

Assessment of the potential for drugs to cause cardiac arrhythmias

Evolving response to a problem in drug development

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FDA/CDER

Drugs Removed From Market for Arrhythmia Risk

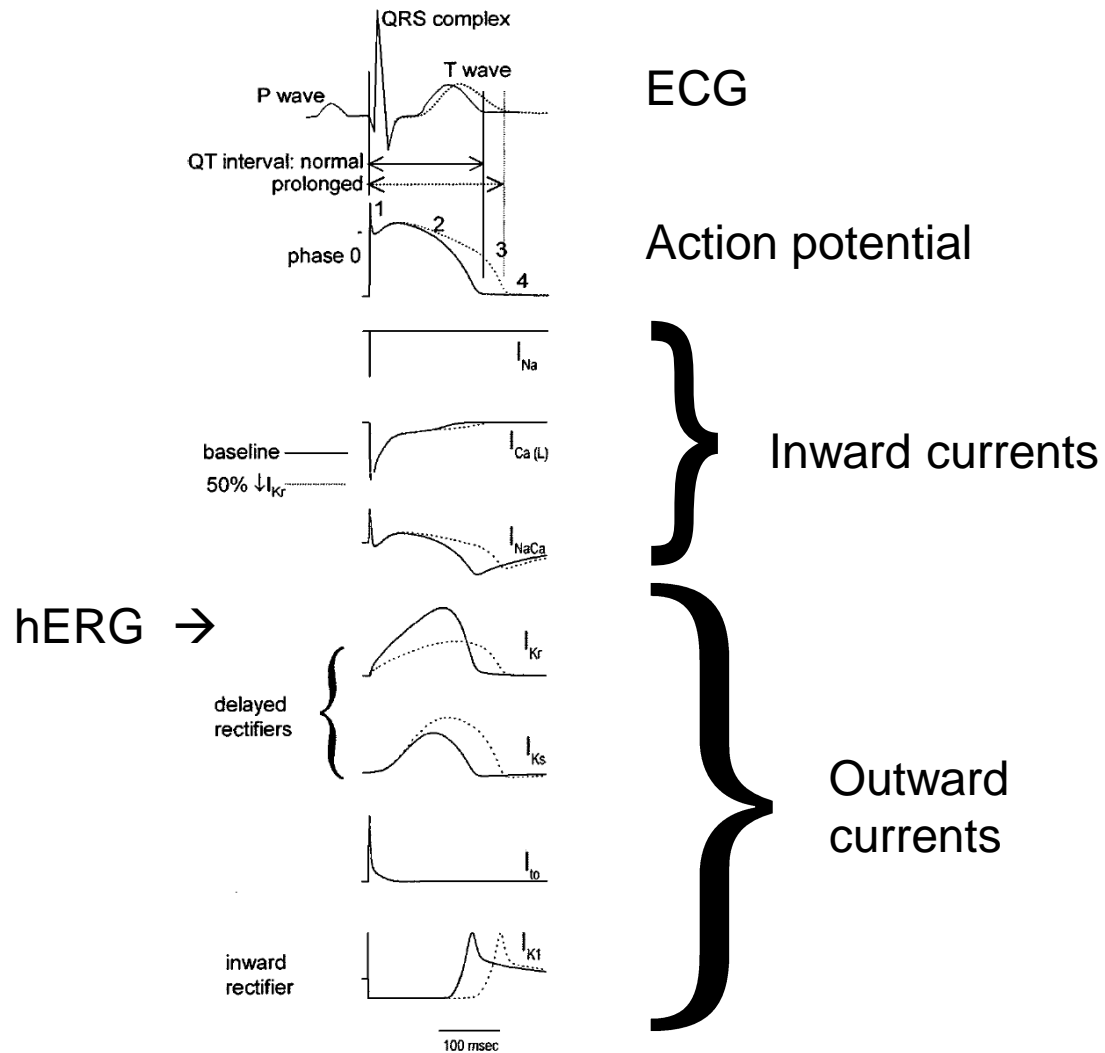
- **Encainide (Enkaid[®])** **1991 (1986)**
- **Terfenadine (Seldane[®])** **1998 (1985)**
- **Astemizole (Hismanal[®])** **1999 (1988)**
- **Grepafloxacin (Raxar[®])** **1999 (1997)**
- **Cisapride (Propulsid[®])** **2000 (1993)**
- **Levomethadyl (Orlaam[®])** **2003 (1993)**

