Tolterodine (bladder antispasmodic)</td>
<td>May cause TdP in patients with long QT syndrome</td>
</tr>
<tr>
<td></td>
<td>Vardenafil (phosphodiesterase inhibitor)</td>
<td>May be associated with TdP</td>
</tr>
</tbody>
</table>

ADHD, attention deficit hyperactivity disorder; CNS, central nervous system; HIV, human immunodeficiency virus; TdP, torsades de pointes.

Source: Adapted from ArizonaCERT QT Drug Lists, www.torsades.org

Clearly, the list of drugs that have the potential to cause TdP, in at least some (predisposed) patients, is long, although fatal drug-induced arrhythmias are relatively rare events. However, even a low frequency of TdP may be concerning where (1) the drug is used in large numbers of patients (treatment of common conditions) or (2) the risk-reward balance does not justify the increased risk of arrhythmia (treatment of relatively benign conditions).11

The former case may be illustrated by certain antibiotics and antidepressants (which are among the most commonly prescribed QT prolongers),7 and perhaps by some antimalarials (which can be used on a large scale in the developing world).52 The latter case is exemplified by certain antihistamine products, originally approved for the treatment of hay fever symptoms, and later withdrawn from the market due to their association with fatal arrhythmias.

2.5. Mechanism of Cardiotoxicity of Proarrhythmic Drugs

Discussions of the mechanism of cardiotoxicity of proarrhythmic drugs are complicated by the apparently multifactorial nature of arrhythmia generation. In brief, the genesis of a drug-induced arrhythmia may involve an interaction between (1) multiple known and unknown predisposing factors (see Section 2.6) or (2) drug effects on 1 or more ion channel proteins.
“alternatives to the use of the thorough QT/QTc study are under active investigation.” Examples include evaluating the relationship between concentration and QT/QTc effects or more intensively evaluating ECGs, based on data collected during early-phase clinical studies.

### 3.4. Other Regulatory Agency Documents

One document\(^5\) was found suggesting that the basic outline of a thorough QT/QTc study provided in E14 is becoming outdated. The document suggests that, with regard to the TQT study, “Additional nuances are becoming apparent as industry, academics, and the Food and Drug Administration (FDA) gain experience with these studies.”\(^5\)

As a consequence, the Center for Drug Evaluation and Research (CDER) has recently established an interdisciplinary review team (IRT) for the review of thorough QT study protocols and findings.\(^5\) The IRT comprises medical officers, cardiovascular pharmacologists/toxicologists, regulatory project managers and data managers from the Division of Cardiovascular and Renal Products (DCRP), and clinical pharmacologists from the Office of Clinical Pharmacology.

It is envisaged that the IRT will provide expert review advice (both to sponsors and FDA/CDER) on thorough QT studies, including the development of a practical guide to the design of thorough QT studies. It is thought that this practical guide could eventually become the basis of a new “Guidance for Industry” document.\(^5\) In addition, it is hoped that the IRT will contribute to the development of “alternative methods for evaluating repolarization effects.” This appears to be a de facto acknowledgment that current methods are not ideal.

### 3.5. Regulatory Decision-Making

TdP is a rare event; for example, terfenadine appeared to cause only 125 deaths during more than a decade of monitoring (1985–1998), representing over 10 million prescriptions.\(^8\) If this frequency is typical of drug-induced TdP, it is unlikely to be picked up in the clinical trials phase (typically no more than 3,000 patients). Therefore, the regulators are heavily reliant on surrogate markers of TdP. Unfortunately, the currently recommended markers for TdP liability are contentious and not ideal in terms of sensitivity and specificity (see Chapter 4).
Impact of QT Effects Discovered in Clinical Trials

The consequences of identification of a QT-prolonging effect may vary according to the disease for which the drug would be indicated. For example, a QT-prolonging drug may still be approved if it provides greater benefits at the same risk, or equal benefits at a lower risk, than the currently available alternative treatment.19,27 Similarly, if a QT-prolonging drug addresses a serious condition for which there is no alternative treatment, or if it significantly prolongs life (e.g., torsadogenic arsenic compounds in the treatment of leukemia), then the QT effect per se would be unlikely to prevent approval of the drug. The regulatory decision may be more complicated where a QT-prolonging drug is intended to reduce the risk of developing disease, as the regulators then must balance, for example, a drug-induced reduction in blood pressure with a drug-induced increase in incidence of TdP.27 In general, it is said to be difficult to progress a compound if preclinical data suggest a QT effect at a margin of less than 30-fold the therapeutic concentration, especially if the drug is intended for a non–life-threatening illness.3,13

A drug that is associated with a QT prolongation in clinical trials may require significant postmarketing surveillance. However, such surveillance is complicated by the element of voluntary reporting of adverse events by health workers, which may result in selective reporting of events associated with new drugs, and the possibility of patient noncompliance with the recommendations for drug use.23

4.5. Screening for “Direct” Cardiotoxicity

Markers of Cardiac Damage

Screening for nonproarrhythmic cardiotoxic potential generally involves either direct monitoring of myocardial necrosis or measuring accepted surrogates of cardiac damage. Potentially useful biomarkers for cardiac damage include troponins, atrial natriuretic peptide, brain natriuretic peptide, tumor necrosis factor (TNF)-alpha, and serum lipid peroxide.4,33,36 Of these, the cardiac-specific isoforms of cardiac troponins T and I may have advantages in the monitoring of drug-induced myocardial injury in both clinical and preclinical studies.4
**In Vitro Methods**

In terms of single-cell systems, of the 50 key participants who responded to the question shown in Figure 5.5, the great majority (70%) use patch clamping in mammalian cells that have been transfected only with hERG as their in vitro single-cell screening system. Presumably, this reflects the minimum in vitro screening requirement specified by ICH guidelines (see Chapter 3).