*** year of removal (year of approval)**

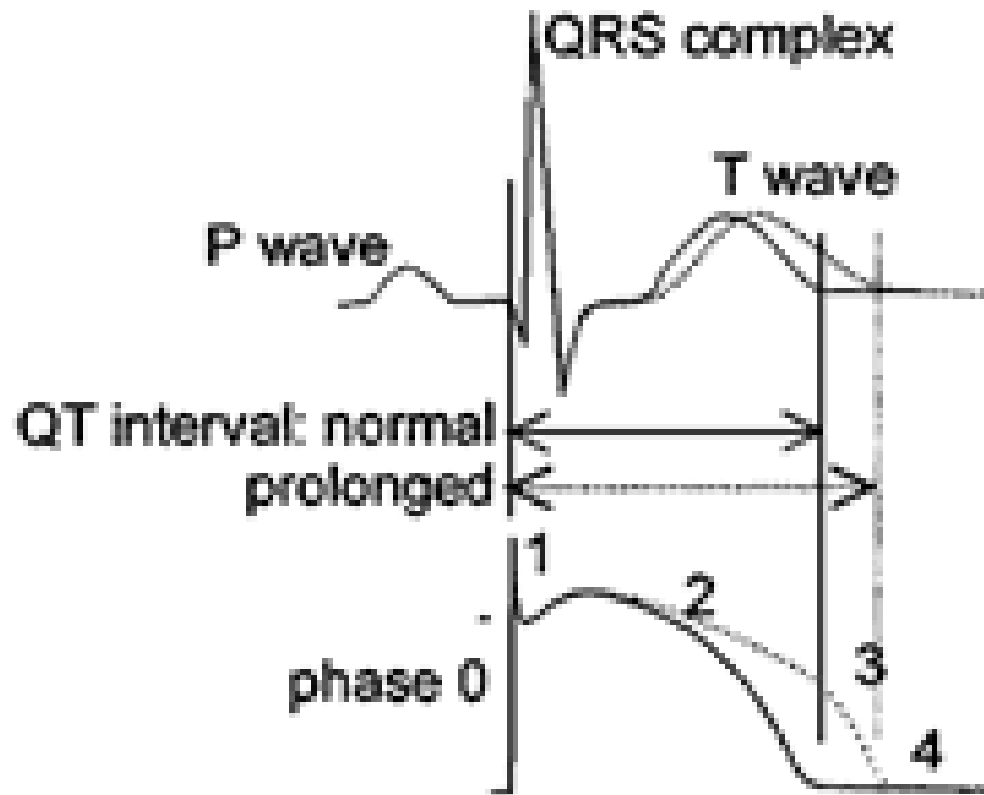
Torsade de Pointes



Cardiac ionic currents



QT prolongation



ICH E14/ S7B: Current FDA Policy

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL
REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

**THE CLINICAL EVALUATION OF QT/QTc INTERVAL
PROLONGATION AND PROARRHYTHMIC POTENTIAL FOR NON-
ANTIARRHYTHMIC DRUGS**

E14

Current *Step 4* version
dated 12 May 2005

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL
REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

**THE NON-CLINICAL EVALUATION OF THE POTENTIAL FOR DELAYED
VENTRICULAR REPOLARIZATION
(QT INTERVAL PROLONGATION)
BY HUMAN PHARMACEUTICALS**

S7B

Current *Step 4* version
dated 12 May 2005

Responses to TdP crisis

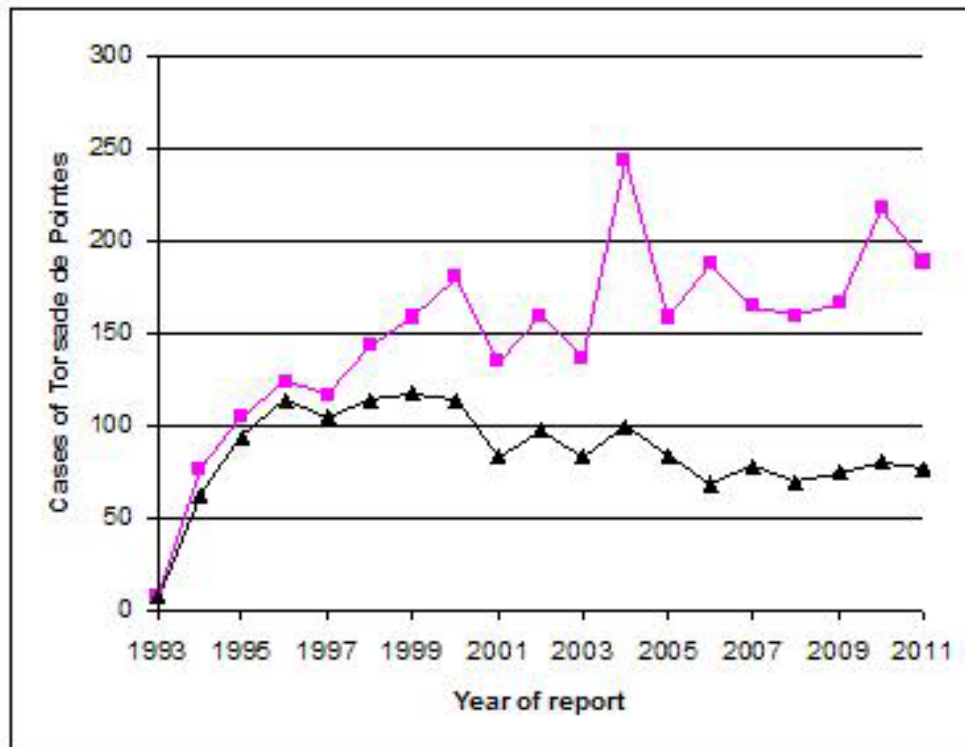
- Regulatory
 - ICH S7B, E14 guidances
 - FDA QT interdisciplinary review team
- Technical
 - HL7 ECG data standard
 - ECG Warehouse
- Community & Research
 - Cardiac Safety Research Consortium
 - Telemetric and Holter ECG Warehouse
 - Specialized QT study vendors
 - ECG Metrics Consortium

Direct costs

- Since 2005
 - Around 300 studies TQT studies reported to FDA
 - Estimated 450 TQT studies performed
 - Estimated cost per study is \$2M
- Total of ~\$1B over 7 years

Success?

- No new withdrawals
- Decline in TdP as a reported adverse event



All drugs

Excluding
anti-arrhythmics

Success? I think not...

- Not all proarrhythmic risk attributes to hERG blockade (false negatives).
 - For example, anti-epileptic drugs are mostly sodium channel blockers
 - Felbamate- SVT, TdP, AF
 - Pregabalin- VF

Success? I think not...

- Not all proarrhythmic risk attributes to hERG blockade (false negatives).
- Not all QT prolongation represents effects on hERG (false positives, part 1).
 - QRS prolongation from blocking Na, Ca (inward) currents
 - True repolarization effects can represent minor potassium currents (we see negative hERG and then a plateau effect on QT of 10 ms or so)

Success? I think not...

- Not all proarrhythmic risk attributes to hERG blockade (false negatives).
- Not all QT prolongation represents effects on hERG (false positives).
- Some true hERG blockers are *anti*-arrhythmic, because of effects on inward currents, too (worse false positives).
 - Verapamil
 - Ranolazine
 - Amiodarone

Success? I think not...

- Not all proarrhythmic risk attributes to hERG blockade (false negatives).
- Not all QT prolongation represents effects on hERG (false positives).
- Some true hERG blockers are anti-arrhythmic, because of effects on inward currents, too (worse false positives).
- Optimizing against hERG reduces selectivity for target receptor and against other off-target receptors (bad bargain).