**Figure 5.5. In Vitro Single-Cell Systems Used**

Which of the following in vitro single-cell systems do you or your organization use in assessing signals of TdP liability by ion channel patch clamping? (Check all that apply)

<table>
<thead>
<tr>
<th>System Description</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammalian cells transfected with hERG only</td>
<td>35</td>
</tr>
<tr>
<td>Primary cardiac myocyte-type cells</td>
<td>17</td>
</tr>
<tr>
<td>Mammalian cells transfected with hERG and 1 or more other cardiac ion channel genes or auxiliary proteins</td>
<td>13</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
</tr>
<tr>
<td>Stem or progenitor cells induced to differentiate into cardiac myocyte-type cell</td>
<td>3</td>
</tr>
</tbody>
</table>

\[ n = 50 \]

*Source: Insight Pharma Reports Cardiotoxicity Survey—December 2007*

A significant minority (13 individuals, 26%), however, use mammalian cells transfected with hERG and 1 or more other cardiac ion channels or auxiliary proteins. This may reflect the feeling that hERG blockade is only part of the story of TdP liability, and that a fuller picture of TdP liability is provided by assessing the effect of experimental compounds on 2 or more ion channels (as indicated by the Cardiotoxicity Webinar, discussed above).
The great majority of the top 29 companies focus on the in vitro proarrhythmia screening subsegment (Figure 6.3). Some companies offer both in vitro and in vivo services, and thus fall into both categories.

Table 6.1. Top Providers of Products/Services for Proarrhythmia Screening (cont.)

<table>
<thead>
<tr>
<th>Company</th>
<th>Relevant Product or Service</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sophion (Ballerup, Denmark)</td>
<td>Automated patch clamp technology</td>
<td>Privately held. Sophion’s products include the QPatch 16 system (a 16-channel automated patch clamp system; i.e., allows 16 patch clamp experiments to be performed in parallel) and the QPatch HT system (a 48-channel automated patch clamp system, said to allow collection of up to 3,500 data points/day).</td>
</tr>
<tr>
<td>Zenas Technologies (New Orleans, LA)</td>
<td>In vitro preclinical cardiovascular risk assessment services</td>
<td>Privately held. Little information available.</td>
</tr>
</tbody>
</table>

Source: Insight Pharma Reports

Figure 6.3. Activity Split Among the Top 29 Companies

Source: Insight Pharma Reports
CHI: Just to wrap up: Given what we have discussed today, how would you expect current regulatory guidelines to change in the future, and over what kind of timeframe?

Dr. Malik: In my opinion, to change an ICH document is a process that, from an organizational and bureaucratic point of view, is almost impossible. I can’t remember any example of an ICH document being withdrawn. There is an ICH Q&A committee; I believe that they have been accumulating questions but no answers as yet, but eventually they may produce a Q&A document that can be read in addition to E14, and perhaps something similar will happen for S7B. However, the timeframe is difficult to predict. Also, there may evolve unwritten understandings between regulators and sponsors that allow particular elements of the guidelines to be overlooked. For example, the guidelines may suggest inclusion of QT data corrected by Bazett’s formula, but I suspect that sponsors probably could submit data without this, as the regulators know that Bazett-corrected data are useless and add no value. So there may be an unwritten understanding that this type of omission would have no impact on the submission. There may be document updates, most likely by the addition of a Q&A document, but this is likely to be very slow, and before then, unwritten, informal understandings on how to interpret the guidelines are likely to be developed.

Dr. Umesh Patel, PhD

Director, R&D, Ion Channel Group, BioScience Division, Millipore UK, Cambridge, United Kingdom

CHI: To what extent is in silico TdP liability screening now routine among the pharmaceutical industry? Is the software sufficiently robust to be used to eliminate compounds from further development?

Umesh Patel: Most pharmaceutical companies now use in silico techniques, often at the very early stages of drug discovery. Typically, an in silico chemical library will be compared to a database of compound structures with a history of hERG inhibition and torsades generation, and will be modified as necessary to remove structures that appear to have a risk of hERG inhibition. So a primary function of in silico techniques is to design libraries free of hERG blockers before compound synthesis. In addition, in silico screens can be used for compounds that have already been synthesized, to identify those that the medicinal chemists need to modify further to remove potential hERG-binding characteristics. So in silico techniques are used both at a very early stage...