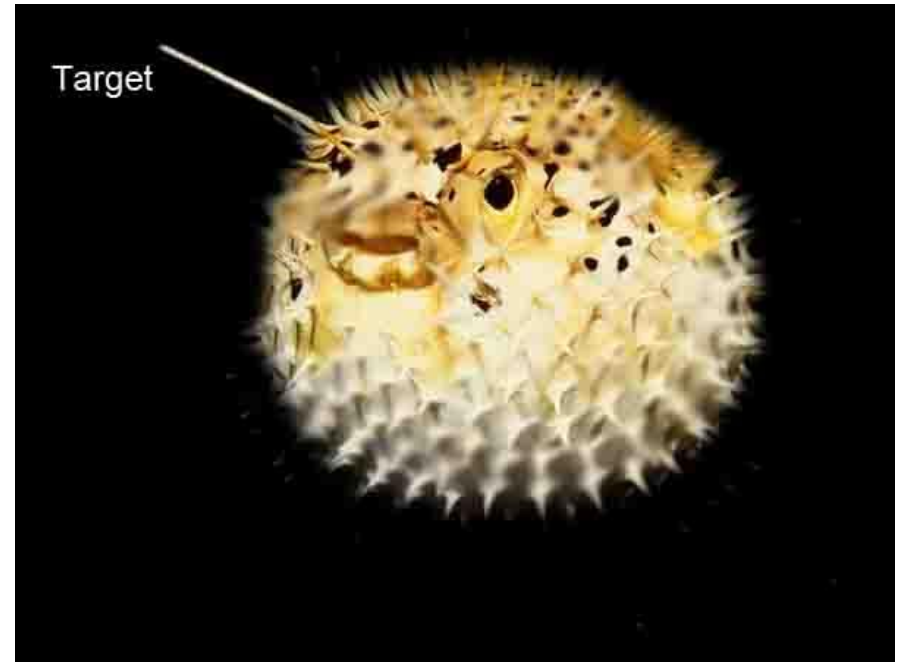
Drug design

- Design space of ~1000 receptors
- Not all distinct (nature physically separates processes, an option not generally available to drug designers)



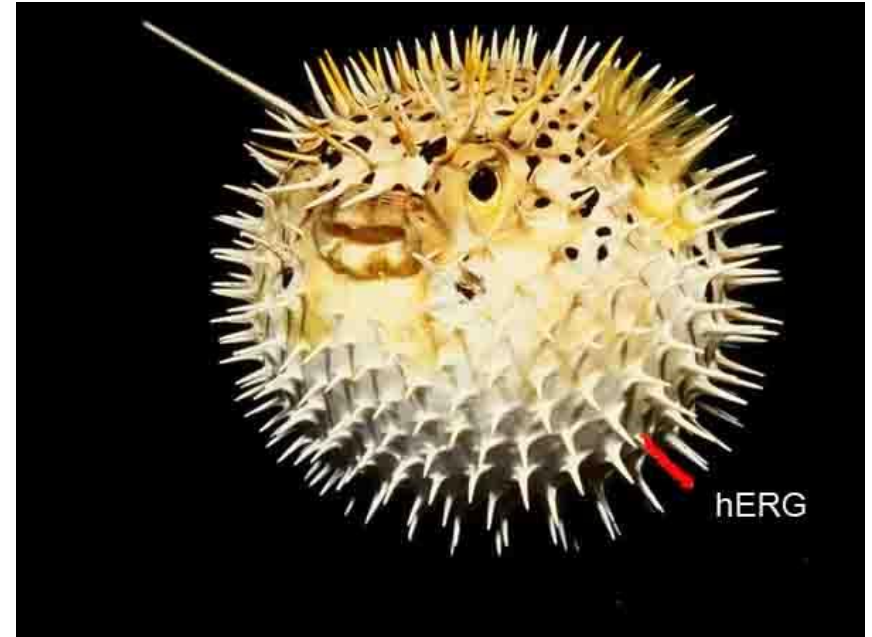
Optimum

- High affinity for target receptor
- No affinity for anything else
- Can't be done



Industry strategy

- “Synthetic chemist, make hERG go away”



Result of hERG-centric strategy

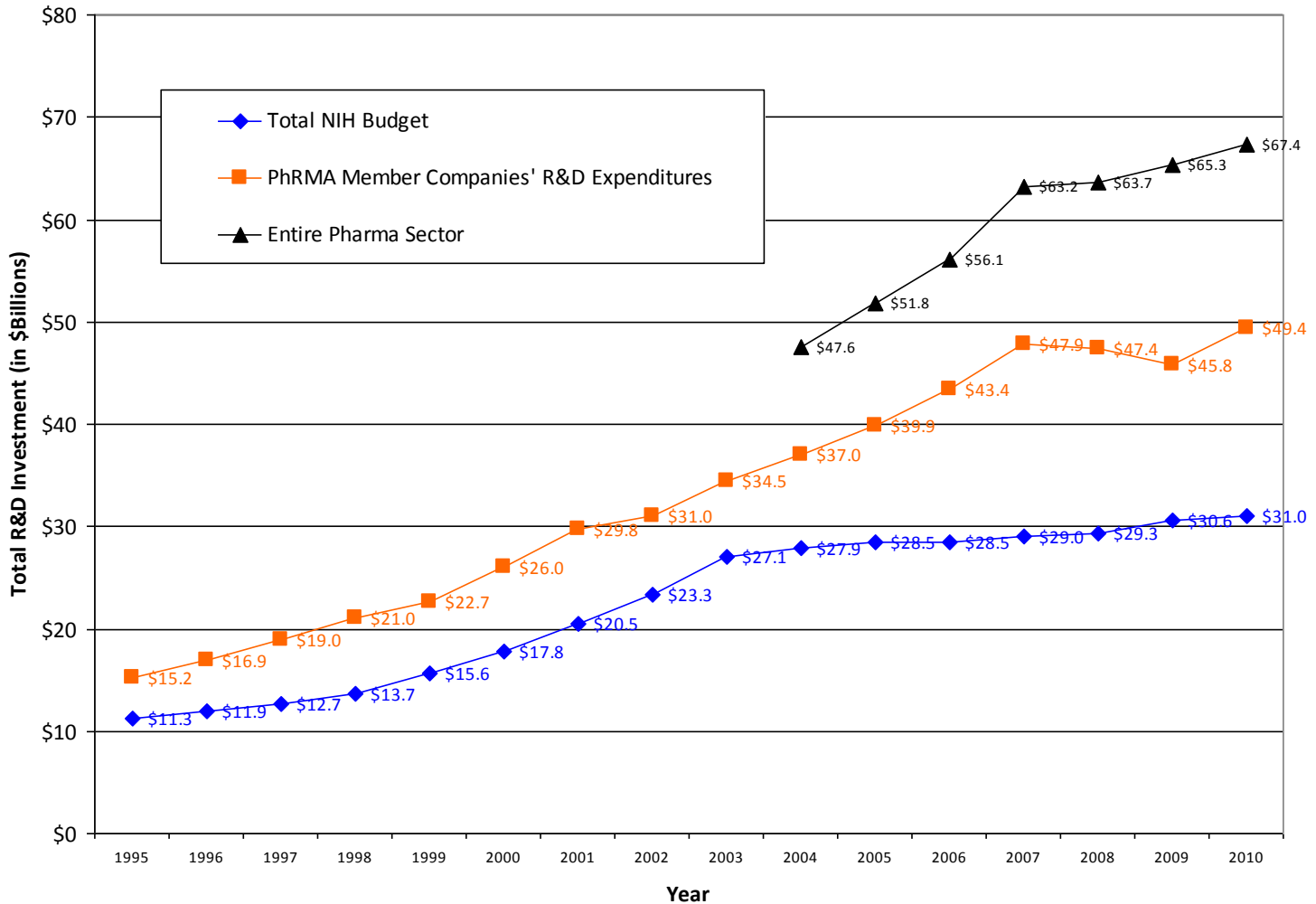
- Reduced affinity for the desired target
- New off-target effects

Or

- No drug candidate at all

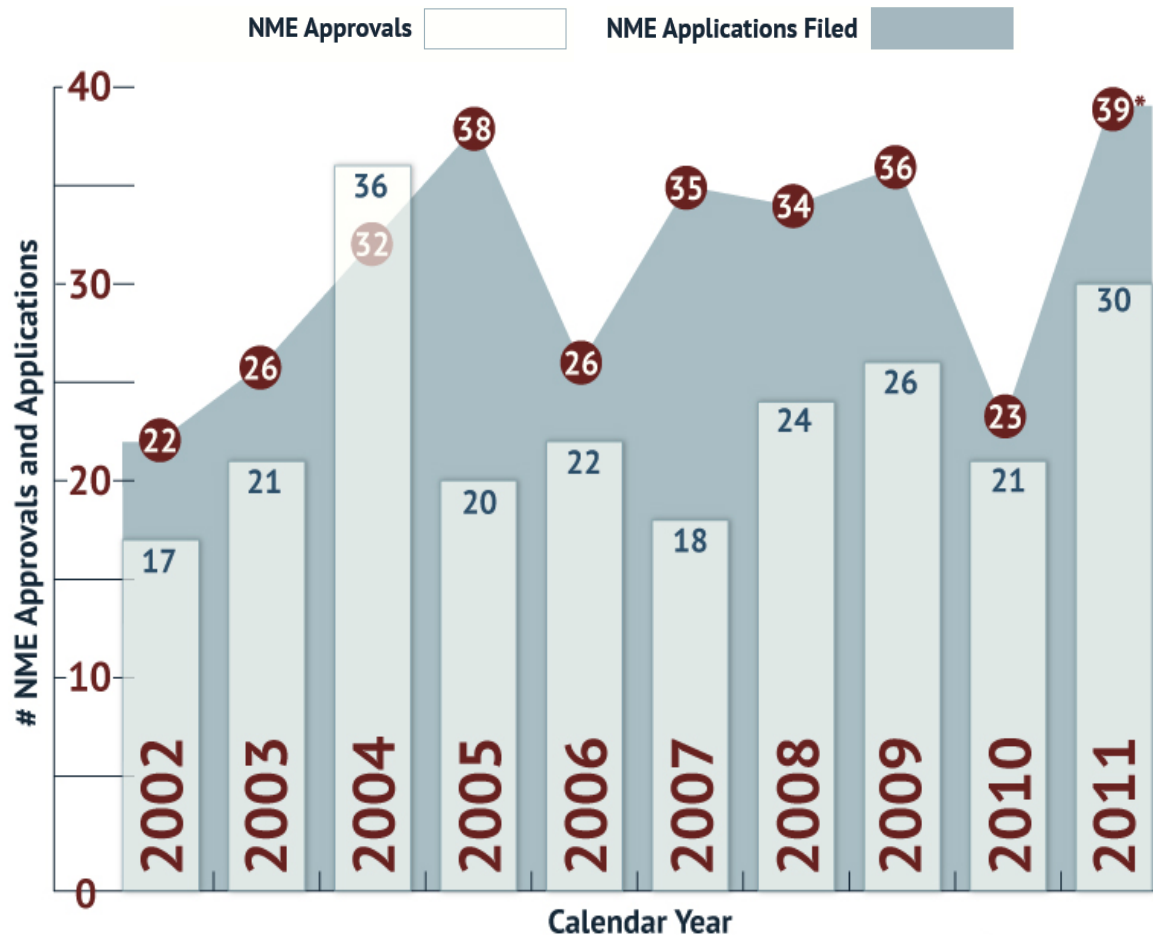


R & D Spending



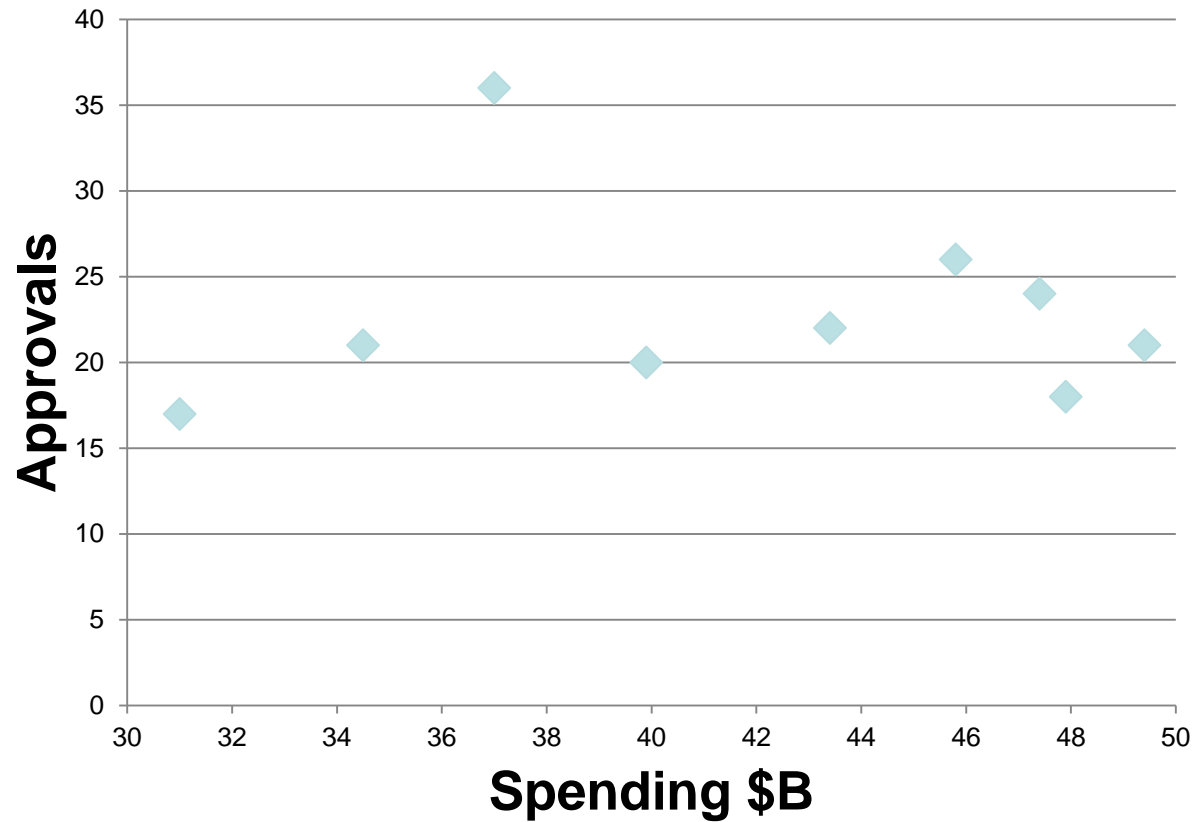
Source: Burrill & Company, PhRMA, NIH Office of Budget

30 NMEs Approved in 2011



**The final number of NME Applications filed in 2011 is projected, pending final validation of the data and dependent outcome of 12 applications submitted in late 2011.*

Approvals by Investment



Working towards rational approach to assess arrhythmia

- Darell Abernethy/FDA
- Arthur Brown/Chantest
- Thomas Colatsky/FDA
- Gary Gintant/Abbott
- Christine Garnett/Pharsight
- Lars Johannesen/FDA
- John Koerner/FDA
- Naomi Kruhlak/FDA
- Derek Leishman/Lilly
- Marek Malek
- Sebastian Polak/Smcyp
- Philip Sager
- Mary Ross Southworth/FDA
- David Strauss/FDA
- Robert Temple/FDA
- Nick Thomas/GE
- Douglas Throckmorton/FDA
- Jiwen Zhang/GE

Candidate Comprehensive Proarrhythmia Assay

- Screening
 - Structure-activity relationship modeling
 - Receptor affinity assays
- Characterization
 - Whole-cell patch clamp of isolated cardiac myocytes
- Interpretation
 - Computer models of myocytes and the heart
- Verification
 - Human ECG

Issues with isolated myocytes

- Can you make inferences about what will happen in the adult human heart?
 - How similar are its properties to those of an adult human heart?
 - Voltage, time dependence
 - Channel density
- How variable are cell properties within a batch or across batches

Mitigation strategies

- Characterize differences and model human heart cells
- Use high-throughput electrophysiology tests
- Incorporate controls to assay variable characteristics

Summary

- Drug development has entered an era in which the decision to advance a compound into development is based upon a very one dimensional assessment of proarrhythmic risk. This decision process is likely to exclude potentially safe and effective drugs. We need a more comprehensive assessment of ion channel effects of potential new drugs to make informed decisions about risks, and we probably need to accept more uncertainty at the time of approval about what risk we have excluded.
- Isolated cardiac myocytes should play an important role in such a comprehensive assay, but further work is needed to allow application of their results to the intact heart.